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PROTOCOL NUMBER: 997HA309

PHASE OF DEVELOPMENT: 3b

PROTOCOL TITLE: A Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) Manufactured at 15K Scale and at Different Vial Strengths in Previously Treated Subjects With Severe Hemophilia A

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SPONSOR SIGNATURE

Protocol 997HA309 was approved by:

[redacted] _____ [redacted]

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Global Development
Biogen MA Inc.

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1. SPONSOR INFORMATION

This study is being conducted by Biogen MA Inc. (Biogen). Biogen is the sponsor of the study, responsible for initiating and managing the study.

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

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

2. LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AUC_{inf}	area under the concentration-time curve from time zero to infinity
BSA	body surface area
BU	Bethesda unit
BUN	blood urea nitrogen
CI	confidence interval
CL	clearance
C_{max}	maximum activity
CHMP	Committee for Medicinal Products for Human Use
CRO	contract research organization
DHA	Directions for Handling and Administration
EDC	electronic data capture
eCRF	electronic case report form
ED	exposure day
EMA	European Medicines Agency
FcRn	neonatal Fc receptor
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IR	incremental recovery
IV	intravenous
IXRS	Interactive Voice/Web Response System
MRT	mean residence time
PK	pharmacokinetic
PK1	pharmacokinetic assessment 1, with 2K rFVIIIFc
PK2	pharmacokinetic assessment 2, with 15K rFVIIIFc
PK3	pharmacokinetic assessment 3, with 15K rFVIIIFc

PT	prothrombin time
PTP	previously treated patient
PVG	pharmacovigilance
rFVIIIFc	recombinant factor VIII Fc fusion protein
SABR	Safety and Benefit-Risk Management
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TP	Treatment Period
$t_{½}$	half-life
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
vWF	von Willebrand factor
WBC	white blood cell
WFH	World Federation of Hemophilia
WHO	World Health Organization
2K	2000 liter (i.e., the bioreactor scale for the manufacturing of the drug substance that is ultimately packaged into vials that constitute the finished 2K drug product)
15K	15,000 liter (i.e., the bioreactor scale the manufacturing of the drug substance that is ultimately packaged into vials that constitute the finished 15K drug product)

3. SYNOPSIS

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

Protocol Number:	997HA309
Protocol Title:	A Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) Manufactured at 15K Scale and at Different Vial Strengths in Previously Treated Subjects with Severe Hemophilia A
Version Number:	1
Name of Study Treatment:	rFVIIIFc (Eloctate; Elocta; BIIB031)
Study Indication:	Hemophilia A
Phase of Development:	3b
Rationale for the Study:	Biogen is increasing the scale of manufacture of rFVIIIFc drug substance from a 2000 L (2K) to a 15,000 L (15K) bioreactor. In addition, at the 15K scale, Biogen is increasing the highest manufactured vial strength from 3000 IU/vial to 6000 IU/vial, to provide more vial strength options. The purpose of this study is to compare the PK of rFVIIIFc drug product manufactured at the 15K scale with the PK of rFVIIIFc manufactured at the current scale (2K). The study will also characterize the PK of rFVIIIFc 15K product in 1000 IU vials and 6000 IU vials, characterize the PK of 15K rFVIIIFc after 13 weeks of prophylactic dosing, and evaluate the safety of 15K rFVIIIFc during extended prophylaxis/treatment for at least 26 weeks. This study is designed to be in accordance with the European Medicines Agency (EMA) requirements for clinical investigation of recombinant and human plasma-derived factor VIII products [EMA (EMA/CHMP/BPWP/144533/2009) 2011].
Study Objectives and Endpoints:	**Objectives** Primary:

The primary objective of the study is as follows:

- To compare the PK of rFVIIIFc manufactured at the current scale of 2000 L (2K) to the PK of rFVIIIFc manufactured at the 15,000 L (15K) scale in previously treated subjects with severe hemophilia A

Secondary:
Secondary objectives are as follows:

1. to characterize the PK of 15K rFVIIIFc at the 15K baseline and after 13 weeks of treatment

2. to characterize the PK of 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths

3. to evaluate the safety of 15K rFVIIIFc

Endpoints

Primary:

The primary endpoint includes the following PK parameters for pharmacokinetic assessment 1 with rFVIIIFc manufactured at 2K scale (PK1) and for pharmacokinetic assessment 2 with rFVIIIFc manufactured at 15K scale (PK2), including:

- area under the concentration-time curve from time zero to infinity (AUC_{inf})

- incremental recovery (IR)

as estimated from the coagulation factor VIII (FVIII) activity data, measured by the one-stage (aPTT) clotting assay.

Secondary:

The secondary endpoints include the following:

1. PK parameters, including but not be limited to AUC_{inf}, IR, the maximum FVIII activity (C_{max}), half-life ($t_{½}$), clearance (CL), volume of distribution at steady state (V_{ss}), and mean residence time

(MRT).

PK will be assessed using the one-stage (aPTT) clotting assay and the two-stage chromogenic assay.

PK parameters will be assessed for the following

- 15K rFVIIIFc at the 15K baseline (i.e., at PK2) and after 13 weeks of treatment (at pharmacokinetic assessment 3, with 15K rFVIIIFc [PK3])
- 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths
- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) [except AUC_{inf} and IR, which are included in the primary endpoint]

2. Development of inhibitors as measured by the Nijmegen-modified Bethesda assay
3. Evaluation of adverse events (AEs) and serious adverse events (SAEs)

Study Design:

Overview:

This is an open-label, multicenter, randomized study. A minimum of 16 subjects who are at least 12 years of age and have had at least 150 exposure days (150 EDs) to any FVIII product will complete 3 PK assessments and a 26-week treatment period. Approximately 24 subjects may be enrolled in order to obtain the necessary number of evaluable subjects as defined in Section 7.5.

In this study, subjects will have PK assessments of 2K rFVIIIFc at the 1000 IU/vial strength (PK1) followed by PK assessment of either 15K rFVIIIFc (1000 IU/vial strength) or 15K rFVIIIFc (6000 IU/vial strength) at PK2. After 13 weeks of treatment with15K rFVIIIFc (1000 IU/vial or 6000 IU/vial strength) will be re-evaluated at Pharmacokinetic assessment 3 (PK3). Following PK3, subjects will continue prophylactic dosing until they reach 26 weeks of treatment with 15K rFVIIIFc (total, starting from the PK2 assessment).

Safety will be assessed over the course of the study. All bleeding episodes and dosing information will be captured in the study diary that the subject (or the subject's caregiver) will maintain throughout the study.

After completion of the study, eligible subjects living in countries where rFVIIIFc is not commercially available will be offered enrollment into extension study 8HA01EXT.

Screening, PK Assessments, Treatment, and Follow-Up:

Pharmacokinetic Assessment 1 (PK1): Subjects will undergo washout (96 hours of washout for a short-acting FVIII product, or 120 hours of washout for a long-acting FVIII product) prior to the first PK assessment. Following screening and washout, all subjects will undergo a 96-hour PK assessment with 50 IU/kg of rFVIIIFc manufactured at the 2K scale using 1000 IU/vial.

Pharmacokinetic Assessment 2 (PK2): It is recommended that the second PK assessment be performed within 2 to 6 weeks after the first. However, prophylaxis and treatment of bleeding episodes are permitted during the intervening period, provided that subjects undergo a minimum of 120 hours of washout of rFVIIIFc prior to the PK2 assessment.

Subjects will be randomized in a 1:1 ratio to 2 groups for the second PK assessment:

- Group 1 will receive 15K rFVIIIFc (1000 IU/vial strength), 50 IU/kg.
- Group 2 will receive 15K rFVIIIFc (6000 IU/vial strength), 50 IU/kg.

Treatment Period (TP): After PK2, subjects will begin receiving treatment with rFVIIIFc (15K vials), for at least 26 weeks. After 13 weeks in the treatment period, subjects will undergo washout in preparation for the PK3 assessment. Following the PK3 assessment, they will resume treatment, until they reach a minimum of 26 weeks.

Pharmacokinetic Assessment 3 (PK3): Subjects will undergo a minimum of 120 hours of washout prior to the third PK assessment. Subjects will undergo a third PK assessment with 15K rFVIIIFc (50 IU/kg) at the same vial

strength they received in PK2. If PK3 does not occur within 13 weeks after PK2, a Treatment Period visit will be performed in its place.

Rationale for Dose and Schedule Selection:

The 50 IU/kg dose was used in the Phase 3 Study (997HA301) PK assessment and is consistent with the EMA guidance [EMA (EMA/CHMP/BPWP/144533/2009) 2011].

Prophylactic treatment dose and regimen:

Following PK2 assessments, subjects will receive prophylactic treatment.

The specific choice of the dosing regimen for any given subject and the subsequent dose or interval adjustment will be based on the subject's response and will be at the Investigator's discretion. Subjects may use any of 5 available 15K vial strengths during the treatment phase.

Suggested prophylactic starting dosing regimens are:

- 50 IU/kg every 3 to 5 days

  OR

- 65 IU/kg weekly

The proposed prophylactic starting regimens are based on the results of the Phase 3 study (997HA301) in adults and adolescents.

Vial Strength

The EMA guidance [EMA (EMA/CHMP/BPWP/144533/2009) 2011] requires that, for products marketed at different strengths, the pharmacokinetics of the lowest and highest concentration should be investigated unless otherwise justified.

The 1000 IU/vial strength was chosen as the lowest strength for this study following CHMP agreement that it is the lowest strength suitable for PK assessment at a dose of 50 IU/kg, although vial strengths as low as 250 IU are produced.

The 6000 IU/vial strength was selected as the highest

	strength for this study because it is the highest vial strength of 15K rFVIIIFc currently intended for commercialization.
Study Location:	Multinational (approximately 3 countries)
Number of Planned Subjects:	Approximately 24 enrolled subjects (12 in Group 1 and 12 in Group 2) are planned, in order to obtain the necessary number of evaluable subjects as defined in Section 7.5.
Study Population:	This study will be conducted in subjects who are male previously treated patients (PTPs) ≥12 years of age with severe hemophilia A (FVIII <1%) and ≥150 EDs to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products. Detailed criteria are described in Section 8.
Treatment Groups:	Treatment of approximately 24 subjects is planned. All subjects will undergo an initial PK assessment with rFVIIIFc manufactured at the 2K scale (1000 IU/vial)[PK1]. On Day 1 of PK1, subjects will be randomized (for the purposes of the subsequent PK2 and PK3 assessments) to 2 groups of approximately 12 subjects each, both receiving drug product manufactured at the 15K scale: • Group 1 will receive 15K rFVIIIFc (1000 IU vials) for PK2 and PK3. • Group 2 will receive 15K rFVIIIFc (6000 IU vials) for PK2 and PK3. In the treatment period that follows PK2, all subjects will receive treatment with 15K rFVIIIFc for a minimum of 26 weeks, during which time subjects will be offered the option of prophylactic treatment.
Duration of Treatment and Follow-Up:	The duration of a subject's participation will be approximately 43 weeks, including up to 8 weeks of screening, 3 PK assessments, a minimum of 26 weeks of prophylactic dosing, and a follow-up telephone call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period. A subject's participation in the study may be extended due to the treatment of bleeding episodes or

surgery.

