AN OPEN-LABEL STUDY TO EVALUATE PROPHYLAXIS TREATMENT, AND TO CHARACTERIZE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF B-DOMAIN DELETED RECOMBINANT FACTOR VIII ALBUMIN FREE (MOROCTOCOG ALFA [AF-CC]) IN CHILDREN WITH HEMOPHILIA A

Date of Original Protocol:	09 Mar 2007
Amendment 1:	12 Jun 2007
Amendment 2:	27 Aug 2007
Amendment 3:	22 Jan 2009
Amendment 4:	15 Sep 2009
Amendment 5:	20 Jul 2010
Amendment 6:	10 Mar 2011
Amendment 7:	31 Aug 2011
Amendment 8:	19 Oct 2012
Amendment 9:	29 Jan 2013
Amendment 10:	02 Oct 2015

Sponsor: Wyeth Pharmaceuticals Inc. acting through its division Wyeth Research, a Pfizer Company

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

TABLE OF CONTENTS

APPENDICES

1. DISCLOSURE STATEMENT

Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the Sponsor. You may disclose the contents of this document only to study personnel under your supervision, institutional review boards (IRBs)/independent ethics committees (IECs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, or published without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the Sponsor of any such disclosure. All other nonpublic information provided by the Sponsor, as well as any information that may be added to this document, also is confidential and proprietary to the Sponsor and must be kept in confidence in the same manner as the contents of this document.

2. CONTACTS

NOTE: Emergency Contact, Regional Contact and Global Study Team Contact information is located in the Study Reference Manual.

3. ABBREVIATIONS

Abbreviation	Term
ABR	Annualized bleed rate
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{∞}	Area under the curve to infinity
AUC_t	Area under the curve to last measurable concentration
AUMC	Area under moment curve
BDDrFVIII	B-Domain deleted recombinant factor VIII, commercially available as ReFacto® or as, the investigational drug moroctocog alfa (AF-CC), (marketed in certain regions of the world as Xyntha®)
BU	Bethesda unit
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary cells (host cell line for moroctocog alfa [AF-CC] production)
CL	Clearance
$C_{0.5\ hr}$	FVIII:C at 0.5 hours after the start of the study drug infusion
CRF	Case report form
CSA	Clinical study agreement
C_t	FVIII:C observed at a specified time (t)

Abbreviation	Term
E-DMC	External-Data Monitoring Committee
eCRF	Electronic case report form
ED	Exposure day
EIU	Exposure in-utero
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EDP	Exposure during pregnancy
FDA	United States Food and Drug Administration
FVIII	Factor VIII
FVIII:C	Factor VIII activity in plasma
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HSA	Human serum albumin
IEC	Independent ethics committee
IND	Investigational new drug application
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
LETE	Less than expected therapeutic effect
LLN	Lower limit of normal
mITT	Modified intent to treat
moroctocog alfa (AF-CC)	B Domain Deleted Recombinant FVIII, Albumin Free
MRT	Mean residence time
NSAID	Nonsteroidal anti-inflammatory drug
OD	On-demand
OS	One-stage FVIII activity assay
pdFVIII	Plasma-derived FVIII
PK	Pharmacokinetics
PT	Prothrombin time
PTP	Previously treated patient
PUP	Previously untreated patient
rFVIII	Recombinant FVIII
RP	Routine prophylaxis
SAE	Serious adverse event
SD	Standard deviation
$t_{½}$	Terminal phase half-life
ULN	Upper limit of normal
V_{ss}	Steady state volume of distribution
WHO	World Health Organization

4. DEFINITIONS

Term	Definition
Anti-CHO antibodies	Antibodies to proteins derived from the Chinese hamster ovary (CHO) host cell line used to produce moroctocog alfa (AF-CC).
Anti-FVIII antibodies	Neutralizing and nonneutralizing antibodies to FVIII.
Anti-TN8.2 antibodies	Antibodies to the affinity ligand (TN8.2) used during the moroctocog alfa (AF-CC) purification process.
Bleeding episode	Hemorrhage (bleeding) caused by injury or occurring spontaneously at 1 or more anatomic sites. A bleeding episode is documented by a subject/caregiver's report in the Subject Diary (or by the investigator in the subject's source document). A subject/caregiver's report does not need to be independently verified.
Bleeding (breakthrough)	Bleeding occurring since last routine prophylactic dose of FVIII therapy.
Bleeding (spontaneous)	Bleeding occurring in the absence of known injury or any antecedent cause.
Bleeding (traumatic)	Bleeding occurring because of an injury or activity that would lead to a bleed in a hemophilic patient (for example, exercise).
Caregiver	For the purpose of this protocol, a person who provides for and/or oversees the general care of the subject. The person may administer study drug to the subject for home use and performs many activities required by this protocol including, but not limited to, reporting of bleeds and study drug usage. The person could be a parent, other family member, or legal acceptable representative.
Case report form	A printed or electronic document designed to record all the protocol-required information to be reported to the Sponsor on each study subject.
Central laboratory	The reference laboratory designated by the Sponsor to analyze selected samples as described in this protocol. There may be multiple central laboratories.

Term	Definition
Completed subject	Any subject who completes the study activities through the Final Study Contact and who is not withdrawn early.
Designee	A person with the appropriate qualifications to whom a task has been delegated without relinquishing responsibilities of the specified person/role.
Exposure day (ED)	Any day during which the subject receives study drug. One (1), or more than 1, dose of study drug may be administered on a single ED.
FVIII inhibitor (confirmed)	A neutralizing antibody to FVIII with a titer of ≥0.6 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay.
FVIII inhibitor (de novo)	Development of a confirmed FVIII inhibitor during the course of the study in a subject with no prior clinical history of FVIII inhibitor, or prior history of measurable inhibitor activity by Bethesda Inhibitor Assay or by any other method.
FVIII inhibitor (history of)	A history of FVIII inhibitor (clinical or laboratory-based assessment). For laboratory-based assessments, any measured Bethesda inhibitor titer of ≥ 0.6 BU/mL, regardless of the laboratory normal range, or any measured Bethesda inhibitor titer greater than the ULN for the laboratory performing the assay.
FVIII replacement product	A concentrated recombinant or plasma-derived formulation of the Factor VIII protein made for use in the treatment and prevention of bleeding in patients with hemophilia A (for the purposes of this protocol fresh frozen plasma, cryoprecipitate and blood are not considered FVIII replacement products).
Hematology panel	Measurement of the complete blood count, which includes hemoglobin, hematocrit, white blood cell count and differential, red blood cell and platelet count.
Incremental recovery	The IU/dL of FVIII:C increase per IU/kg of FVIII infusion.
Independent ethics committee (IEC)	Throughout this document, the term ethics committee refers to all appropriate and properly constituted committees or boards recognized to be the appropriate regulatory agencies for approving clinical studies. These include independent ethics committees and institutional review boards.

Term	Definition
Intent-to-treat population	The intent-to-treat population consists of subjects who sign the consent/assent form. (Screen failures are excluded).
Investigator	A person, with the appropriate qualifications, responsible for the conduct of the study at a study site.
Lack of efficacy	Failure of expected pharmacologic action or therapeutic benefit.
Less than expected therapeutic effect, LETE (on-demand)	Less than Expected Therapeutic Effect (LETE) occurs in the on-demand setting if the subject/caregiver records 2 successive "No Response" ratings after 2 successive infusions of study drug, respectively. The infusions must have been administered within 24 hours of each other for treatment of the same bleeding event in the absence of confounding factors as described in this protocol.
Less than expected therapeutic effect, LETE (prophylaxis)	Less than Expected Therapeutic Effect (LETE) occurs in the prophylaxis setting if there is a *spontaneous* bleed within 48 hours (≤ 48 hours) after a regularly scheduled prophylactic dose of study drug (which was not used to treat a bleed) in the absence of confounding factors as described in this protocol.
Less than expected therapeutic effect, LETE (low recovery)	Lower than expected recovery of FVIII in the opinion of the investigator following injection of study drug in the absence of confounding factors as described in this protocol.
Medical records	Legal documentation (written or electronic) of a patient's medical history, current illness, diagnosis, treatments, and/or other medical data that is maintained by the investigator. For the purposes of this study, these can serve as source documents.
Modified intent-to-treat population	The modified intent-to-treat population consists of subjects who receive at least 1 dose of study drug (moroctocog alfa [AF-CC]).
Monitor	A person, with the appropriate qualifications and assigned by the Sponsor, to oversee the progress of a study, and to ensure that it is conducted, recorded, and reported in accordance with the protocol and other applicable requirements.
On-demand (OD) Subject	A study subject that practices on-demand therapy with moroctocog alfa (AF-CC) for the first segment of the study, followed by routine prophylaxis for the second segment.