Criteria for Evaluation:

Pharmacokinetics: FVIII activity will be assessed using the following assays:

- One-stage (aPTT) clotting assay
- Two-stage chromogenic assay

PK parameters will include but not be limited to AUC_{inf}, IR, C_{max}, $t_{½}$, CL, V_{ss}, and MRT.

Safety: The safety profile of rFVIIIFc will be assessed based on the following criteria:

- Nijmegen-modified Bethesda assay for the development of inhibitors
- AEs and SAEs

Statistical Methods: Natural log transformed primary PK endpoints (AUC_{inf} [if data permit] and IR following rFVIIIFc dosing for 2K and 15K at the 15K baseline measured by the one-stage (aPTT) clotting assay) will be analyzed using a mixed effect model with period and treatment as fixed effects and subject as a random effect. Estimates of the adjusted mean differences (15K/2K) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be back transformed (exponentiated) to provide estimates of the ratio of adjusted geometric means (15K/2K) and 90% CIs for the ratios.

For descriptive purposes only, similar analyses may be performed for the other secondary PK parameters measured by the one-stage (aPTT) assay and for all relevant PK parameters measured by the two-stage chromogenic assay.

Comparability of the 2 manufacturing scales will be concluded if the 90% CIs for the ratio of adjusted geometric means for both AUC_{inf} and IR fall within the range of (68%, 146%).

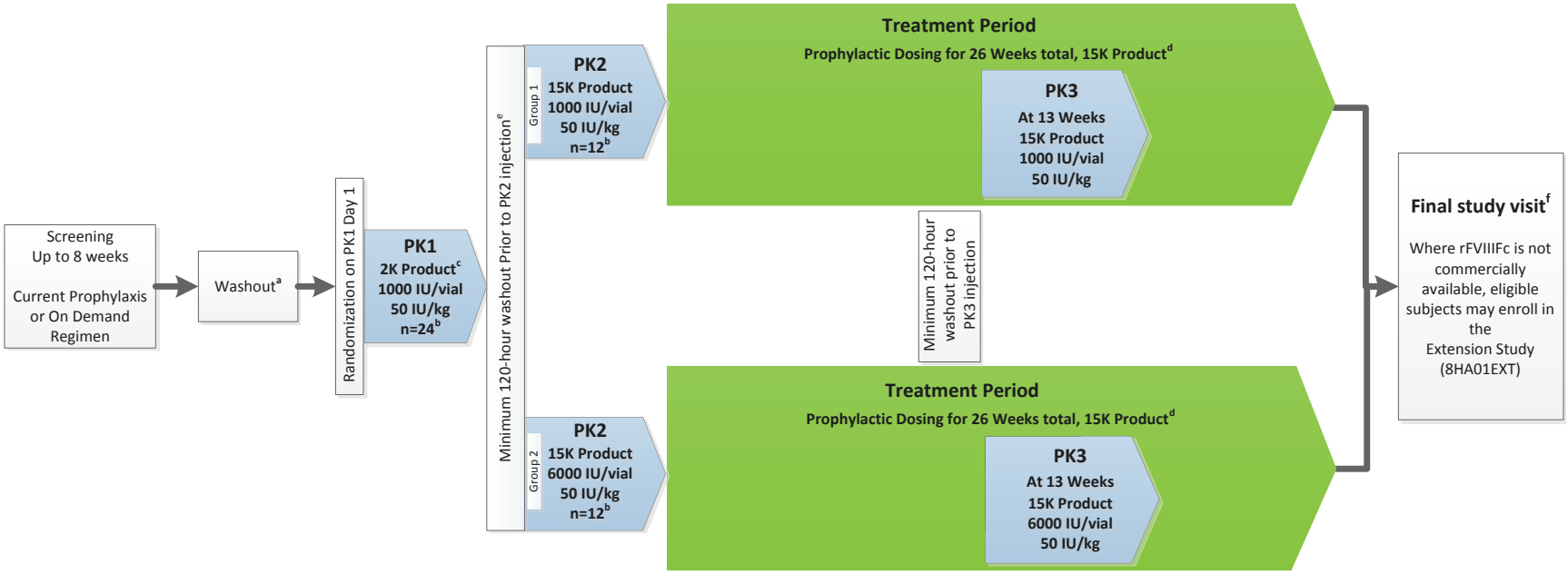
In addition, the PK endpoints (including AUC_{inf}, IR, C_{max},

	$t_{1/2}$, CL, V_{ss}, and MRT) will be summarized descriptively by manufacturing scale, vial strength, and by type of assay (one-stage [aPTT] clotting assay and two-stage chromogenic assay). Summary statistics will include, but not be limited to the mean, CI, standard deviation, median, minimum and maximum values and the geometric means (antilog of the means of the logs) and coefficients of variation. Safety endpoints, including AEs and SAEs, will be summarized descriptively using standard listings. The occurrence of inhibitors will be provided in a listing.
Interim Analysis:	Interim analyses of PK and/or safety data may be conducted during the study, for example, as required to support regulatory submissions, future studies, and/or publications.
Sample Size Determination:	The sample size is consistent with the EMA guidance for PK assessment of hemophilia products, and has sufficient power to demonstrate comparability between the primary PK endpoints.
Study Stopping Rules:	Biogen may terminate this study for safety reasons at any time, after informing Investigators. The study will be discontinued if an unacceptable risk is identified that precludes continued treatment with rFVIIIFc.

4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 997HA309

4.1. Study Schematic

Figure 1: Study Design



Abbreviations: 2K=rFVIIIFc produced at 2000 L scale; 15K=rFVIIIFc produced at 15,000 L scale; PK=Pharmacokinetic sampling period
[a]Minimum of 96 hours of washout for a short-acting FVIII product, or 120 hours of washout for a long-acting FVIII product.
[b]Approximately N=24 subjects may be enrolled in order to complete the study as described in Section 7.5.
[c]If more than 2 bleeds occur during the PK1 assessment period, it will not be rescheduled. The subject may continue on the study in the treatment period.
[d]See Section 10.1.2, for dosing regimens and Section 4.2 for time windows.
[e]The 120-hour washout period for PK2 may begin at the time of the PK1 injection and include the period when the patient is undergoing the PK1 assessment if no additional treatments are needed for bleeds before the PK2 assessment.
[f]There will be a follow up phone call 7 + 7 days after the last dose of rFVIIIFc during the treatment period unless the subject has already enrolled into the extension study, Study 8HA01EXT, by that time.

4.2. Schedule of Events

Each subject will participate in the following visits: Screening; PK1 period (visits on Days 1, 2, 3, 4, and 5); PK2 period (visits on Days 1, 2, 3, 4, and 5); a PK3 period (visits on Days 1, 2, 3, 4, and 5); the Final Study Visit; and a final study telephone call. In addition, unscheduled visits may be conducted for inhibitor monitoring, as well as perisurgical visits (as described in the Schedule of Events tables). If PK3 does not occur within 13 weeks after PK2, a TP visit will be performed in its place.

4.2.1. Screening

Tests and Assessments	Screening
	Week -8 to 0[1]
Informed consent and assent[2]	X
Assessment of subject eligibility[3]	X
Demographics[4]	X
Medical, surgical, and hemophilia history[5]	X
Physical examination	X
Height	X
Weight	X
Vital signs[6]	X
CD4 count, viral load[7]	X
Hematology[8, 9]	X
Blood chemistry[8, 10]	X
PT and vWF antigen[8]	X
Nijmegen-modified Bethesda assay (inhibitor assay)[8, 11, 12]	X
Anti-rFVIIIFc antibody[8, 12]	X
FVIII activity (one-stage [aPTT] clotting and two-stage chromogenic assays)[8, 12]	X
Serum and plasma samples[8, 13]	X
Study diary training/administration/review	X
Subject's completion of study diary	ongoing
SAEs[14]	X
Concomitant therapy/procedures recording[15]	ongoing

FVIII = coagulation factor VIII; PT=prothrombin time; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE=serious adverse event; vWF = von Willebrand factor.
NOTE: See Figure 1 for the relative timing of the Screening, the 3 PK periods, and the treatment period.

[1] Subjects should attend screening at trough for FVIII activity testing (to confirm severe hemophilia A, i.e., endogenous FVIII <1%). The Screening period can be extended for subjects who have a bleeding episode requiring treatment with FVIII within 96 hours prior to Day 1. Subjects must then repeat the washout. If screening is prolonged more than 8 weeks, then the inhibitor, biochemistry, hematology, vital signs, and physical examination screening assessments must be repeated to ensure continued eligibility.

[2] Informed consent must be obtained from the subject or the subject's legal guardian prior to any study-related procedures, including any instruction to washout current therapy specifically for entry into the study. Subject assent must also be obtained, if applicable (i.e., if the subject is under 18 years of age).

[3] Eligibility should be assessed for all criteria pending the central laboratory screening results at screening and should be re-confirmed prior to Day 1 of pharmacokinetic assessment 1 (PK1).

[4] Includes sex, race, date of birth (year only), and ethnicity as permitted by local regulations.

[5] Medical history should include smoking and alcohol consumption habits. Hemophilia history includes (but is not limited to) the date of diagnosis; severity of disease; genotype; number of prior exposures to FVIII; types of FVIII products administered; current dose and regimen of FVIII; last dose of FVIII received; inhibitor history; allergic/anaphylaxis history; and hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) serology.

[6] Vital signs include blood pressure, pulse, respiratory rate, and temperature (°C), and should be taken after the subject has been resting supine for 5 minutes.

[7] CD4 count and viral load are required at screening for all subjects known to be HIV antibody positive. If no results are available from within 26 weeks prior to screening, the CD4 count and viral load must be performed at the central laboratory.

[8] Testing will be performed by the central laboratory.

[9] Hematology includes: white blood cell (WBC) count, differential, platelet count, hemoglobin, and hematocrit.

[10] Blood chemistry includes: electrolytes (sodium, potassium, and chloride), glucose, total protein, total bilirubin, ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), BUN (blood urea nitrogen), and serum creatinine.