Term	Definition
On-demand treatment	Treatment of hemorrhages, as needed, by administering an unscheduled bolus infusion of study drug to stop bleeding and control hemostasis.
Patient	For the purposes of this protocol, a person with hemophilia A.
Previously treated patients (PTPs)	Patients who have received FVIII replacement therapy. For the purposes of this study, PTPs are those who have accrued ≥20 exposure days to any FVIII replacement product.
Previously untreated patients (PUPs)	Patients who have not received any FVIII replacement therapy or any blood products.
Prophylaxis	FVIII replacement therapy administered at a routine interval such as every other day, for a prolonged period of time, to prevent occurrence of spontaneous musculoskeletal bleeding episodes.
Regimen A	Study drug prophylaxis regimen of 45 ±5 IU/kg, administered twice per week. The interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days.
Regimen B	Study drug prophylaxis regimen of 25 ±5 IU/kg, administered every other day. The interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc).
Regimen escalation	During prophylaxis, criteria for prophylaxis regimen escalation are the occurrence, over a 4-week period (and in the absence of a confirmed FVIII inhibitor), of (a) 2 or more spontaneous bleeds into a major joint and/or target joint, **OR** (b) 3 or more spontaneous bleeds (consisting of joint bleeds and/or *significant* soft tissue/muscle or other site bleeds). If either criterion is met, the subject will be escalated to a more intense prophylaxis regimen of 45 ±5 IU/kg, administered every other day. Subjects who meet dose escalation criteria while on this more intensive regimen may dose escalate to a higher intensity regimen designated by the investigator. *Significant* spontaneous bleeds are defined as those that lead to a transient or persistent loss of function.

Term	Definition
Regulation	The term *regulation* refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations; the European Clinical Trials Directive; the Good Clinical Practice: Consolidated Guideline (Canada); the International Conference on Harmonisation Guideline for Good Clinical Practice; the Pharmaceutical Affairs Law and Good Clinical Practice (Japan); the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; and other regulations if they apply.
Regulatory agency	The term *regulatory agency* refers to all health and regulatory agencies with oversight responsibility for the study. These may be international, national, or local and may include but are not limited to the Australian Therapeutic Goods Administration (TGA); the Canadian Health Products and Food Branch (HPFB); the European Medicines Agency (EMA); the Japanese Ministry of Health, Labor, and Welfare (MHLW); the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); the US Food and Drug Administration (FDA); and other regulatory agencies if they apply.
Routine Prophylaxis (RP) Subject	A study subject that practices routine prophylaxis therapy with moroctocog alfa (AF-CC) according to the randomly assigned regimens for the first and second segments of the study.
Screening period	Interval starting from the signing of the informed consent/assent (study visit 1) and extending up to study day 1 (study visit 2). There are up to approximately 35 screening days.
Serum chemistry	Measurement of sodium, potassium, chloride, CO_2 (serum bicarbonate), ALT, AST, calcium, glucose, creatinine, blood urea nitrogen (BUN), (total) bilirubin, phosphorus, alkaline phosphatase, total protein, amylase, cholesterol and albumin.
Source documentation	Original documents, data, and/or records (eg, patient medical record, Subject Diary).
Sponsor	The term *Sponsor* refers but is not limited to the sponsors listed in the front of this document and any contract research organization that is being used for the study.

Term	Definition
Study drug	Test article, moroctocog alfa (AF-CC) (marketed in certain regions of the world as Xyntha®), and the solutions and materials accompanying moroctocog alfa (AF-CC) preparations.
Study start date	Date that the first study subject provides informed consent/assent.
Study end date	Date of Final Study Contact for the last subject.
Study Reference Manual(s)	A general term describing instructions and materials for completing study activities. Supplied to study sites by the Sponsor in addition to this protocol.
Study Site	The location(s) where study-related activities are actually conducted.
Subject	A participant in a clinical study. A subject may be healthy or have a disease. For obtaining informed consent, this term also includes a legally acceptable representative where applicable.
Subject Diary	Collection of forms (or electronic data) filled out directly by the subject or caregiver while the subject is away from the study site. The forms will collect information on infusions, bleeding and bleeding response to study drug, adverse events and other required study information. The diary is turned in at each study visit and replaced with a new diary. For the purposes of this study, can serve as source documents.
Target joint	A major joint (eg, hip, elbow, shoulder, knee, ankle) into which repeated bleeding occurs (frequency of 3 or more bleeding episodes over 6 months), and/or clinical signs and/or symptoms of underlying target joint damage (synovitis, persistent swelling, effusion, limitation of range of motion, eg any objective limitation or joint held in flexion or “frozen”).
Test article	Any drug, comparator, placebo, nutritional product, dietary supplement, herbal product, vaccine, biologic product, or device used in the Sponsor’s studies. For test article accountability, this term applies to such articles when they are required by the protocol and supplied (shipped) by the Sponsor (including diluents such as sterile water for injection).
Time on study	Time from signing the informed consent/assent to last study contact reported for study participation.
TN8.2	The affinity ligand used during the moroctocog alfa (AF-CC) purification process.

Term	Definition
Treatment phase of the study	Period of time during which subject receives study drug. The period starts at study visit 2 (day 1) and ends at the Final Study Visit (visit 15, month 18 or visit 19, month 24, depending on the cohort into which the subject is enrolled).
Washout	The time between the last dose of FVIII replacement product or blood product (eg, fresh frozen plasma, cryoprecipitate, blood) and the collection of FVIII activity or other laboratory information. For this study, the minimal washout time is 72 hours. The intent of the washout is to allow complete clearance of previous FVIII replacement therapy from the blood.

5. SYNOPSIS

<table>
<tr><td colspan="6">Study Title: An Open-Label Study to Evaluate Prophylaxis Treatment, and to Characterize the Efficacy, Safety, and Pharmacokinetics of B-Domain Deleted Recombinant Factor VIII Albumin Free (moroctocog alfa [AF-CC]) in Children With Hemophilia A</td></tr>
<tr><td>Protocol Number</td><td colspan="2">3082B2-313-WW – Amendment 10</td><td>Phase</td><td>Type</td><td>Interventional</td></tr>
<tr><td colspan="6">Condition/Disease: Hemophilia A</td></tr>
<tr><td colspan="6">Approximate</td></tr>
<tr><td colspan="2">Number of Subjects</td><td>80 Subjects
56 RP subjects
24 OD subjects, OD Cohort Closed</td><td colspan="2">Duration of Subject Participation</td><td>26 months (RP Subjects)

20 or 26 months (OD Subjects) Cohort Closed</td></tr>
<tr><td colspan="2">Number of Study Centers</td><td>Approximately 40 globally</td><td colspan="2">Duration of Study</td><td>8 years; includes 26 months after last RP subject enrolled</td></tr>
<tr><td colspan="6">Rationale: While prophylaxis therapy with factor VIII (FVIII) products has increasingly been prescribed worldwide, direct clinical information on optimal prophylaxis dosing strategies is limited. Therefore, this study will directly evaluate the efficacy of moroctocog alfa (AF-CC), a recombinant FVIII product in clinical development, prophylaxis to reduce bleed rates relative to moroctocog alfa (AF-CC) on-demand therapy, and will compare the clinical outcomes of a high- versus low-frequency prophylaxis dosing regimen in a randomized crossover design. In addition, younger hemophilia A patients may respond differently to FVIII therapy compared with older children and adults. Thus, it is important to continue to characterize the pharmacokinetics (PK) of moroctocog alfa (AF-CC) in patients with hemophilia. In addition to the FVIII PK data following moroctocog alfa (AF-CC) administration already collected in this study from children younger than 6 years of age, additional opportunity for PK data collection is being provided. Furthermore, the efficacy and safety of moroctocog alfa (AF-CC) during routine prophylaxis treatment will be described in these young patients.