[11] For study eligibility, subjects must have no history of a positive inhibitor test, clinical signs of decreased response to FVIII administrations, or measurable inhibitor activity using the Nijmegen-modified Bethesda assay (≥0.6 Bethesda units [BU]/mL is considered positive) at screening.

[12] A washout of at least 48 hours is recommended prior to sample collection (for FVIII inhibitor testing purposes). Separate blood samples will be obtained for inhibitor testing and for anti-rFVIIIFc antibody testing. If inhibitor development is suspected during the study, additional testing will be performed for inhibitor status and anti-rFVIIIFc antibodies. If the results are positive, an independent confirmatory sample will be collected 2 to 4 weeks later for testing.

[13] Samples will be archived for testing (if required) for immunology or further coagulation assays, for clarification of any clinical or laboratory AE, or for genotype analysis in case of inhibitor development.

[14] Before treatment, report SAEs only.

[15] Medications administered up to 30 days prior to screening will be recorded.

4.2.2. Pharmacokinetic Assessments

Tests and Assessments	PK1[1], PK2, and PK3								
	PK Day 1					PK Days 2-5			
Hours (postdose)	Predose[2]	Dosing	0.5 h (±5 min)	1 h (±10 min)	6 h (±10 min)	24 h (±60 min)	48 h (±60 min)	72 h (±60 min)	96 h (±60 min)
Assessment of subject eligibility[3]	X								
Randomization[4]	X								
Physical examination	X								
Weight	X								
Vital signs[5]	X		X						
Nijmegen-modified Bethesda assay (inhibitor assay) [6, 7]	X								
Anti-rFVIIIFc antibody[6,7]	X								
FVIII activity (one-stage [aPTT] clotting and two-stage chromogenic assays)[8]	X		X	X	X	X	X	X	X
rFVIIIFc in-clinic administration		X							
rFVIIIFc dosing/dispensation/accountability[9]									X
Study diary training/administration/review	X								
Subject's completion of study diary	<<<<<<<<<<<<<<<<< Ongoing >>>>>>>>>>>>>>>>>								
AE/SAE monitoring and recording	<<<<<<<<<<<<<<<<< Ongoing; Monitor and record at all visits >>>>>>>>>>>>>								
Concomitant therapy/procedures recording	<<<<<<<<<<<<<<<<< Ongoing; Monitor and record at all visits >>>>>>>>>>>>>>>>>>								

AE = adverse event; FVIII = coagulation factor VIII; h = hours; min = minutes; PK1, PK2, orPK 3 = pPharmacokinetic aAssessment 1, 2, or 3; PT = prothrombin time; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event;TP = Treatment Period.

NOTE: See Figure 1 for the relative timing of the Sscreening period, the 3 PK periods, and the treatment periods. PK3 will occur 14 weeks ± 7 days following PK2.

[1] If more than 2 bleeding episodes occur during the PK1 assessment period, the PK assessment will not be rescheduled. The subject may continue on the study in the TP.

[2] Washout periods: Before PK1, a minimum of 96 hours (for a short-acting product; or 120 hours of washout for a long-acting product such as rFVIIIFc). Before PK2 and PK3, a minimum of 120 hours. The 120-hour washout period for PK2 may begin at the time of the PK1 injection and may include the period when the subject is undergoing the PK1 assessment if no additional treatments are needed for bleeding episodes before the PK2 assessment.

[3] Eligibility should be assessed for all criteria pending the central laboratory screening results at screening and should be re-confirmed prior to Day 1 of PK1.

[4] On Day 1 of PK1, subjects will also be randomized in a 1:1 ratio to receive either 1000 IU/kg or 6000 IU/kg of 15K rFVIIIFc (a single intravenous [IV] injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments.

[5] Vital signs include blood pressure, pulse, respiratory rate, and temperature (°C), and should be taken after the subject has been resting supine for 5 minutes; measured pre-injection and 30 minutes ±15 minutes from the start of the injection at dosing visits.

[6] A washout of at least 48 hours is recommended prior to sample collection (for FVIII inhibitor testing purposes). The blood sample should be collected at trough on Day 1 of each injection, before the i.e., pre-injection is given. Separate blood samples will be obtained for inhibitor testing and for anti-rFVIIIFc antibody testing. If inhibitor development is suspected during the study, additional testing will be performed for both inhibitor status and anti-rFVIIIFc antibodies. If the results are, and if positive, an independent confirmatory sample will be collected 2 to 4 weeks later for testing at the central laboratory.

[7] Testing will be performed by the central laboratory.

[8] Samples for measurement of FVIII activity should be drawn at the post-dosing times specified at the top of each column.

[9] Subjects will receive supplies of rFVIIIFc for home administration from the study site. Each time, the study site staff will perform full medication exchange and accountability with the subject or the subject's caregiver. After the third PK assessment, the subject will continue to receive 15K rFVIIIFc until he reaches a minimum of 26 weeks of treatment with 15K rFVIIIFc in total.

4.2.3. Treatment Period

Tests and Assessments	Treatment Period Visit[1] 13 Weeks After PK2 Injection (14 weeks ± 7 days)	Final Study Visit[2] 26 weeks (+7 days) After PK2 Injection or at Early Termination	Follow-Up 7 (+ 7) days after last dose[3]
Weight	X	X	
Physical examination	X	X	
rFVIIIFc dosing/dispensation/accountability[4]	X	X	
Nijmegen-modified Bethesda assay (inhibitor assay)[5, 6]	X	X	
Anti-rFVIIIFc antibody[5, 6]	X	X	
Hematology[5, 7]	X	X	
Blood chemistry[5, 8]	X	X	
Subject diary review	X	X	X
Telephone call[3]	X	X	X
AE/SAE monitoring and recording	Monitor and record at all visits; telephone call every 8 weeks		
Concomitant therapy/procedures recording	Monitor and record at all visits; telephone call every 8 weeks		

AE=adverse event; FVIII = coagulation factor FVIII; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; PK1, PK2, PK3 = pharmacokinetic assessment 1, 2, or 3; SAE = serious adverse event; TP = Treatment Period

NOTE: See the Figure 1 for the relative timing of the Screening period, the 3 PK periods, and the treatment period.

[1] This visit is needed only if the PK3 assessment period does not occur as scheduled after 13 weeks (14 weeks ± 7 days).

[2] A Final Study Visit will be performed if the subject is at the end of the Treatment Period (after a minimum of 26 weeks following the PK2 injection), the subject terminates from the study early, or the Sponsor declares the end of study. If subjects terminate from study early, all end-of-study assessments will be done at the Termination Visit.

[3] There will be a telephone call every 8 weeks to monitor AEs and SAEs. A Follow-Up Telephone Call is required 7 (+ 7) days after the last dose of rFVIIIFc during the Treatment Period to monitor AEs, SAEs, and concomitant medications and therapies. Any subject who terminates early or is withdrawn from study for any reason is required to undergo the follow-up telephone visit 7 (+ 7) days after the last dose, if possible. This follow-up is not required if the subject has entered directly into extension study 8HA01EXT.

[4] Subjects will receive supplies of rFVIIIFc for home administration from the study site. Each time study treatment is dispensed, the study site staff will perform full medication exchange and accountability with the subject or the subject's caregiver.

[5] Testing will be performed by the central laboratory.

[6] A washout of at least 48 hours is recommended prior to sample collection (for FVIII inhibitor testing purposes). Separate blood samples will be obtained for inhibitor testing and for anti-rFVIIIFc antibody testing. If inhibitor development is suspected during the study, additional testing will be performed for inhibitor status and anti-rFVIIIFc antibodies. If the results are positive, an independent confirmatory sample will be collected 2 to 4 weeks later for testing at the central laboratory.

[7] Hematology includes: white blood cell (WBC) count, differential, platelet count, hemoglobin, and hematocrit.

[8] Blood chemistry includes: electrolytes (sodium, potassium, and chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.

4.2.4. Surgery Visits

Tests and Assessments[1]	Presurgery Visit 1	Visit 2[2]	Visit 3[3]	Visit 4[3]
	Week -12 to Week -1 Before Surgery	Day of Surgery	1-2 Weeks After Surgery	Last Postoperative Visit
Physical examination	X	X		X
Weight	X	X	X	X
Vital signs (temperature, blood pressure, pulse rate, respiratory rate)		X		
Hematology[4, 5]	X	X	X	X
Blood chemistry[4, 6]	X	X	X	X
FVIII activity (one-stage [aPTT] clotting and two-stage chromogenic assays) [4,7]	X	X	X	X
Nijmegen-modified Bethesda assay (inhibitor testing) [4,8]	X	X	X	X
Anti-rFVIIIFc antibody assay[4, 8]	X	X	X	X
Bleeding and dosing information collected[9]	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

AE=adverse event; FVIII = coagulation factor FVIII; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; SAE = serious adverse event

[1] All tests and assessments should be collected for major surgery and minor surgery, where available. Subjects may be allowed to have a PK assessment performed by the central laboratory prior to surgery if needed in the opinion of the Investigator.
[2] All assessments to be performed prior to surgery.
[3] Visit 3 (1 to 2 weeks after 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 resumes a regular rFVIIIFc regimen as determined by the Investigator, and is not required if resumption of the regular rFVIIIFc regimen occurs at Visit 3.
[4] Testing will be performed by the central laboratory.
[5] Hematology includes WBC, differential, platelet count, hemoglobin, and hematocrit.

[6] Blood chemistry includes: electrolytes (sodium, potassium, and chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.

[7] FVIII activity levels should be measured prior to the pre-operative (loading) dose of rFVIIIFc, and at 30 minutes ± 5 minutes after 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. One-stage (aPTT) clotting and two-stage chromogenic assays to be performed at central laboratory.

[8] Inhibitor and anti-rFVIIIFc antibody testing to be performed 2 to 4 weeks prior to surgery, pre-operatively on the day of surgery, 1 to 2 weeks after surgery, and at the last post-operative visit (for minor surgery, testing is not performed at the last 2 timepoints). A washout of at least 48 hours is recommended prior to sample collection (for FVIII inhibitor testing purposes). Separate blood samples will be obtained for inhibitor testing and for anti-rFVIIIFc antibody testing. If inhibitor development is suspected during the study, additional testing will be performed for inhibitor status and anti-rFVIIIFc antibodies, and if positive, a confirmatory sample will be collected 2 to 4 weeks later for testing.

[9] Information to be collected will include number of injections and dose per injection to maintain hemostasis during the surgical period, estimated blood loss (mL) during surgery and post-operative period, and number of blood product units transfused during surgery.