Enrollment into the on-demand (OD) cohort has been closed. To date, there are data indicating that prophylaxis therapy controls bleeding episodes better than on-demand therapy. Because of availability of FVIII:C PK data following Xyntha administration in children with the Food and Drug Administration (FDA) approval, enrollment into the PK assessment is optional. Given that prophylaxis has replaced OD therapy as the preferred standard of medical care, the study will continue enrollment into the routine prophylaxis (RP) cohort to assess the effect of a high (25 IU/kg every other day) versus low (45 IU/kg twice per week)-frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis for male subjects ≥6 months to <16 years of age.</td></tr>
<tr><td colspan="6">Primary Objective:
To demonstrate that moroctocog alfa (AF-CC) prophylaxis reduces annualized bleeding rates (ABRs) relative to on-demand therapy. Enrollment into the on-demand (OD) cohort has been closed.

Secondary Objectives:
To assess the effect of a high (25 IU/kg every other day)- versus low (45 IU/kg twice per week)-frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis.
To continue to characterize the PK of FVIII after moroctocog alfa (AF-CC) administration in children ≥6 months to <16 years of age.
To describe moroctocog alfa (AF-CC) efficacy and safety in children, including characterization of the incidence of “less than expected therapeutic effect”.</td></tr>
<tr><td colspan="6">Design: This 2-segment study will be an open-label, multicenter trial. There will have been two cohorts enrolled into the study; one in which the subject practices on-demand therapy for the first segment of the study, followed by routine prophylaxis for the second segment, and, another cohort in which the subject practices routine prophylaxis for both segments. Study subjects will be hereafter referred to by their</td></tr>
</table>

segment 1 treatment modality: on-demand (OD) subjects and routine prophylaxis (RP) subjects. Enrollment for the OD cohort has been closed. Enrollment for the RP cohort is ongoing. All RP subjects will practice prophylaxis with moroctocog alfa (AF-CC) study drug according to one of two randomly assigned moroctocog alfa (AF-CC) regimens, each delivering approximately 90 IU/kg/week, but differing in dosing schedule. Randomization will be stratified by hemophilia A severity: FVIII activity <1% or 1-2% (central laboratory screening result). Each segment will be 12 months in duration. In the first segment, subjects will be randomly assigned to Regimen A: 45 ± 5 IU/kg, administered twice per week or Regimen B: 25 ± 5 IU/kg, administered every other day. After completion of the first segment, all subjects will cross over to the second prophylactic regimen for segment 2. Subjects who received Regimen A in segment 1 will follow Regimen B in segment 2. Conversely those subjects who received Regimen B in segment 1 will follow Regimen A in segment 2. During prophylaxis, a subject's treatment will be escalated to a higher intensity prophylaxis regimen comprised of the most intensive components of both regimens A and B (45 ±5 IU/kg, administered every other day) if criteria justifying regimen escalation are met: over a 4-week period, the occurrence of 2 or more spontaneous joint bleeds or the occurrence of 3 or more spontaneous bleeds (consisting of joint bleeds, and/or significant soft tissue/muscle or other site bleeds). Subjects who meet dose escalation criteria while on this more intensive regimen may dose escalate to a higher intensity regimen designated by the investigator. During prophylaxis, subjects will also use moroctocog alfa (AF-CC), as needed, for the treatment of bleeds (ie, on-demand), should they occur. Clinical and laboratory examinations, including assessments for FVIII inhibitor development, will be conducted during the course of the study. Moroctocog alfa (AF-CC) efficacy and safety will be assessed over the entire treatment period. A subset of subjects may participate in assessments for FVIII PK characterization after administration of moroctocog alfa (AF-CC). This subset of subjects will undergo a baseline PK assessment, receiving a single open-label dose of moroctocog alfa (AF-CC) (50 ± 5 IU/kg, rounded to the closest complete vial) with blood sampled for FVIII activity measurements before and at 0.5, 8, 24, 28 (optional), and 32 hours after the start of infusion.
Main Inclusion Criteria: Males ≥6 months to <16 years of age at the time of screening visit with moderately severe to severe hemophilia A (FVIII activity ≤2%), with previous FVIII replacement therapy experience (≥20 exposure days).
Main Exclusion Criteria: Current or history of FVIII inhibitor.
Concomitant Treatment: Regular medication, other than FVIII concentrates, may continue unchanged.
Test Articles(s) and Administration: Moroctocog alfa (AF-CC) study drug; single 50 ±5 IU/kg (rounded to closest complete vial) intravenous infusions administered for PK assessment;either 45 IU/kg twice per week or 25 IU/kg every other day for prophylaxis treatment (or according to investigator prescription in the event that escalation criteria are met while the subject is practicing the initial protocol-defined escalated regimen).
Safety Evaluation: Safety variables will be as follows: the incidence of adverse events (by severity and by relationship to moroctocog alfa (AF-CC)); the incidence of FVIII inhibitor development, development of antibodies to moroctocog alfa (AF-CC), CHO cell proteins, and TN8.2. Laboratory-based assessments for FVIII inhibitor will be conducted at intervals of approximately every 3 months.
Efficacy Evaluation: Efficacy variables will include ABR, number of moroctocog alfa (AF-CC) infusions per bleed, response of bleed to moroctocog alfa (AF-CC) treatment (4-point scale of assessment), time

interval between bleed onset and prior moroctocog alfa (AF-CC) routine prophylaxis dose, incidence of prophylaxis regimen escalation, incidence of less than expected therapeutic effect (LETE), consumption of moroctocog alfa (AF-CC), and compliance with assigned prophylaxis regimen. All subjective assessments will be provided by the caregiver or investigator.

Pharmacokinetics: FVIII activity in plasma (FVIII:C) will be analyzed using noncompartmental methods and the following PK parameters calculated for each subject: FVIII:C 0.5 hours after the beginning of the infusion ($C_{0.5hr}$), incremental recovery, area-under-the FVIII:C-time curve to the last measureable FVIII:C (AUC_t) and AUC extrapolated to infinity (AUC_∞), terminal phase half-life ($t_{½}$), clearance (CL), steady-state volume of distribution (V_{ss}), and mean residence time (MRT). Summary statistics of each parameter will be reported.

Statistical Considerations, General: This study will provide descriptive safety, efficacy and PK data of moroctocog alfa (AF-CC) treatment in previously treated pediatric patients at least 6 months to <16 years of age. The sample size of each cohort of the study was based on the statistical comparison of ABR between the first and second segments. Additional information regarding sample size estimates is provided below.

Statistical Considerations, Primary Objective: The primary objective of this study is to demonstrate a mean change in ABR during a period of protocol-defined moroctocog alfa (AF-CC) prophylaxis (~25 ±5 IU/kg, administered every other day) compared to a period of on-demand therapy with moroctocog alfa (AF-CC). Only subjects who practice on-demand therapy with moroctocog alfa (AF-CC) during segment 1, before starting protocol-defined moroctocog alfa (AF-CC) prophylaxis in segment 2, will be included in this analysis. For these subjects, an analysis of variance (ANOVA) will be conducted to compare the mean ABR during their on-demand and prophylaxis treatment periods. In a completed ReFacto Previously Untreated Patients (PUP) study (3082A1-301-WW), a reduction in the ABR was observed for subjects during their periods of prophylaxis (≥2 infusions per week) compared to their periods of on-demand therapy (reduction of 5.7 ±6.9 bleeds per year [11.85 to 6.15 bleeds per year], ABR decrease of 48%, N=39). Based upon this experience, a more conservative decrease in ABR of 40% (corresponding to a mean change of 4.75 bleeds per year) and a standard deviation of 7 were selected for use in sample size calculations. A sample size of 18 OD subjects who practice on-demand therapy in segment 1, followed by prophylaxis in segment 2, provides 80% power to detect such a difference using a 2-sided alpha level of 0.05. Due to an expected attrition rate of up to 25%, approximately 24 OD subjects, who practice on-demand therapy during segment 1, were planned to be enrolled to ensure that 18 are evaluable for the comparison of ABRs in the on-demand versus the prophylaxis setting. Because enrollment into the OD cohort has been closed, all available data will be analyzed.

Statistical Considerations, Secondary Objectives: A secondary objective is to evaluate the effect of dosing schedule on prophylactic efficacy. For the comparison of high-versus low-frequency prophylaxis dosing schedule, a subset analysis of data from the completed ReFacto PUP study (Wyeth protocol 3082A1-301-WW) revealed an ABR of 5.7 ±5.2 (N=26) in patients receiving a high-frequency prophylaxis regimen (3 infusions per week) compared to an ABR of 7.1 ±4.1 (N=13) in patients receiving a lower-frequency prophylaxis regimen (2 infusions per week). However, the treatment assignment was not randomized and prophylaxis regimens were not controlled in that study. To avoid selection bias and inter-patient variability affecting outcome, two protocol-defined prophylaxis regimens (a high- and a low-frequency dosing regimen) will be assessed in a crossover design. Assuming an intra-class correlation of 30% and a standard deviation of 6 bleeds per year based on this previous ReFacto PUP study, a within-subject standard deviation of 5 bleeds per year was used for sample size calculations for the comparison between the 2 protocol-defined prophylaxis regimens (A and B). Given this, 36 RP cohort subjects are needed to provide 80% power to demonstrate equivalence of the two regimens. Allowing for an attrition rate of 25%, approximately 48 RP subjects need to be enrolled to support this objective.

Based on a sample size re-estimation using data from the ongoing study, a difference of means of 1.3 bleeds per year between the two protocol-defined prophylaxis regimens with a corresponding standard deviation of the difference of 6.5 was obtained requiring 38 subjects to provide 80% power to demonstrate equivalence

of the two regimens (A and B). Allowing for an attrition rate of 30%, approximately 56 RP subjects would need to be enrolled. The two prophylaxis regimens will be considered equivalent if the limits of the 2-sided 90% confidence interval for the difference in observed mean ABRs fall wholly within the interval defined by fewer than 4 bleeds per year.

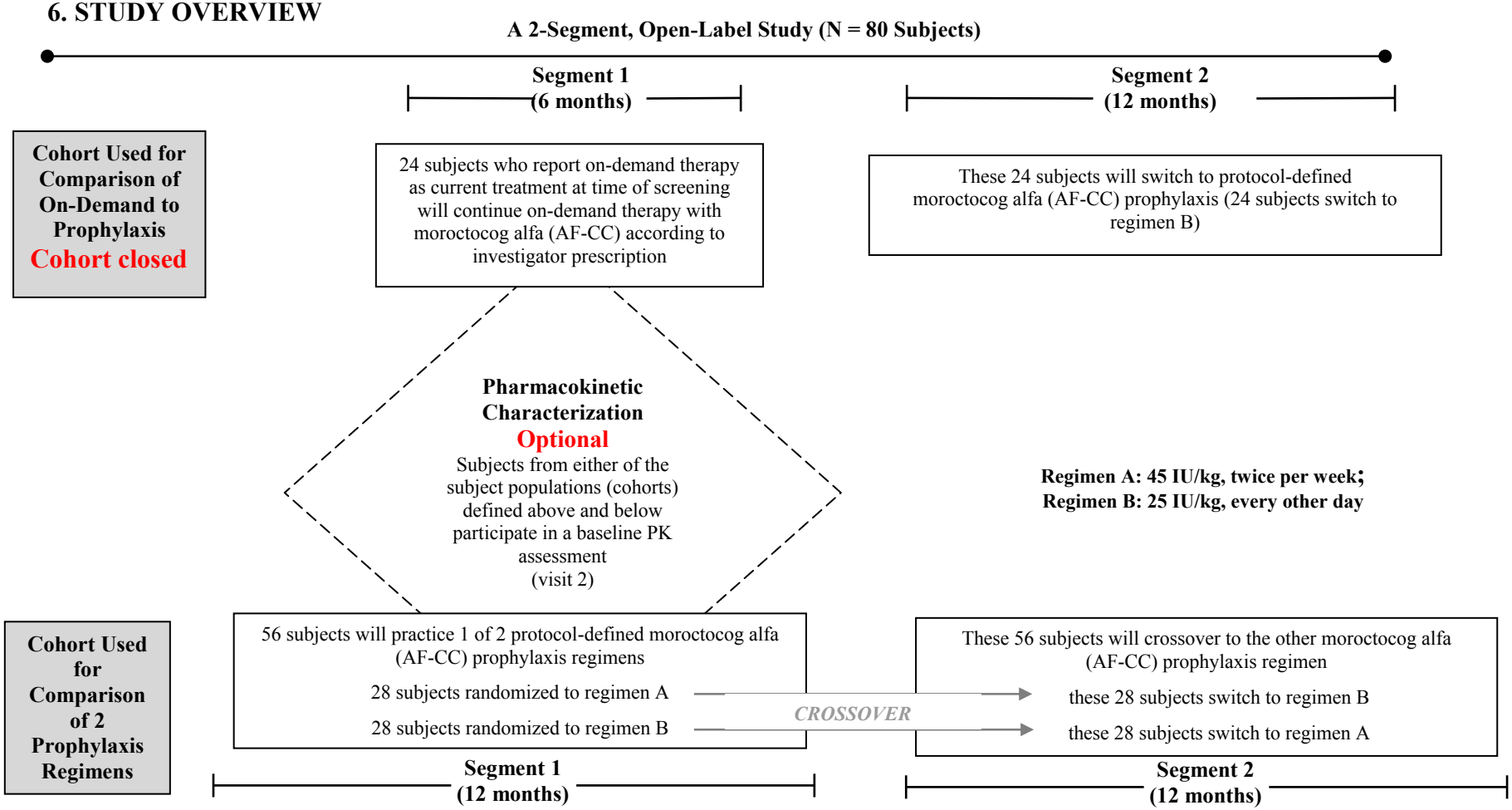
FVIII:C pharmacokinetics after administration of moroctocog alfa and moroctocog alfa (AF-CC) have been well described in a wide range of ages. Younger patients (median age 10 ±8.3 months, N=59) had lower recoveries than older patients (median age 26 ±12 years, N=101), with mean values of 1.5 ±0.6 and 2.4 ±0.4 IU/dL per IU/kg, respectively. Younger children have also been observed to have higher clearance of FVIII:C when adjusted by weight and shorter half-lives. A secondary objective of this study allows for continued characterization of the FVIII:C PK after administration of moroctocog alfa (AF-CC) in children younger than 16 years of age, thus improving our understanding the FVIII:C pharmacokinetics in children. Descriptive statistics of single-dose PK parameters will define this characterization. Subjects opting to participate are required to be ≥6 months to <16 years of age at the time of the baseline PK assessment.

Interim Report and Analysis: An independent data monitoring committee will provide guidance during the course of the study, with review intervals of approximately every 6 months. Prior to study completion, selected (safety, efficacy and/or PK) data from this study may be summarized and reported to regulatory authorities to support regulatory submissions or requests. The analyses for these summaries would be based on descriptive statistics.

Per discussions with the FDA, a final report for the OD cohort will be submitted comparing prophylaxis efficacy and safety versus on-demand therapy according to Section 3.3 of the statistical analysis plan. Additionally, after approximately 38 evaluable RP subjects, who practiced prophylaxis for both segment 1 and segment 2, complete the study, a final report for the RP cohort will be submitted.

Ethical Considerations: This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. Before any procedures specified in the protocol are performed, the subject's legally authorized representative must sign and date the IRB/IEC-approved informed consent form.