5. INTRODUCTION

Study 997HA309 is designed to investigate the pharmacokinetic (PK) profile of rFVIIIFc manufactured at the 15K scale relative to the PK of rFVIIIFc manufactured at the current scale (2K). The study will also characterize the PK of 15K rFVIIIFc in 6000 IU vials, the highest vial strength currently intended for commercialization, and the lower, 1000 IU vial strength, in accordance with European Medicines Agency (EMA) guidance [EMA (EMA/CHMP/BPWP/144533/2009) 2011]. The study will provide 26 weeks of safety and PK data about treatment with 15K rFVIIIFc. The study population will consist of eligible male, previously treated subjects aged ≥12 years with severe hemophilia A.

Overview of Hemophilia A

Hemophilia A is an X-chromosome-linked bleeding disorder caused by mutations and/or deletions in the F8 gene resulting in a deficiency of coagulation factor VIII (FVIII) activity [Bolton-Maggs and Pasi 2003; Mannucci and Tuddenham 2001]. The coagulation disorder occurs predominantly in males and affects approximately 1 in 5,000 male births [Skinner 2012]. 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.

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 (prophylactic treatment) [MASAC 2009; WFH 2005]. The frequency of administration of FVIII products varies across patients and is tailored to the patient's clinical status, taking into consideration the type of bleeding episode, frequency of bleeding, and goal of treatment for the subject. The dose of FVIII required also varies and has been based on observations over the years as well as guidelines established by organizations such

as the National Hemophilia Foundation of the United States and the World Federation of Hemophilia [WFH 2005].

The use of FVIII-containing plasma-derived coagulation products for people with hemophilia A, available for almost 40 years, has led to vast improvements in quality of life and has increased life expectancy. Manufacturing methods for plasma-derived products are now considered to be highly effective in reducing the risk of transmission of enveloped viruses such as human immunodeficiency virus (HIV) and hepatitis B and C. 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 and Tuddenham 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 (t½) 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].

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 immunoglobulin G (IgG) from degradation and confers IgG the 3-week t½ observed in humans [Ghetie and Ward 2000; Roopenian and Akilesh 2007]. The FcRn is present in humans throughout life and protects IgG from catabolism [Junghans and Anderson 1996]. rFVIIIFc was designed to offer a longer circulating t½ than currently available FVIII products, aiming to provide hemophilia A patients with prolonged protection and prophylaxis from bleeding with less frequent dosing.

rFVIIIFc has marketing authorization for the treatment of individuals with hemophilia A in the United States and several additional countries.

5.1. Profile of Previous Experience With rFVIIIFc

Nonclinical Experience

A number of nonclinical comparability studies support the scale-up from the 2000 L to the 15,000 L bioreactor scale, including PK, pharmacology, and immunogenicity studies in the HemA mouse model and in vitro studies of activation and inactivation rates. These studies found that PK parameters, ex vivo efficacy, and the immunogenic potential of rFVIIIFc produced at the 2 scales were comparable in HemA mice. The 2000 L drug substance and 15,000 L drug substance were also similar in biochemical assays, including activation by thrombin and inactivation by activated protein C.

For further details regarding other nonclinical studies conducted with rFVIIIFc, see the rFVIIIFc Investigator's Brochure.

Clinical Experience

Study 998HA101, a completed Phase 1/2a study, investigated the safety and PK of a single dose of rFVIIIFc given as an IV injection to subjects with severe hemophilia A and compared the PK of rFVIIIFc with Advate® (antihemophilic factor [Recombinant], Plasma/Albumin-Free Method, [INN] octocog alfa). PK profiles were performed for Advate at 2 dose levels (25 and 65 IU/kg), followed by PK profiles for rFVIIIFc at equivalent doses. 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 longer t½, increased systemic exposure, and a reduction in CL, with comparable C_{max} and recovery.

Study 997HA301, a Phase 3 study in previously treated subjects aged 12 years or older with severe hemophilia A, has also been completed. A total of 164 subjects (including 13 subjects aged 12 to 17 years) received at least 1 dose of rFVIIIFc. This included 146 subjects treated for at least 26 weeks and 23 subjects treated for at least 39 weeks, for a total of 102.05 subject-years on study. Compared with Advate, rFVIIIFc demonstrated improved PK activity, as indicated by a 53% longer $t_{½}$, a 56% increase in systemic exposure, and a 36% reduction in CL, with comparable C_{max} and incremental recovery (one-stage [aPTT] clotting assay). rFVIIIFc was well tolerated. No subject developed an inhibitor to rFVIIIFc. Common AEs observed were consistent with those expected in patients with hemophilia A. Adverse drug reactions were generally mild and manageable, and the majority were not treatment limiting. One nonserious event of rash required discontinuation of treatment and resolved. There were no Grade 2 or greater allergic reactions or serious vascular thrombotic events. No treatment-related SAEs were observed.

Study 8HA02PED (referred to as the pediatric study) is a completed, open-label, multicenter study evaluating the safety, PK, and efficacy of rFVIIIFc in previously treated pediatric patients with severe hemophilia A who were <12 years of age and had at least 50 exposure days (EDs) to FVIII products prior to enrollment. A total of 71 male subjects enrolled (36 subjects <6 years of age and 35 subjects 6 to <12 years of age). A total of 60 subjects completed the week 26 visit (i.e., 26 weeks of prophylactic treatment for all but 1 subject) to attain at least 50 EDs. A total of 53 subjects (23 subjects <6 years of age and 30 subjects 6 to <12 years of age) underwent an evaluation of the PK profile of both prestudy FVIII and rFVIIIFc. No subject developed an inhibitor during the study, including 61 subjects with at least 50 EDs to rFVIIIFc. There were no reports of anaphylaxis or serious hypersensitivity events associated with rFVIIIFc; and no vascular thrombotic events were reported. Assessment of the PK of rFVIIIFc revealed 12.28 and 13.45 hours t½ for the <6 years of age cohort and 6 to <12 years of age cohort, respectively.

Study 997HA307 is an ongoing randomized, open-label crossover study to evaluate the pharmacokinetics of 2 vial strengths of rFVIIIFc in previously treated subjects with severe

hemophilia A, who are ≥12 years of age and had >150 EDs to FVIII products prior to enrollment. Approximately 16 subjects will be enrolled to ensure that at least 12 subjects provide evaluable PK profiles for both vial strengths being tested (1000 IU/vial and 3000 IU/vial).

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

For further details regarding the clinical studies conducted with rFVIIIFc, see the rFVIIIFc Investigator's Brochure.

5.2. Study Rationale

Biogen is increasing the scale of manufacture of rFVIIIFc drug substance from 2000 L (2K) to 15,000 L (15K). The purpose of this study is to compare the PK of rFVIIIFc manufactured at the 15K scale with the PK of rFVIIIFc manufactured at the current scale (2K), in order to investigate whether there were any effects of changes in the manufacturing process on the activity of rFVIIIFc. In addition, at the 15K scale, Biogen is increasing the highest manufactured vial strength from 3000 IU/vial to 6000 IU/vial. The study will also characterize the PK of 15K rFVIIIFc in 1000 IU and 6000 IU vials, will characterize the PK of 15K rFVIIIFc after 13 weeks of prophylactic dosing, and will evaluate safety of 15K rFVIIIFc during the extended prophylaxis/treatment for at least 26 weeks. This study will provide clinical data to complement nonclinical, bioanalytical, and physicochemical comparability data on rFVIIIFc from the 2K and 15K scale product.

This study is designed to be in accordance with the European Medicines Agency (EMA) requirements for clinical investigation of recombinant and human plasma-derived factor VIII products [EMA (EMA/CHMP/BPWP/144533/2009) 2011], particularly with regard to the following:

- A PK assessment of the pre-change product (i.e., 2K rFVIIIFc) versus the post-change product (i.e., 15K rFVIIIFc) will be performed.
- A PK assessment of the post-change product (i.e., rFVIIIFc manufactured at the 15K scale) after 13 weeks of dosing will be performed.
- Subjects will complete a minimum of 26 weeks of dosing with 15K rFVIIIFc.
- The PK of the lowest and highest vial strengths is being investigated. Although vial strengths as low as 250 IU are produced, the 1000 IU/vial strength was chosen for this study because it is the lowest strength suitable for PK assessment at a dose of

50 IU/kg. The 6000 IU vial represents the highest vial strength intended for commercialization and, therefore, was selected for this study.

5.3. Rationale for Dose and Schedule Selection

The dose for the PK assessments (50 IU/kg) is within the 25 to 50 IU/kg specified in EMA guidance [EMA (EMA/CHMP/BPWP/144533/2009) 2011] and is the same as that used in the Phase 3 study (997HA301) for PK assessment.

In the treatment period that follows PK2, all subjects will receive a minimum of 26 weeks of prophylactic treatment with 15K rFVIIIFc. The specific choice of the dose for any given subject, and the subsequent dose adjustment, will be based on the subject's response and will be at the Investigator's discretion. The recommended dosing regimens are as follows:

- 50 IU/kg rFVIIIFc every 3 to 5 days. The dose may be adjusted in the range of 25 to 65 IU/kg at 3 to 5 day intervals.
- 65 IU/kg rFVIIIFc once weekly

5.4. Potential Risks and Benefits

See the 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 Objectives

The primary objective of the study is to compare the PK of rFVIIIFc manufactured at the current scale of 2000 L (2K) to the PK of rFVIIIFc manufactured at the 15,000 L (15K) scale in previously treated subjects with severe hemophilia A.

6.1.2. Secondary Objectives

Secondary objectives are as follows:

- To characterize the PK of 15K rFVIIIFc at the 15K baseline and after 13 weeks of treatment
- To characterize the PK of 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial strengths
- To evaluate the safety of 15K rFVIIIFc

6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint includes the following PK parameters following dosing in PK1 (rFVIIIFc manufactured at 2K scale) and in PK2 (rFVIIIFc manufactured at 15K scale) at the 15K baseline, including:

- AUC_{inf}
- IR

as estimated from the coagulation factor VIII (FVIII) activity data, as measured by the one-stage (aPTT) clotting assay.

6.2.2. Secondary Endpoints

The secondary endpoints include the following:

1. PK parameters, including but not be limited to AUC_{inf}, IR, C_{max}, $t_{½}$, CL, V_{ss}, and MRT.

   PK will be assessed using the one-stage (aPTT) clotting assay and the two-stage chromogenic assay for the following:

- 15K rFVIIIFc before treatment (at PK2) and after 13 weeks of treatment (at PK3)
- 15K rFVIIIFc at 1000/vial and 6000 IU/vial strengths
- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) [only C_{max}, $t_{½}$, CL, V_{ss}, and MRT; other parameters comprise the primary endpoint]

2. The development of inhibitors as measured by the Nijmegen-modified Bethesda assay
3. Evaluation of AEs and SAEs

7. STUDY DESIGN

7.1. Study Overview

This will be a randomized, open-label, multicenter study to evaluate the PK of a single dose of rFVIIIFc manufactured at 2 different scales (2K and 15K) and 15K rFVIIIFc. PK of rFVIIIFc produced at different vial strengths will be evaluated at the 15K baseline (PK2) and after 13 weeks on the study (PK3). Subjects will receive treatment with 15K rFVIIIFc for at least 26 weeks while on study, and will be followed for safety during that time. Subjects will be PTPs who are ≥12 years of age. Approximately 24 subjects will be enrolled in order to obtain the necessary number of evaluable subjects as defined in Section 7.5.