6. STUDY OVERVIEW



7. STUDY FLOWCHART 1: ROUTINE PROPHYLAXIS (RP) COHORT STUDY PROCEDURES

Study Procedures[a]	**Screening**[b]		**SEGMENT 1** ***(Routine Prophylaxis Treatment Phase)***												
Study Visit/Contact ID	**1**		**2**		**3**	**4**		**5**	**6**		**7**	**8**		**9**	**10**
Study Interval[c]	**(Day –35** to –1)		**Day1**		**Mo.1** (±1wk)	**Mo.2** (±1wk)		**Mo.3** (±1wk)	**Mo.4.5** (±1wk)		**Mo.6** (±1wk)	**Mo.7.5** (±1wk)		**Mo.9** (±1wk)	**Mo.10.5** (±1wk)
Informed consent/assent	X	**72-hour FVIII washout**		**72-hour FVIII washout**			**72-hour FVIII washout**			**72-hour FVIII washout**			**72-hour FVIII washout**		
Demographics, medical history, hemophilia A information	X														
Physical examination[d]	X		X		X			X			X			X	
CD4 cell count (HIV subjects only)	X														
PT or INR	X														
Hematology panel[e]	X		X[e]												
Serum chemistry[e]	X														
FVIII activity (FVIII:C)[f]	X[a,f]		X		X			X			X			X	
FVIII inhibitor[f]	X[a,f]		X		X			X			X			X	
Anti-FVIII antibody[f]	X[f]		X		X			X			X			X	
Anti-CHO antibody[f]	X[f]		X												
Anti-TN8.2 antibody[f]	X[f]		X												
Subject diary[g]	X		X		X			X			X			X	
PK assessment[h] (optional)			X[h]												
Randomization to regimen[i]	X[i]														
Study drug dispensed			X		X			X			X			X	
Study drug accountability					X			X			X			X	
Telephone contact[j]						X			X			X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT														
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT														

STUDY FLOWCHART 1: Routine Prophylaxis (RP) COHORT study procedures (Continued)

Study Procedures[a]		**SEGMENT 2** ***(Routine Prophylaxis Treatment Phase)***												**Final Contact**
Study Visit/Contact ID		**11**	**12**		**13**	**14**		**15**	**16**		**17**	**18**		**19**	**20**
Study Interval[c]		**Mo.12** (±1wk)	**Mo.13.5** (±1wk)		**Mo.15** (±1wk)	**Mo.16.5** (±1wk)		**Mo.18** (±1wk)	**Mo.19.5** (±1wk)		**Mo.21** (±1wk)	**Mo.22.5** (±1wk)		**Mo.24** (±1wk)	**Mo.25** (+10 days)
Informed consent/assent	**72-hour FVIII washout**			**72-hour FVIII washout**			**72-hour FVIII washout**			**72-hour FVIII washout**			**72-hour FVIII washout**		
Demographics, medical history, hemophilia A information															
Physical examination[d]		X			X			X			X			X	
CD4 cell count														X	
PT or INR															
Hematology panele		X												X	
Serum chemistry[e]		X												X	
FVIII activity (FVIII:C)[f]		X			X			X			X			X	
FVIII inhibitor[f]		X			X			X			X			X	
Anti-FVIII antibody[f]		X			X			X			X			X	
Anti-CHO antibody[f]		X												X	
Anti-TN8.2 antibody[f]		X												X	
Subject diary[g]		X			X			X			X			X	
PK assessment[h] (optional)															
Randomization to regimen[i]															
Study drug dispensed		X			X			X			X				
Study drug accountability		X			X			X			X			X	
Telephone contact[j]			X			X			X			X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT														
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT														

Abbreviations: Mo = month; wk = week; PT = prothrombin time; INR = international normalized ratio for prothrombin time; FVIII = factor VIII; CHO = Chinese hamster ovary; TN8.2 = affinity ligand used in study drug purification process; PK = pharmacokinetic.

a. All testing will be performed by the central laboratory. The local laboratory will also perform FVIII activity and FVIII inhibitor testing to confirm eligibility.
b. Screening period. Interval starting from the signing of the informed consent/assent and extending up to visit 2 (day 1). There are up to approximately 35 days in this interval (day -35 to day -1).
c. Study day or month. Visits/contacts 3 (month 1) through 19 (month 24) to be conducted within ± 1 week of indicated study month. Final Study Contact (Visit 20, month 25) to be conducted at least 28 days (+10 days) from Final Study Visit (Visit 19, month 24).
d. Includes collection of vital signs and weight. Also includes collection of height at visits 1 (Screening) and 11 (month 12).
e. See Protocol Definitions. For visit 2 (day 1), hematology panel is only collected for subjects participating in the optional PK assessment.
f. Subjects will observe a minimum 72-hour FVIII washout before sample collection. For screening purposes, subjects will be instructed to return to the clinic following a

72-hour FVIII washout for this sample collection if the washout was not observed before the initial screening visit.

g. Subject diary dispensed and/or collected. Subject diary is reviewed at each visit (information about adverse events, concomitant medications, study compliance, study drug infusions and assessments, less than expected therapeutic effect, and dose escalation and/or changes, if applicable, is reviewed).
h. See Study Flowchart 2 for activities related to this assessment.
i. Randomization will occur only after study eligibility criteria have been confirmed and documented. Only those subjects who will practice prophylaxis during both study segments will be randomized to 1 of the 2 protocol-defined prophylaxis regimens to be followed for 12 months during segment 1; these subjects will then crossover to the other protocol-defined prophylaxis regimen for 12 months during segment 2.
j. Information about adverse events, concomitant medications, dose escalation and/or changes, if applicable, and study compliance will be collected during these contacts. Can be conducted at appropriately scheduled clinic visits if preferred.
k. Collected at each visit/contact from the time the consent/assent form is signed to the final study contact.

8. STUDY FLOWCHART 2: PHARMACOKINETIC ASSESSMENT VISIT 2 (DAY 1)

Study Procedures[a]		**Predose: -2-0 hr**	**Dose: 0 hr**	**0.5 hr** (± 3 min)	**8 hr** (± 48 min)	**24 hr** (± 1 hr)	**28 hr**[b] (± 1 hr)	**32 hr** (± 1 hr)
Physical exam and Weight	**72-hour FVIII washout**	X						
Vital signs		X				X		
Blood sample collections for:								
FVIII activity		X		X	X	X	X	X
FVIII inhibitor		X						
Anti-FVIII antibody		X						
Anti-CHO antibody		X						
Anti-TN8.2 antibody		X						
Hematology panel[c]		X						
Study drug administration (50 ± 5 IU/kg, rounded to nearest complete vial)			X					
Concomitant medications		COLLECTED for the COURSE of the ASSESSMENT						
Adverse events		COLLECTED for the COURSE of the ASSESSMENT						

Abbreviations: FVIII=factor VIII; hr=hour; min=minute; CHO=Chinese hamster ovary; TN8.2=affinity ligand used in study drug purification process.

a. Optional pharmacokinetic assessment is conducted at visit 2 (day 1). Subjects must be in a nonbleeding state for this assessment. All testing will be performed by the central laboratory.
b. The 28-hour sample collection is optional.
c. See Protocol Definitions.

9. BACKGROUND INFORMATION AND RATIONALE

9.1. The History of ReFacto and Moroctocog alfa (AF-CC)

Hemophilia A is an X-linked recessive disease in which clotting factor VIII (FVIII) is deficient or inactive. Patients with a low level of FVIII have an increased tendency to bleed. When the levels of FVIII are very low (≤2% of normal), spontaneous bleeding episodes may occur. Infusing patients with a concentrated formulation of the missing FVIII protein can control the bleeding. Until the late 1980s, such concentrates were produced exclusively from human (or porcine) plasma. However, a combination of the risk of transmission of viral diseases, especially the human immunodeficiency virus (HIV), and rapidly evolving recombinant technology drove the development of recombinant DNA-derived coagulation products. Recombinant DNA technology also provides the potential to produce virtually unlimited quantities of virally safe products.

The first recombinant FVIII products (rFVIII) were referred to as "full-length" in that they were derived from plasmid DNA expression constructs containing the entire coding sequence of the FVIII protein. Later, it was observed that removal of the central B domain of FVIII increased the manufacturing yield without compromising the biological activity of the molecule.[1,2] To enhance the production of rFVIII, a B-domain deleted (BDD) rFVIII was developed. This culminated in the licensure of ReFacto®. The active substance of ReFacto is a recombinant B-domain deleted, murine monoclonal-antibody purified, solvent-detergent treated, and albumin-free formulated FVIII, (BDDrFVIII). The amino acid sequence is comparable to the 90 + 80 kDa form of FVIII and posttranslational modifications are similar to those of the plasma-derived molecule.[3, 4] ReFacto has functional characteristics comparable to those of endogenous Factor VIII.[3, 4, 5]

9.2. Manufacturing Changes for Moroctocog alfa (AF-CC)

ReFacto was manufactured using 2 raw materials that carry with them a minor but finite risk of introducing viral contaminants into the process stream. Human serum albumin (HSA) was used in the cell culture medium, and the purification process used a murine monoclonal antibody that was manufactured by a process employing bovine and human-derived components. To address these potential risks, Wyeth developed an alternative manufacturing process for ReFacto which included (1) the use of a reformulated, HSA-free cell culture medium for growth and production, (2) the use of a chemically synthesized polypeptide affinity ligand (TN8.2) in a column chromatography purification step in lieu of the murine monoclonal-antibody purification step, and (3) the addition of a virus-retaining membrane to the final manufacturing steps. These manufacturing changes expanded upon the comprehensive multifaceted viral safety program already in place for ReFacto.[6, 7] This improved process eliminates the use of all human or animal-derived proteins at any stage of the manufacturing process, and the new product has been designated moroctocog alfa (AF-CC).

Later, additional changes were also incorporated into the manufacturing process for moroctocog alfa (AF-CC), coincident with a manufacturing site transfer, to allow use of the common one-stage (OS) assay for monitoring moroctocog alfa (AF-CC) replacement therapy.

The BDDrFVIII DNA construct and the final formulation are identical for ReFacto and moroctocog alfa (AF-CC). Biochemical characterizations indicate that the active substance, BDDrFVIII, produced by both manufacturing processes (ReFacto and moroctocog alfa [AF-CC]) is comparable with respect to structure and function.

ReFacto/moroctocog alfa (AF-CC) has been licensed for use since 1999 in the European Union (EU) and since 2000 in the United States (US). In the EU moroctocog alfa (AF-CC) is marketed under the trade name ReFacto AF. In the US, moroctocog alfa (AF-CC) is distributed under the trade name Xyntha. Globally, as of August 2014, moroctocog alfa (AF-CC) was approved in 48 countries and marketed in 19 countries.[8]

9.3. Clinical Experience With Moroctocog alfa (AF-CC)

Extensive clinical trial experience had already been compiled for moroctocog alfa (AF-CC) before the last manufacturing changes (ie, before the modifications facilitating use of the OS assay and the change of manufacturing site): a pharmacokinetic crossover study showed bioequivalence to ReFacto (study 3082B1-305-GL); and 2 open-label, single-arm studies were initiated to assess safety and efficacy in previously treated patients (PTPs) at least 6 years of age (studies 3082B1-306-GL [study 306] and 3082B1-307-GL [study 307]). Results from study 306 showed moroctocog alfa (AF-CC) to be safe and efficacious for hemophilia A treatment in 110 PTPs (median moroctocog alfa (AF-CC) exposure days [EDs] = 58), and study 307 demonstrated the long-term safety of moroctocog alfa (AF-CC) in 98 of these PTPs who elected to participate in this extension study after completing study 306 (median moroctocog alfa [AF-CC] EDs = 169 over median duration of 521 days).

The safety and efficacy of moroctocog alfa (AF-CC) manufactured with the most recent manufacturing changes (ie, modifications allowing use of the OS assay and new manufacturing site), has been evaluated in 2 clinical trials in PTPs at least 12 years of age, completed study 3082B2-310-WW (study 310) and completed study 3082B2-311-WW (study 311).

Study 310 was an open-label safety and efficacy evaluation of moroctocog alfa (AF-CC) for the control and prevention of bleeding in PTPs with severe or moderately severe hemophilia A during moroctocog alfa (AF-CC) prophylaxis treatment. In this open-label study, patients used moroctocog alfa (AF-CC) according to an assigned routine prophylaxis regimen, accruing a minimum of 50 EDs over a 6-month period. The 310 study also included a comparative pharmacokinetic evaluation. While prior pharmacokinetic studies have demonstrated the bioequivalence of ReFacto and the full-length plasma-derived FVIII (pdFVIII) using the chromogenic substrate assay,[9] a double-blind, crossover evaluation in the 310 study used the OS assay to demonstrate the bioequivalence of moroctocog alfa (AF-CC) and a full-length recombinant FVIII product (Advate®).

Study 311 was also an open-label study with the primary efficacy objective of characterizing the ability of moroctocog alfa (AF-CC) to support patients during and after surgery. The safety and efficacy of moroctocog alfa (AF-CC) was assessed in patients with severe or moderately severe hemophilia A undergoing major elective surgery. Factor VIII infusions were administered as bolus injections or as a continuous infusion, over a period of at least 6 days following the surgical procedure.

Collectively, results from studies 310 and 311 support the use of moroctocog alfa (AF-CC) for the control and prevention of bleeding episodes, and for surgical prophylaxis in PTPs with hemophilia A.

9.4. Rationale for the Current Moroctocog alfa (AF-CC) Study (3082B2-313-WW)

While studies 310 and 311 are designed to evaluate the safety and efficacy of moroctocog alfa (AF-CC) in PTPs who are 12 years of age or older, the current study will provide these data for moroctocog alfa (AF-CC) treatment in pediatric PTPs who are younger than 6 years of age. Because early treatment may be necessary in patients with the more severe forms of hemophilia A, it is important to demonstrate product safety and efficacy in the youngest patients.

Prophylaxis therapy (ie, the regularly scheduled administration of a factor replacement product for the prevention of bleeding) is widely advocated as the optimal treatment modality for patients affected with the more severe forms of hemophilia A. Several studies have concluded that it is preferable to on-demand therapy, as prophylaxis affords lower bleeding rates, better retention of joint integrity, and quality of life improvements (eg, fewer hospitalizations and greater academic achievement).[10, 11, 12, 13, 14] In view of the established benefits of prophylaxis in pediatric patients with hemophilia, the National Hemophilia Foundation (NHF),[15] the World Federation of Hemophilia (WFH),[16] and the World Health Organization (WHO) now endorse prophylaxis. Despite the increasing collection of data favoring prophylaxis over on-demand therapy, more specific questions still exist. For example, direct clinical information on optimal prophylaxis dosing strategies is limited. Recently, the Cochrane collaboration recommended conducting additional prospective, randomized controlled trials to determine optimal prophylactic regimens and to assess the effectiveness of clotting factors.[17] Although many of the favorable outcomes associated with prophylaxis are best achieved when the therapy is initiated at an early age, perceived dosing frequency requirements are often a major obstacle for its practice in pediatric populations. Thus, corollary data, establishing associations between dosing frequency and effective prophylaxis, would be especially meaningful for younger patients.