After eligibility is confirmed, subjects will undergo PK assessments at clinic visits, when safety assessments, drug accountability, and review of dosing and bleeding data will also be performed.

Prior to the first PK assessment (PK1) subjects will undergo a minimum washout period of 96 hours (for short-acting products) or 120 hours (for long-acting products). In the event that bleeding occurs during the washout period, the subject must repeat the washout.

Subjects will then undergo the PK1 assessment with 2K rFVIIIFc (a single IV injection of 50 IU/kg using 1000 IU/vial material). During the PK1 assessment period, subjects will also be randomized in a 1:1 ratio to receive either 1000 IU/kg or 6000 IU/kg of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. If more than 2 bleeding episodes occur during the PK1 assessment, the PK assessment will not be rescheduled, and the subject may proceed to the 26-week Treatment Period.

Just prior to the PK2 and PK3 injections, there will be a minimum washout of 120 hours. It is recommended that the second PK assessment, PK2, be performed within 2 to 6 weeks after the first (Section 10.1.1). There are no limits on the number of bleeding episodes during the washouts and the PK2 and PK3 assessment periods. Subjects who cannot complete all 3 PK assessments may continue to the 26-week Treatment Period.

After PK2 (irrespective of PK evaluability), subjects will begin treatment with 15K rFVIIIFc for at least 26 weeks (Section 10.1.2). During treatment, subjects will be offered prophylaxis (dosing either every 3 to 5 days or once-weekly) using 15K rFVIIIFc. Subjects will be allowed to switch from one regimen to another if approved by the Investigator and will be allowed to use any of several available vial strengths.

After 13 weeks on treatment, there will be a third PK assessment (PK3) with the same vial strength of 15K rFVIIIFc that the subject previously received. The subject will continue to receive 15K rFVIIIFc for a minimum of 26 weeks of treatment with 15K rFVIIIFc in total. After completion of the study, eligible subjects living in countries where rFVIIIFc is not commercially available will be offered enrollment into extension study 8HA01EXT.

Discontinued subjects or subjects unable to complete all 3 PK assessments may be replaced if needed to attain the number of subjects required to complete the study as described in Section 7.5.

See Figure 1 for a schematic of the study design.

7.2. Study Specifics

7.2.1. Inhibitor Testing

For FVIII inhibitor testing, a washout of at least 48 hours is recommended. Inhibitor testing will be performed at screening, prior to each PK dose (or at the 14 week ± 7 day visit if PK3 does not take place at 13 weeks; see Section 4.2.3), and at the Final Study Visit. If inhibitor development is suspected at any time during the study (for example, if 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 confirmed positive inhibitor will result in withdrawal of the subject from the study.

7.2.2. 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 used for this test is approximately 10- to 20-fold more sensitive than the Nijmegen-modified Bethesda assay. At the same timepoints when samples are drawn for inhibitor testing, a blood sample will be collected for testing of anti-rFVIIIFc antibody (see Section 4.2.2 and Section 4.2.3).

7.3. Overall Study Duration and Follow-Up

The study period will consist of screening, 3 PK assessment periods, a treatment period, and follow-up.

7.3.1. Screening

Subject eligibility for the study will be determined within 8 weeks prior to study entry. The Screening Period will also include the washout of FVIII prior to initial study dosing. During screening, subjects will continue with their prior FVIII product and treatment regimen. However, prior to the first rFVIIIFc PK assessment, subjects must have a washout of at least 96 hours for a short-acting FVIII product, or at least 120 hours of washout for a long-acting FVIII product. The Screening Period can be extended for subjects who require treatment with

FVIII for a bleeding episode within 4 days (96 hours) prior to the first injection on Day 1 of PK1 or during the PK1 assessment periods. Subjects will be given diaries at the Screening Visit and will be instructed to start recording all injections and bleeding episodes. Further details will be provided in the Diary Instruction Manual.

If screening is longer than 8 weeks, then the inhibitor, biochemistry, hematology, vital signs, and physical examination screening assessments must be repeated to ensure continued eligibility. The reason for prolongation of screening should be clearly documented.

Eligibility should be assessed for all criteria pending the central laboratory screening results at screening and should be re-confirmed prior to Day 1 of PK1.

7.3.2. Pharmacokinetic Assessments

A washout period with no FVIII treatment will be required prior to each injection of rFVIIIFc for all PK assessments (96 hours for short-acting products or 120 hours for long-acting products).

Eligible subjects will report to the study site for the PK assessments. Every subject is expected to participate in all 3 PK assessments:

- PK1: At the first visit, the subject will receive a single IV injection of 2K rFVIIIFc (50 IU/kg of 1000 IU/vial) in the clinic under medical supervision. PK sampling will occur just before the PK injection and at 7 time points: 0.5 hour (±5 minutes); 1 hour and 6 hours (±10 minutes); and 24, 48, 72, and 96 hours (±60 minutes). The subject will receive 50 IU/kg of 15K rFVIIIFc at either the 1000 IU/vial or 6000 IU/vial strength in subsequent PK assessments.

- PK2: The second PK assessment will be performed, preferably, within 2 to 6 weeks after the first PK assessment. PK sampling will occur just before the PK injection and at 7 time points: 0.5 hour (±5 minutes); 1 hour and 6 hours (±10 minutes); and 24, 48, 72, and 96 hours (±60 minutes) after each injection.

- PK3: After 13 weeks (14 weeks ± 1 week) on treatment with 15K rFVIIIFc, the subject will have a third PK assessment at the same vial strength as in PK2. PK sampling will occur just before the PK injection and at 7 time points: 0.5 hour (±5 minutes); 1 hour and 6 hours (±10 minutes); and 24, 48, 72, and 96 hours (±60 minutes) after each injection.

7.3.3. Treatment

Subjects will receive supplies of rFVIIIFc from the study site for home administration, either at study site visits for PK assessments or between study visits consistent with Section 11. Subjects will be provided rFVIIIFc for a total of at least 26 weeks of treatment, unless the end-of-study criteria have been reached (Section 7.5). After that time, eligible subjects living in countries

where rFVIIIFc is not commercially available will be offered enrollment into extension study 8HA01EXT.

Dosing regimens are described in detail in Section 10.1.2.

7.3.4. Follow-Up

There will be a Follow-up Telephone Call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period, unless the subject has entered directly into extension study 8HA01EXT by that time.

7.4. Study Stopping Rules

Biogen may terminate this study for safety reasons at any time, after informing Investigators. Biogen (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated. The study will be discontinued if an unacceptable risk is identified that precludes continued treatment with rFVIIIFc.

7.5. End of Study

The study will be considered complete when

- At least 16 subjects (8 in each arm) have evaluable PK data AND
- At least 12 subjects have had at least 26 weeks of treatment with 15K rFVIIIFc.

When this occurs, all ongoing subjects will return to the clinic for end-of-study assessments (see Section 4.2.3). End of study will occur when the last subject has had his last visit (Last Subject Last Visit [LSLV]).

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening, or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject or his/her legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information 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. Male, age ≥12 years old at the time of informed consent, and weighing at least 40 kg.

3. Have severe hemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII as determined by one-stage clotting assay from the central laboratory at Screening. If the screening result is ≥1%, then the severity of hemophilia A may be confirmed by documented historical evidence from a certified clinical laboratory demonstrating <1% FVIII:C as determined by the one-stage clotting assay from the medical record.

4. Previously treated subject, defined as having at least 150 documented prior EDs to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products at Day 1. Fresh frozen plasma treatment must not be considered in the count for documented EDs.

5. No history of a positive inhibitor test or clinical signs of decreased response to FVIII administrations. Family history of inhibitors will not exclude the subject.

6. No measurable inhibitor activity using the Nijmegen-modified Bethesda assay (≥0.6 BU/mL is considered positive) at Screening.

7. Willingness and ability of the subject or a surrogate (a caregiver or a family member ≥18 years of age) to complete training in the use of the study diary and to complete the study diary in a timely manner throughout the study.

8. Platelet count ≥100,000 platelets/μL at Screening (test performed by the central laboratory and reviewed prior to Day 1 of the first PK assessment).

   The following inclusion criteria refer to tests performed within 26 weeks prior to Screening. If not available, the test should be conducted by the central laboratory, sampled at Screening and reviewed prior to Day 1 of the first PK assessment.

9. CD4 lymphocytes >200 mm^3 if known as HIV antibody positive at Screening.

10. Viral load of <400 copies/mL if known HIV antibody positive at Screening.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

1. Current enrollment in any interventional clinical study in which an investigational drug or approved therapy for investigational use is administered within 30 days prior to the Baseline Visit OR prior participation in any of the following Biogen studies: 998HA101, 997HA301, 8HA02PED, 997HA307, and 8HA01EXT.

2. Previous participation in this study.

3. Inability to comply with study requirements in the opinion of the Investigator.

4. Any concurrent clinically significant major disease that, in the opinion of the Investigator or Biogen, makes the subject unsuitable for participation in the study.

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

6. History of hypersensitivity or anaphylaxis associated with FVIII or IV immunoglobulin administration.

7. Currently taking (or likely to require during the study) acetylsalicylic acid (ASA), except for low-dose ASA as prophylaxis (other non-steroidal anti-inflammatory drugs are permitted).

8. Concurrent systemic treatment with immunosuppressive drugs within 12 weeks prior to Day 1 of the first PK assessment. Exceptions to this include: ribavirin for treatment of HCV, and/or systemic steroids (a total of 2 courses of pulse treatments lasting no more than 7 days within 12 weeks prior to Day 1) and/or inhaled steroids.

9. Major surgery within the previous 8 weeks.

10. Abnormal renal function (serum creatinine >2.0 mg/dL) [test performed by the central laboratory and reviewed prior to Day 1 of the first PK assessment].

11. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN) [test performed by the central laboratory and reviewed prior to Day 1 of the first PK assessment].

12. Serum total bilirubin >3 × ULN (test performed by the central laboratory and reviewed prior to Day 1 of the first PK assessment).