To achieve its objectives, this study evaluates moroctocog alfa (AF-CC) in the context of two settings. A cohort of subjects was enrolled who practiced on-demand therapy for a 6-month period during segment 1, then switched to prophylaxis with moroctocog alfa (AF-CC) for a 12-month period in segment 2, practicing a protocol-defined regimen (25 ±5 IU/kg, administered every other day). This regimen has been well characterized and has demonstrated efficacy relative to on-demand therapy, although in a different patient population.[12] A second cohort, comprising all other subjects, will practice a single moroctocog alfa (AF-CC) treatment modality, prophylaxis, during this study, but treatment

will include practice of each of the two protocol-defined regimens; these subjects will follow one of the two randomly assigned protocol-defined regimens for a 12-month period (segment 1), and then will crossover to the other regimen for a second 12-month treatment period (segment 2). Study subjects will be hereafter referred to by their segment 1 treatment modality: on-demand (OD) subjects and routine prophylaxis (RP) subjects. This study design allows direct evaluation of moroctocog alfa (AF-CC) in the prophylaxis and on-demand settings, as well as a direct comparison between 2 different moroctocog alfa (AF-CC) prophylaxis-dosing schedules. The duration of moroctocog alfa (AF-CC) treatment in this study (18 - 24 months depending on the cohort) ensures that sufficient experience with moroctocog alfa (AF-CC) is obtained.

Pharmacokinetic assessment of FVIII:C after FVIII therapy has shown lower FVIII:C recovery, in young children. For moroctocog alfa, this has also been observed: a mean incremental recovery of 1.5 ±0.6 IU/dL per IU/kg, in 59 children with median age 10 ±8.3 months was reported compared with mean incremental recovery of 2.4 ±0.4 IU/dL per IU/kg in 101 patients with a median age of 26 ±12 years.[18] Younger patients also have higher clearance, when adjusted for body size and shorter half-lives compared with older children and adults. A secondary objective of this study is to continue to characterize the pharmacokinetics of moroctocog alfa (AF-CC) in pediatric patients. To achieve this objective, a subset of enrolled subjects will participate in a pharmacokinetic assessment conducted at the start of the study.

Another secondary objective of this study is to define the safety and efficacy of moroctocog alfa (AF-CC) in pediatric patients, including the characterization of the incidence of "less than expected therapeutic effect".

Enrollment into the on-demand (OD) cohort has been closed. To date, there are data indicating that prophylaxis therapy controls bleeding episodes better than on-demand therapy. Subsequent to the initiation of this protocol, Xyntha has been approved for on-demand use in children. The availability of the completed pharmacokinetic assessment in the submission means enrollment into the pharmacokinetic (PK) assessment is optional. Given that prophylaxis has replaced OD therapy as the preferred standard of medical care, the study will continue enrollment into the RP cohort to assess the effect of a high (25 IU/kg every other day) versus low (45 IU/kg twice per week) frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis for male subjects ≥6 months to <16 years of age.

Refer to the most recent version of the investigator's brochure for a summary of findings from nonclinical studies that potentially have clinical significance and from clinical studies that are relevant to the study. Also refer to the most recent version of the investigator's brochure for a summary of the known and potential risks and benefits, if any, to human subjects.

10. OBJECTIVES

10.1. Primary Objective

To demonstrate that moroctocog alfa (AF-CC) prophylaxis reduces annualized bleeding rates relative to on-demand therapy. Enrollment into the on-demand (OD) cohort has been closed.

10.2. Secondary Objectives

- To assess the effect of a high (25 IU/kg every other day)- versus low (45 IU/kg twice per week)-frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis.

- To continue to characterize the PK of FVIII:C after administration of moroctocog alfa (AF-CC) in children ≥6 months to <16 years of age. Enrollment into the PK assessment is optional.

- To describe moroctocog alfa (AF-CC) efficacy and safety in children, including characterization of the incidence of "less than expected therapeutic effect" (see Section 18.2).

11. STUDY DESIGN

11.1. Description

There will have been two cohorts enrolled into the study; one in which the subject practices on-demand therapy for the first segment of the study, followed by routine prophylaxis for the second segment, and, another cohort in which the subject practices routine prophylaxis for both segments. Study subjects will be hereafter referred to by their segment 1 treatment modality: on-demand (OD) subjects and routine prophylaxis (RP) subjects. Enrollment into the OD cohort has been closed. Enrollment for the RP cohort is ongoing.

Enrollment for the RP cohort will continue and will be conducted as an open-label, multicenter trial of moroctocog alfa (AF-CC) in approximately 56 subjects (≥6 months to <16 years of age) with moderately severe to severe hemophilia A. The study will be conducted in two 12-month segments (Also refer to Section 6).

At study start, a subset of subjects may participate in optional assessments to characterize the PK of FVIII after moroctocog alfa (AF-CC) administration. Subjects who are eligible and opt to participate will undergo a baseline PK assessment, receiving a single open-label dose of moroctocog alfa (AF-CC) (50 ±5 IU/kg rounded to the nearest complete vial) with blood sampled for FVIII activity measurements before and at 0.5, 8, 24, 28 (optional), and 32 hours after the start of the infusion.

All RP subjects will practice prophylaxis with moroctocog alfa (AF-CC) according to 1 of 2 randomly assigned moroctocog alfa (AF-CC) regimens, each delivering approximately 90 IU/kg/week, but differing in dosing schedule. Randomization will be stratified by hemophilia A severity: FVIII activity <1% or 1-2% (central laboratory screening result). Each segment will be 12 months in duration.

In the first segment, subjects will be randomly assigned to Regimen A: 45 ± 5 IU/kg, administered twice per week or Regimen B: 25 ± 5 IU/kg, administered every other day.

For regimen A, the interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days. For regimen B, the interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc).

After completion of the first segment, all subjects will cross over to the alternate prophylactic regimen for segment 2. Subjects who received Regimen A in segment 1 will follow regimen B in segment 2. Conversely, those subjects who received Regimen B in segment 1 will follow Regimen A in segment 2.

During prophylaxis, a subject's treatment will be escalated to a higher intensity prophylaxis regimen comprised of the most intensive components of both regimens A and B (45 ±5 IU/kg, administered every other day) if criteria justifying regimen escalation are met (see Section 15.3.3). Subjects who meet dose escalation criteria while on this more intensive regimen may dose escalate to a higher intensity regimen designated by the investigator. The subject will follow the assigned regimen(s) until the respective 12-month period of prophylaxis with study drug has been completed (segment 1 or 2); the 12-month period is inclusive of treatment time on all the prophylaxis regimens assigned during the respective study segment. During prophylaxis, subjects will also use moroctocog alfa (AF-CC), as needed, for the treatment of bleeds (ie, on-demand), should they occur.

Clinical and laboratory examinations, including assessments for FVIII inhibitor development, will be conducted during the course of the study.

11.2. Approximate Duration of Subject Participation

Subjects enrolled in the OD subject cohort participated in the study for approximately 20 or 26 months, while subjects enrolled in the RP cohort will participate in the study for approximately 26 months. This includes approximately 35 days for screening, a 6-month or 12-month treatment period during segment 1, a 12-month treatment period during segment 2, and approximately 1 month (at least 28 days) for a final safety follow-up assessment (Final Study Contact). Completion of the Final Study Contact concludes the subject's participation in the study.

11.3. Approximate Duration of Study

The duration of this study will be approximately 98 months (including 26 months after the last RP subject is enrolled). The end of the study is the Final Study Contact of the last subject (Final Study Contact occurs at least 28 days after the Final Study Visit). A final safety follow-up assessment is performed during the Final Study Contact; this follow-up assessment includes the reporting of any adverse events that may have occurred during the time between the Final Study Visit and the Final Study Contact and also includes the reporting of medications used during this period.

11.4. Approximate Number of Subjects

Approximately 56 subjects will be enrolled in the RP cohort of this study at approximately 40 sites globally. Approximately 24 subjects were enrolled in the OD cohort. Enrollment in the OD cohort has been closed. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

12. SELECTION OF SUBJECTS

Subjects (and legal acceptable representative, if required) must participate in the informed consent/assent process and sign and date the informed consent/assent form before any study procedures or screening activities specified in this protocol are performed (*the informed consent/assent form for signature must have been approved by both the institutional review board (IRB)/independent ethics committee (IEC)* ***and*** *the Sponsor*). Prospective subjects may be notified of the study's existence, but no study procedures may be performed before obtaining informed consent/assent. The investigator will maintain a subject-screening logbook at the study site. All subjects screened at the study site will be entered into the logbook (see Section 23).