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

9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects (or their legally authorized representative [e.g., parent or legal guardian], where applicable) must provide informed consent/assent before any screening tests are performed (see Section 17.3). 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. Subjects will be registered as screened in the Interactive Voice/Web Response System (IXRS) following completion of all screening assessments.

The Screening Period can be extended for subjects who have a bleeding episode requiring treatment with FVIII during the washout period prior to the first injection on Day 1 of PK1 Injection 1 (see Section 7.3.1 for details).

Once the required washout is complete and all inclusion and exclusion criteria have been met (see Section 8.1 and Section 8.2), the subject will be enrolled into the study and randomized as described in Section 9.2.

Discontinued subjects or subjects unable to complete all 3 PK assesments may be replaced if needed to attain the number of subjects required to complete the study as described in Section 7.5.

9.2. Randomization and Registration of Subjects

Subjects will be enrolled after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment. As confirmation, the Investigator will receive written verification of the subject's registration by mail or fax.

Subjects will be randomized on Day 1 of PK1 via the IXRS. The randomization will determine their PK2 and PK3 group assignments, to 1 of 2 groups, in a 1:1 ratio. Subjects will receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc.

Refer to the Study Reference Guide for details on registration and randomization.

9.3. Blinding Procedures

Not applicable.

10. STUDY TREATMENT

The Sponsor will provide rFVIIIFc to sites via its designated distributors.

Refer to Section 11 for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

10.1. Treatment Schedule

Refer to and follow the Directions for Handling and Administration (DHA).

Refer to Figure 1 for a schematic of the study design and to Section 4.2 for study schedules.

During the PK assessment, rFVIIIFc injections will be prepared and administered in the clinic by study personnel. During the Treatment Period, rFVIIIFc injections will be prepared and administered at home.

10.1.1. Pharmacokinetic Assessments

The PK assessments will be performed following a single dose of rFVIIIFc, as follows:

- PK1: 2K rFVIIIFc, 1000 IU/vial, 50 IU/kg
- PK2 and PK3:
    - Group 1 will receive 15K rFVIIIFc, 1000 IU/vial, 50 IU/kg for both assessments.
    - Group 2 will receive 15K rFVIIIFc, 6000 IU/vial, 50 IU/kg for both assessments.

Assignment of study treatment kits appropriate to a particular subject's PK assessment is described in Section 11.1.4 .

Following the minimum washout (96 hours of washout for a short-acting product, or 120 hours of washout for a long-acting product such as rFVIIIFc) and confirmation of eligibility, subjects will receive their first injection of rFVIIIFc (on Day 1 of PK1). At the time of the PK1 assessment, subjects will be randomized in a 1:1 ratio to receive 15K rFVIIIFc at either the 1000 IU/vial or the 6000 IU/vial strength in the subsequent PK2 and PK3 assessments.

Treatment of bleeding episodes is permitted during the PK1 assessment. Prophylaxis and treatment of bleeding episodes is permitted in the period between PK1 and PK2 if needed. Subjects must use only 2K 1000 IU/vial rFVIIIFc and must undergo a minimum of 120 hours of washout of rFVIIIFc prior to the PK2 assessment. It is recommended that the PK2 assessment

be performed within 2 to 6 weeks after the PK1 assessment. Washout is also required prior to the PK3 assessment.

Study procedures to be carried out during PK assessments are summarized in Section 4.2.2. Blood samples for PK analysis will be collected just prior to the injection and at the following timepoints: 0.5 hour (±5 minutes); 1 hour and 6 hours (±10 minutes); and 24, 48, 72, and 96 hours (±60 minutes) after each injection. In cases of bleeding episodes during the PK assessment, subjects should be treated according to Table 1 and Table 2. There will be a limit of 2 bleeding episodes (i.e., a total of 3 attempts to perform the PK assessment) for PK1, but no limit on the number of bleeding episodes during PK2 and PK3 (see Table 1). If PK assessments cannot be completed, the subject will enter the Treatment Period (see Section 10.1.2) and may be replaced.

Subjects who experience a bleed during a PK sampling period should complete the required washout and reschedule the planned PK injection followed by blood sampling for PK assessment as soon as is feasible following resolution of the bleed. Instructions for handling bleeding episodes during the PK assessments are provided in Table 1. Additional information on bleeding episodes is provided in Section 10.1.3.

Table 1: Instructions for Treatment of Bleeding Episodes, Washout, and PK Sampling During the PK Assessment

If a bleeding episode occurs:	
During the washout prior to PK1	**Washout** • Bleeding episodes can be treated with prestudy FVIII product. • Washout is 96 hours for a short-acting product, or 120 hours for a long-acting product. • Washout may be repeated. The 8-week Screening Period can be extended if necessary.
After the PK1 injection and before the 96-hour sample	**Washout** • Bleeding episodes must be treated with 2K rFVIIIFc 1000 IU/kg (Table 2). • New washout of at least 120 hours is then required before the PK1 Injection is repeated. • Additional attempts at washout are permitted. However, if more than 2 bleeding episodes occur during the PK1 assessment period, the PK will not be rescheduled, and the subject may be replaced. The subject may continue on the study in the Treatment Period.

If a bleeding episode occurs:	
After the PK1 Injection and prior to the 96-hour sample (cont'd.)	**PK Sampling** • Collection of PK samples to 96 hours is required.
During the 120-hour washout period between PK1 and PK2	**Washout** • Bleeding episodes must be treated with 2K rFVIIIFc 1000 IU/kg (Table 2). • New washout of at least 120 hours is then required before PK2 injection. • Additional attempts at washout are permitted. It is recommended PK2 be performed within 2 to 6 weeks following PK1.
After the PK2 injection and before the 96-hour sample	**Washout** • Any bleeding episode after the PK2 injection is treated with 15K rFVIIIFc at any of the available vial strengths (Table 2). • Washout of at least 120 hours is then required before the PK2 Injection is repeated. • Additional attempts at washout are permitted. Completion of the second PK within 2 to 6 weeks following PK1 is recommended. **PK Sampling** • Collection of PK samples to 96 hours is required.
Between PK2 and PK3	**Washout** • Any bleeding episode after the PK2 injection is treated with 15K rFVIIIFc at any of the available vial strengths (Table 2). • Washout of at least 120 hours is then required before the PK3 Injection. • Additional attempts at washout are permitted.

If a bleeding episode occurs:	
After the PK3 injection and before the 96-hour sample	**Washout** • Any bleeding episode after the PK3 injection is treated with 15K rFVIIIFc at any of the available vial strengths (Table 2). • Washout of at least 120 hours is then required before PK3 Injection is repeated. • Additional attempts at washout are permitted. **PK Sampling** • Collection of PK samples to 96 hours is required.
After PK3, through the end study	Any bleeding episode after the PK3 injection is treated with 15K rFVIIIFc at any of the available vial strengths (Table 2).

10.1.2. Treatment Period

After completing the PK2 assessment, all subjects (whether or not evaluable for PK) will begin receiving treatment with 15K rFVIIIFc exclusively. Subjects will receive prophylactic dosing. The specific choice of regimen for any given subject and any subsequent dose adjustments will be based on the subject's response and will be at the Investigator's discretion. Subjects may use any of 5 available 15K vial strengths during the treatment phase.

Recommended starting dosing regimens include the following:

- A prophylactic regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days. Further dose and interval adjustments will be based on individual clinical response per Investigator's discretion. Dosing may be adjusted in the range of 25 to 65 IU/kg at 3 to 5 day intervals.
- A prophylactic regimen of 65 IU/kg administered every 7 days may be considered for appropriate subjects who will be selected based on the opinion of the Investigator.

Subjects will be allowed to switch from one regimen to another if approved by the Investigator and will be allowed to use any of the several available vial strengths.

Study procedures to be carried out during the Treatment Period are summarized in Section 4.2.3. Information on study treatment (injection date, time, dose, and whether the injection was for prophylaxis or a bleeding episode) will be recorded in the subject's study diary. The subject/subject's caregiver should enter study diary information in a timely manner to facilitate appropriate medical review and dosing guidance.

After 13 weeks in the treatment period, subjects will undergo washout in preparation for the PK3 assessment using 15K rFVIIIFc in either 1000 IU or 6000 IU vials (see Section 10.1.1). Following the PK3 assessment, subjects will resume to treatment in the Treatment Period until they complete a total of at least 26 weeks of treatment. A subject's participation in the study may be extended due to the treatment of bleeding episodes or surgery.

After study completion, in countries where rFVIIIFc is not commercially available, eligible subjects will be offered enrollment into a long-term safety and efficacy extension study (8HA01EXT). All subjects will have a follow-up telephone call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period, unless they have entered directly into Study 8HA01EXT by that time.

Refer to the Directions for Handling and Administration (DHA) for additional instructions.

10.1.3. Bleeding Episodes

If a subject has a bleeding episode during the study, the Investigator should be notified. The Investigator will provide guidance on the dosing for treatment of bleeding episodes as described in Table 2. The impact of the treatment of bleeding episodes on planned PK assessments is described in Table 1.

Table 2: rFVIIIFc Dosing for Treatment of Bleeding

Severity of Bleed	Desired Peak Factor VIII Level (IU/dL or % of normal)	Dose (IU/kg)/ Frequency of Doses (hrs)
Minor and Moderate For example: joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal. superficial soft tissue, mucous membranes	**40 to 60**	**20 to 30 IU/kg** Repeat every 24-48 hours until bleeding is resolved
Major For example: iliopsoas and deep muscle with neurovascular injury, or substantial blood loss, retroperitoneum, CNS, throat and neck, gastrointestinal	**80 to 100**	**40 to 50 IU/kg** Repeat every 12-24 hours until bleeding is resolved.

Adapted from [WFH 2012].
Subsequent dosage and duration of treatment depends on the individual clinical response, the severity of the factor VIII deficiency, and the location and extent of bleeding.

10.1.4. Surgery

For subjects who require emergent or elective surgery during the study period, the dose and regimen of rFVIIIFc will be that deemed appropriate by the Investigator for the type of surgery to be performed, following the guidance in Table 3.

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's rights to data generated in the trial at an alternative institution deemed appropriate by the Principal Investigator, AND

2. The Investigator and/or appropriate qualified/licensed delegate is available to:

    a. Administer all rFVIIIFc doses required during surgery and during postoperative rehabilitation (if applicable).

    b. Provide medical oversight and guidance throughout the duration of the preoperative and intraoperative 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.

Study procedures to be carried out before, during, and after surgery are summarized in Section 4.2.4. Inhibitor testing should be performed 2 to 4 weeks prior to the scheduled surgery, preoperatively on the day of surgery, 1 to 2 weeks after surgery, and at the last postoperative visit (for minor surgery, testing is not performed at the last 2 timepoints). On the day of surgery, subjects will be given a preoperative loading dose of rFVIIIFc as a bolus, and, in the case of emergency surgery, as soon as possible prior to the procedure. Predose 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 the 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 electronic case report form (eCRF).

During surgery and the postoperative period, the following information will be collected:

- number of injections and dose per injection to maintain hemostasis during the surgical period
- estimated blood loss (mL) during surgery and the postoperative period
- number of blood product units transfused during surgery

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

Table 3: rFVIIIFc Dosing for Perioperative Management

Type of Surgery	**Target Factor VIII Level (IU/dL or % of normal)**	**Dose (IU/kg)/Frequency of Doses (hr)**
Minor Minor operations, including uncomplicated dental extraction	**50 to 80**	**25 to 40 IU/kg** A single infusion may be sufficient. Repeat every 24 hours as needed to control bleeding.
Major Major operations including intra-abdominal and joint replacement surgery	**80 to 120**	An initial preoperative dose of 40 to 60 IU/kg followed by a repeat dose of 40 to 50 IU/kg after 8 to 24 hours and then every 24 hours to maintain FVIII activity within the target range.

10.2. Modification of Dose and/or Treatment Schedule

Subjects will also receive 26 weeks of treatment with 15K rFVIIIFc starting after PK2. Two regimens are recommended based on existing data collected during the clinical development program (Section 10.1.2) but will be chosen and subsequently adjusted based on the subject's response, and at the Investigator's discretion.

Information on all of the potential modifications to the dose and treatment schedule can be found in Section 10.1.

10.3. Precautions

The first dose of rFVIIIFc will be given in the clinic. Subjects will be provided with specific guidance by the Investigator on what to do if they experience a lack of efficacy or AEs at home, including how to seek emergency medical treatment.

For details regarding the risks and benefits of rFVIIIFc, see the rFVIIIFc Investigator's Brochure.

10.4. Compliance

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

Injections for PK assessments will be administered in the clinic under controlled conditions by the investigational staff and recorded in the eCRF to ensure that accurate injection times are recorded for PK profiling.

During the treatment period, subjects or their caregivers will record treatment in a dosing diary that will be reviewed periodically by study site staff and the Clinical Monitor. The subject or the subject's caregiver will record both routine doses and doses for the treatment of bleeding episodes in the study diary. Diary data will be reviewed on a regular basis by site staff.

10.5. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined in Section 10.5.1 and Section 10.5.2 and the reason for all concomitant procedures 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.

10.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between 30 days prior to the Screening Visit and 7 days after the last dose of rFVIIIFc during the Treatment Period for that subject.

Subjects should be instructed to inform the Investigator if they start any new medications.

Allowed Concomitant Therapy

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. All such therapy must be recorded in the eCRF.

Disallowed Concomitant Therapy

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

The following concomitant medications are not permitted during the study:

- ASA, except for low-dose ASA, defined as a dose of ≤81 mg, as prophylaxis.
- Current systemic treatment with chemotherapy and/or other immunosuppressant drugs, with the following exceptions: medications to treat hepatitis and/or HIV, treatment with systemic steroids and/or inhaled steroids (with approval of the Sponsor Medical Monitor) and/or nonsteroidal anti-inflammatory drugs other than high-dose ASA, and routine immunizations.
- Any other FVIII product (see the exceptions listed in Section 12).

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 and the follow-up telephone call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period.

10.6. Continuation of Treatment

Subjects who complete this study in countries where rFVIIIFc is not commercially available will be offered enrollment into extension study 8HA01EXT if they meet all of the inclusion and exclusion criteria. All subjects will have a follow-up telephone call 7 (+7) days after the last dose of rFVIIIFc during the Treatment Period unless they have entered directly into Study 8HA01EXT by that time.

11. STUDY TREATMENT MANAGEMENT

The Sponsor or designee will arrange for all shipments of study treatment from the distribution center to the study site. After shipment of study materials arrives at the site, the Investigator must ensure that the shipment receipt is recorded in the IXRS and investigational medicinal product records in a timely manner.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol, Investigator's Brochure).

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 11.1.4. Dose and dosing regimen of study treatment will be determined by the Investigator.

Study treatment must be dispensed only by a pharmacist, appropriately qualified staff, or designee. Study treatment is to be dispensed only to subjects enrolled in this study or their legal guardian. Once study treatment is prepared for a subject, it can be administered only 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.

Subjects will receive supplies of rFVIIIFc from the study site for home administration, either at study site visits for PK assessments, or between study visits. Between study visits, the subject or the subject's caregiver must return to the study 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 scheduling clinic visits. Each time, the study site staff will perform full medication exchange and accountability with the subject or the subject's caregiver.

11.1. rFVIIIFc

rFVIIIFc is supplied in a kit that contains several components, including, but not limited to, lyophilized drug, a diluent, a vial adapter, and an infusion set (see DHA for further details). The lyophilized 2K product is provided in 1 strength in a 10 mL clear glass vial containing 1000 IU/vial of rFVIIIFc. The lyophilized 15K product is provided in 5 different strengths in a 10-mL clear glass vial containing 250, 1000, 2000, 3000, or 6000 IU/vial of rFVIIIFc. In addition to the rFVIIIFc, the formulation of the lyophilized product contains [redacted] L-Histidine, [redacted] sodium chloride, [redacted] calcium chloride dihydrate, [redacted] (w/v) sucrose, and [redacted] (w/v) polysorbate 20, and is the same for all 5 strengths. The diluent is [redacted] sterile water for injection for reconstitution of rFVIIIFc prior to administration to subjects. The study treatment will be labeled according to the requirements of local law and legislation. Label text will be approved

according to Biogen procedures, and a copy of the labels will be made available to the study site upon request.

The label will include conditions for storage, lot number, potency, and other pertinent information such as manufacturer, protocol number, and caution statement. For sites participating in the United States, the expiration date is provided in the Pharmacy Manual. rFVIIIFc should not be used after the expiration date.

11.1.1. rFVIIIFc Preparation

Once a subject is identified as eligible for the study and assigned a unique subject number, the individual preparing the rFVIIIFc should first carefully review the instructions provided in the DHA or Information for Patients before preparing the dose assigned for the subject. The study Pharmacist or designated staff member will be required to prepare a drug retain if any drug remains in a vial following preparation of the dose for the PK assessment. Instructions for preparing the drug retain are described in the Pharmacy Manual.

The Pharmacist or designated staff member will provide the Investigator or clinical staff with enough rFVIIIFc kits for the subject's dosing regimen. This will be documented according to the requirements in Section 11.1.4.

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

11.1.2. rFVIIIFc Storage

At the study site, study treatment must be stored in a secure location. The rFVIIIFc kit is to be stored at 2ºC to 8ºC in a monitored, locked refrigerator with limited access, or the room in which the refrigerator resides must be locked. The Information for Patients will describe proper storage conditions for the study drug that subjects take home with them.

For the most up-to-date storage requirements, follow the instructions provided in the DHA.

11.1.3. rFVIIIFc Handling and Disposal

The Investigator must return all used and unused kits of rFVIIIFc as instructed by the Sponsor. The instructions for return will be provided at the time the request is made by the Biogen (or its designee).

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

11.1.4. rFVIIIFc Accountability

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

Unless otherwise notified, all vials (used and unused) must be saved for study treatment accountability. The subject/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 drug product supplied, dispensed, and subsequently destroyed or returned to the Sponsor. A written explanation must be provided by the site to the Sponsor for any discrepancies.

The IXRS system will be used to randomize subjects to Group 1 (15K rFVIIIFc, 1000 IU/vial) or Group 2 (15K rFVIIIFc, 6000 IU/vial) for PK2 and PK3. For these PK assessments, the IXRS will direct the site to dispense a specific dosing kit number that is appropriate to that particular subject's PK dosing group. Therefore, it is critical that the study site follow the instructions of the IXRS system in dispensing kits for the PK assessments.

12. DISCONTINUATION OF STUDY TREATMENT AND/OR WITHDRAWAL OF SUBJECTS FROM THE STUDY

If more than 2 bleeding episodes occur during the PK1 assessment period, the PK assessment will not be rescheduled. However, the subject may continue on the study in the Treatment Period.

Discontinued subjects or subjects unable to complete all 3 PKs may be replaced if needed to attain the number of subjects required to complete the study as described in Section 7.5.

A subject must permanently discontinue rFVIIIFc treatment and be withdrawn from the study for any of the following reasons:

- A Grade 2 or greater allergic drug reaction occurs 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 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
- An inhibitor is identified and confirmed by a second test conducted at the central laboratory within 2 to 4 weeks of the first positive test using the Nijmegen-modified Bethesda assay.
- Use of FVIII products other than rFVIIIFc occurs, unless it occurs prior to randomization according to the instructions in Table 1, in an 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 Study diary and electronic case report form, and the Investigator should contact the Sponsor Medical Monitor.
- The subject withdraws consent.
- The parent or legal guardian withdraws the subject from the study.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

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

Subjects who discontinue treatment should remain in the study to complete protocol required tests and assessments as described in Section 4.2 and then must be permanently withdrawn from the study.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Pharmacokinetic (rFVIIIFc Activity) Assessments

All PK samples collected will be analyzed for FVIII activity (one-stage [aPTT] clotting assay and two-stage chromogenic assay) in plasma at a central laboratory. Assay methods as well as procedures for collecting, processing, storing, and transporting to the central laboratory are fully described in the Study Laboratory Manual. See Section 4 for the timing of all assessments.

PK endpoints will include but not be limited to AUC_{inf}, IR, C_{max}, $t_{1/2}$, CL, V_{ss}, and MRT.

The PK of FVIII activity will be assessed using the following:

- One-stage (aPTT) clotting assay
- Two-stage chromogenic assay

14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed:

- Physical examinations
- Weight
- Concomitant therapy
- AE and SAE recording

Refer to Section 4.2 for the timing of assessments.

14.2. Laboratory Assessments

The following laboratory assessments will be performed:

- Inhibitor testing
- rFVIIIFc antibody testing
- Hematology: white blood cell (WBC) count, differential, platelet count, hemoglobin, hematocrit
- Blood chemistry: electrolytes (sodium, potassium, and chloride), glucose, total protein, total bilirubin, ALT, AST, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine.

Refer to Section 4.2 for the timing of assessments.

Procedures for collecting, processing, storing, and transporting to the laboratory are fully described in the Study Laboratory Manual.

14.3. Retention of Plasma Samples

Plasma samples from each subject obtained at each rFVIIIFc PK sampling timepoint will be aliquoted into 2 vials where possible. These 2 aliquots will be shipped to the central laboratory in separate shipments (the second aliquot being a back-up sample in case of damage or loss during shipping). Back-up samples may be used, if clinically or scientifically indicated, for

retesting in the event that a subject develops an inhibitor, is suspected of having developed an inhibitor, or has an anaphylactic reaction to the study treatment, or if additional tests for assessment of coagulation parameters or safety parameters are required. A blood sample will also be collected at study start to be used for any additional immunologic/serologic testing as needed.

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

No samples will be used for genetic analyses except FVIII genotype retesting in case of detection of inhibitors.

The total blood sample volume will not exceed 20 mL at any one time.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

15.1. Definitions

15.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 15.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

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.

Bleeding episodes in this patient population are not considered 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 study diary 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. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.3.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

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

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

15.2.3. Severity of Events

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

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

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen (or designee) according to the Investigator's Brochure for rFVIIIFc.

15.3. Monitoring and Recording Events

15.3.1. Serious Pretreatment Events

A serious pretreatment event experienced by the subject after signing and dating the ICF, but before administration of study treatment, is to be recorded on the SAE form and faxed to Quintiles Pharmacovigilance (PVG) within 24 hours of the study site staff becoming aware of the event (see Section15.3.5).

15.3.2. Adverse Events

Any AE experienced by the subject between the time of the first dose of study drug, rFVIIIFc, and the final follow-up telephone call (7 [+ 7] days after last dose of rFVIIIFc) is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

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

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of signing the ICF through the final telephone follow-up call is to be recorded on the eCRF and SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be collected for up to 14 days after the end of the Treatment Period and reported to Quintiles PVG within 24 hours as described in Section 15.3.5. Follow-up information regarding an SAE also must be reported within 24 hours.

For subjects not entering the extension study 8HA01EXT, SAEs that occur up to 14 days after the subject's last dose of rFVIIIFc must also be recorded on the SAE form. SAEs must be reported to the designated personnel as detailed in the study file.

Any SAE that is ongoing when the subject completes or discontinues 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 7.2.1.
- 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 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.
- Major surgery.

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.

15.3.4. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.3.3.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.3.5. 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 PVG within 24 hours of the study site staff becoming aware of the SAE. At the same time, the event should be recorded in the eCRF. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any SAE that occurs between the time that the subject has signed the ICF and 14 days after the final dose of study treatment must be reported to Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

A report ***must be submitted*** to Biogen SABR (or designee) 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 an SAE, fax a completed SAE form to **Quintiles PVG at the country specific fax number provided in the Study Reference Guide.**

15.3.5.1. Deaths

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

15.3.6. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered. Biogen SABR (or designee) will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

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

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

15.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds 100 IU/kg. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen SABR (or designee) within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen SABR (or designee) even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen SABR (or designee). All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

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

15.4.3.1. Unblinding for Medical Emergency

Not Applicable.

15.5. Contraception Requirements

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

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, as possible.

- Determine the onset and resolution dates of each event.

- Complete an SAE form for each SAE and fax it to Biogen SABR (or designee) 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 Biogen SABR (or designee) within 24 hours of the study site staff becoming aware of new information.

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

- Pursue AE follow-up information, if possible, until the event has resolved or become stable.

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

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

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or the Sponsor's designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Biogen (or 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

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

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan.

16.1. Demography and Baseline Disease Characteristics

The analysis of demography and baseline disease characteristics will be based on the Safety Analysis Set. A description of the Safety Analysis Set is provided in Section 16.3.1.

Demographic and baseline disease characteristics will be summarized categorically and with descriptive statistics, as appropriate, for each treatment sequence group and overall. Demographic data to be tabulated will include age, race, hemophilia history, genotype, and other disease-specific measures.

Baseline disease characteristics, based on general medical and surgical and hemophilia histories, will be summarized by group 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.

16.2. Pharmacokinetics

Primary PK parameters include the following, for 2K rFVIIIFc (PK1) and for 15K rFVIIIFc at the 15K baseline (PK2):

- AUC_{inf}
- IR

as estimated from the coagulation factor VIII (FVIII) activity data, as measured by the one-stage (aPTT) clotting assay.

Secondary PK parameters include but will not be limited to AUC_{inf}, IR, C_{max}, $t_{½}$, CL, V_{ss}, and MRT.

These parameters will be assessed using the one-stage (aPTT) clotting assay and the two-stage chromogenic assay.

PK parameters will be assessed for the following:

- 15K rFVIIIFc at the 15K baseline (i.e., at PK2) and after 13 weeks of treatment (at PK3)
- 15K rFVIIIFc at 1000 IU/vial and 6000 IU/vial
- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) [except AUC_{inf} and IR, which are included in the primary endpoint]

16.2.1. Analysis Populations

16.2.1.1. Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic Analysis Set (PKAS) is defined as all subjects with evaluable PK profiles. A PK profile for a given injection is considered evaluable if all PK parameters can be determined in at least 1 of the 2 assays.

16.2.1.2. Sequential Pharmacokinetic Subgroup

The Sequential Pharmacokinetic Subgroup will consist of all subjects who have evaluable PK profiles for PK2 and for at least 1 ofPK1 and PK3.

16.2.2. Methods of Analysis

Natural log transformed primary PK endpoints (AUC_{inf} [if data permit] and IR following rFVIIIFc dosing for 2K and for 15K at the 15K baseline measured by the one-stage [aPTT] assay) will be analyzed using a mixed effects model with period and treatment as fixed effects and subject as a random effect. Estimates of the adjusted mean differences (15K-2K) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be back transformed (exponentiated) to provide estimates of the ratio of adjusted geometric means (15K/2K) and 90% CIs for the ratios.

For descriptive purposes only, similar analyses may be performed for secondary PK parameters measured by the one-stage (aPTT) assay and for all relevant PK parameters measured by the two-stage chromogenic assay.

Comparability of the 2 manufacturing scales will be concluded if the 90% CIs for the ratio of adjusted geometric means for both primary PK endpoints (AUC_{inf} and IR following rFVIIIFc dosing for 2K and for 15K at the 15K baseline measured by the one-stage [aPTT] assay) fall within the range of (68%, 146%).

The FVIII activity data will be tabulated over time for each subject and summarized by scale (2K [PK1], 15K [PK2] or 15K [PK3]) and vial strength (1000 IU/vial, 6000 IU/vial or overall) using descriptive statistics. Mean FVIII activity will be plotted over time for each scale (with combined vial strengths) and each available combination of scale and vial strength.

The rFVIIIFc PK parameters will be listed for each subject, and summary statistics for the PK endpoints (including AUC_{inf}, IR, C_{max}, $t_{1/2}$, CL, V_{ss}, and MRT) will be summarized descriptively by manufacturing scale (2K [PK1], 15K [PK2] or 15K [PK3]), vial strength (1000 IU/vial, 6000 IU/vial, or overall), and by assay (one-stage [aPTT] clotting assay and two-stage chromogenic assay). Summary statistics for AUC_{inf} and IR measured by the one-stage (aPTT) clotting assay and the two-stage chromogenic assay will include but not be limited to the mean, CI, standard deviation, median, minimum, and maximum values, as well as the geometric means (antilog of the means of the logs) and coefficients of variation. Similar analyses will be performed for the other secondary PK parameters measured by the one-stage (aPTT) assay and for all relevant PK parameters measured by the two-stage chromogenic assay. Arithmetic mean activity by sampling timepoint will be listed side by side for each scale (with combined vial strengths) and each available combination of scale and vial strength.

16.3. Safety

16.3.1. Analysis Population

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

16.3.2. Methods of Analysis

For the analysis of safety, data from the PK assessment and treatment period will be combined, unless specified otherwise. The incidence of AEs will be tabulated overall, by severity, and by relationship to treatment. Subject listings will be provided for all AEs, SAEs, and AEs resulting in discontinuation of the study treatment or withdrawal from the study, drug interruption, and deaths. Additional listings will include but not be limited to the following assessments: bleeding episodes during the treatment period, injections to treat a bleeding episode, all injections and treated bleeding episodes, dose and consumption, and compliance and exposure. Injections and bleeding episodes during the surgical period will be flagged where appropriate. The treatment 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 analyses. Findings in clinical laboratory values will be summarized by descriptive statistics. Listings of vital signs and abnormal laboratory test results will be provided.

The total number of EDs of rFVIIIFc will be summarized overall. An ED is a 24-hour period in which 1 or more rFVIIIFc injections are given.

Data collected during surgeries will be listed. The listings will include, but not be limited to, injections and dose per injection to maintain hemostasis during the surgical period, estimated blood loss (mL) during surgery and the postoperative period, and transfusions.

16.3.2.1. Inhibitor Development

Data for subjects who develop inhibitors following initial rFVIIIFc administration will be provided in a listing.

16.4. Interim Analyses

Interim analyses of PK and/or safety data may be conducted during the study as required to support regulatory submissions, future studies, and/or publications.

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

16.5. Sample Size Considerations

The minimum sample size in this study (16 subjects) is consistent with the EMA guidance for PK assessment of hemophilia products [EMA (EMA/CHMP/BPWP/144533/2009) 2011].

17. ETHICAL REQUIREMENTS

Biogen, Quintiles (the CRO), and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

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

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

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

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

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

Biogen (or designee) 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 Biogen (or designee).

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject

or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

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

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

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

Confirmation of informed consent and assent, if applicable, must also be documented in the subject's medical record.

17.4. Subject Data Protection

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

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

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

Biogen 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 Biogen (or designee). This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

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

18.3. Monitoring of the Study

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

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

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

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

18.4. Study Funding

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

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

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

19.1.1. Contract Research Organization

A CRO, Quintiles, will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, 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 Response Technology

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

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool OR remote data capture tool developed and supported by the Electronic Data Capture (EDC) vendor and configured by Quintiles. In addition, subjects in the study will have a study diary to record information regarding each dose of rFVIIIFc administered by the subject for any reason. **All doses given in the clinic will be entered on the eCRF by the site staff.**

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Biogen to analyze all laboratory samples being collected for this study. Specifics regarding the requirements for laboratory specimen collection, handling, and analysis are provided in the Study Laboratory Manual, which is part of the Study Reference Guide.

19.1.5. Central Facility for Other Assessments

Three laboratories – LabCorp, Esoterix, and the Assay Services Laboratory (ASL) at Biogen – have been selected by Biogen as central laboratories for this study.

19.2. Study Committees

Not applicable.

19.3. Changes to Final Study Protocol

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

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

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

19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. Retention of Study Data

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

19.6. Study Report Signatory

Biogen 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 Biogen.

Biogen 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, "Protocol 997HA309: A Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) Manufactured at 15K Scale and at Different Vial Strengths in Previously Treated Subjects with Severe Hemophilia A," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)