After obtaining informed consent/assent, the investigator and monitor determine a subject's eligibility by history and specific laboratory assays. The central laboratory will be used for all screening blood tests. The local laboratory will also be used specifically for 2 tests: FVIII activity (FVIII:C) and FVIII inhibitor. Local laboratory measurements of FVIII:C and FVIII inhibitor will be used by the investigator to assess eligibility, although parallel samples will be analyzed at the central laboratory and will also be used to confirm eligibility for subjects. (*NOTE*: *During the treatment phase of the study, all tests for FVIII:C and/or FVIII inhibitor performed at the local laboratory should have duplicate samples from the same phlebotomy shipped to the central laboratory for analyses. The treatment phase starts at visit 2 and ends at the Final Study Visit*.) If the local or central laboratory results for either FVIII:C or FVIII inhibitor show the subject is ineligible, the subject will be considered a screen failure. The Sponsor's clinician may be consulted regarding eligibility of particular subjects if circumstances warrant further discussion.

12.1. Inclusion Criteria

For all subjects participating in the study:

1. Male subjects with moderately severe to severe hemophilia A (FVIII:C ≤2%) by **both** the local laboratory and the central laboratory at screening.

2. A negative FVIII inhibitor by **both** the local laboratory and the central laboratory at screening (for local laboratory, a Bethesda inhibitor titer less than the upper limit of normal [ULN] for the laboratory performing the assay and is not reported to be ≥0.6 Bethesda Units [BU]/mL; for central laboratory, Bethesda inhibitor titer <0.6 BU/mL by Nijmegen assay).

3. A medical history negative for a past FVIII inhibitor (see Protocol Definitions).

4. Age ≥6 months to <16 years at the time of screening visit (study visit 1).

5. Previous experience of FVIII therapy (≥20 exposure days to any FVIII replacement product [see Protocol Definitions]).

6. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5.0 × ULN, and bilirubin ≤2 mg/dL (<35 μmol/L).

7. Serum albumin ≥ the lower limit of normal (LLN).

8. Serum creatinine ≤1.25 × ULN.

9. Platelet count ≥100,000/μL.

10. Absolute CD4 count >400/μL for subjects with HIV only.

11. Prothrombin time (PT) ≤1.25 × ULN, or international normalized ratio (INR) ≤1.5.

12. The subject is not receiving treatment for HIV or hepatitis infection, or the subject is on a stable antiviral regimen at the time of signing the consent/assent form (ie, stable dosing for at least 3 months before signing the consent/assent form).

13. The subject is able to comply with the mandatory 72-hour FVIII washout preceding each FVIII:C and FVIII inhibitor assessment during the study.

14. Male subjects able to father children must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

15. Evidence of a personally signed and dated informed consent/assent document indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) has been informed of all pertinent aspects of the study.

16. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

The Sponsor's clinician should be consulted about prospective subjects with complex medical or laboratory histories relevant to inclusion criteria.

Additional criteria for subjects participating in the PK assessment:

1. Male subjects as described immediately above except they must have a FVIII:C of ≤1% confirmed by the central laboratory screening test.

2. Age ≥6 months to <16 years at time of PK assessment (study visit 2).

3. The subject's size is sufficient to permit PK-related phlebotomy.

4. The subject is able to comply with the procedures conducted during the PK assessment, including a mandatory 72-hour washout period preceding the PK assessment.

12.2. Exclusion Criteria

1. A history of FVIII inhibitor (clinical or laboratory-based assessment). For laboratory assessments, any measured Bethesda inhibitor titer ≥0.6 BU/mL, regardless of the laboratory normal range, or any measured Bethesda inhibitor titer greater than the ULN for the laboratory performing the assay.

2. Presence of a bleeding disorder in addition to hemophilia A.

3. Treatment with any investigational drug or device within 30 days before the time of signing the consent/assent form.

4. Major or orthopedic surgery planned to occur within the period following the signing of the consent/assent form to the Final Study Contact (ie, during the course of the study).

5. Regular (eg, daily, every other day) use of antifibrinolytic agents or medications known to influence platelet function such as aspirin or certain nonsteroidal anti-inflammatory drugs (NSAIDs).

6. Regular, concomitant therapy with immunomodulating drugs (eg, intravenous immunoglobulin [IVIG], routine systemic corticosteroids).

7. Known hypersensitivity to hamster protein.

8. Any condition(s) that compromises the subject's ability to comply with and/or perform study-related activities or that poses a clinical contraindication to study participation (these conditions include, but are not limited to, inadequate medical history to assure study eligibility; inability to properly store study drug; expectation of poor compliance in study related documentation).

9. Unwilling or unable to follow the terms of the protocol.

10. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

11. Male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product or longer based upon the compound's half-life characteristics.

The Sponsor's clinician should be consulted about prospective subjects with complex clinical or laboratory histories relevant to Exclusion Criteria.

12.3. Life Style Guidelines

All male subjects who are able to father children and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will select/will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper -containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

12.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains,

at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

13. PRIOR TREATMENT

All treatment received within 30 days before signing the consent/assent form will be recorded.

14. CONCOMITANT TREATMENT

14.1. Prohibited

Concomitant treatment with FVIII concentrates, other than moroctocog alfa (AF-CC) study drug, is not allowed during the treatment phase of this study: the treatment phase starts at visit 2 (day 1) and ends at the Final Study Visit (ie, visit 19, month 24 for RP subjects). After completion of the treatment phase of this study, subjects may use the FVIII concentrate of their choice and should not use study drug.

Subjects should not receive drugs with antiplatelet effects (eg, aspirin) or use certain NSAIDs to a degree that, in the opinion of the investigator or Sponsor's clinician, affects the hemostatic function of the subject, and/or affects the subject's FVIII therapy.

The regular use of immunomodulating drugs (eg, IVIG, routine systemic corticosteroids) is prohibited.

14.2. Permitted

The subject's regular medication, other than FVIII concentrates, may continue unchanged, and will be recorded. Analgesics, as well as other therapy considered necessary for the subject's well-being during the study, may be given at the discretion of the investigator. Subjects must use only study drug (moroctocog alfa [AF-CC]) for FVIII therapy during the treatment phase of this study: the treatment phase starts at visit 2 (day 1) and ends at the Final Study Visit 19, month 24 for RP subjects).

Subjects with HIV and/or hepatitis virus infection(s) will be permitted to continue with any stable, noninvestigational treatment throughout the study. Licensed antiviral medications, including but not limited to protease inhibitors, interferon, and ribavirin, are permitted provided subjects are on stable dosing for at least 3 months before the signing of the

consent/assent form. Subjects must remain on a stable regimen of antivirals over the course of this study. The Sponsor's clinician should be consulted about prospective subjects with circumstances that may conflict with these criteria regarding antiviral medications.

Major surgery or orthopedic surgery planned to occur within the period following the signing of the consent/assent form to the Final Study Contact (ie, during the course of this study) is an exclusion criterion for this study. Required minor surgery, or major/orthopedic surgical procedures which were unplanned at the time of signing the consent/assent form, will be allowed during the course of this study, pending approval from the Sponsor's clinician. Moroctocog alfa (AF-CC) study drug will be the only FVIII replacement product used to achieve and maintain normal hemostasis through a surgical procedure. See Section 15.3.4 for further details.

15. PROCEDURES

The following description provides information on the procedures and activities of subjects/caregivers and investigators (or designees) as the study proceeds.
[*NOTE*: *Enrollment has been closed in the OD cohort. Details of the OD cohort can be found in Amendment 9 of this protocol. The RP cohort enrollment remains active and PK assessment portion continues as optional.*] Due to the young age of some subjects in this study, many activities will be performed by a subject's caregiver (eg, reporting of bleeds and study drug usage); where applicable in this protocol, the term subject will also refer to caregiver. Please also refer to Sections 7 and 8 for an overview of study procedures.

15.1. Study Procedures for RP Cohort

Please also refer to the study flowchart in Section 7, for an overview of study procedures.

15.1.1. Consent/Assent

All subjects must review and sign a consent form that has been approved by both the appropriate IRB/IEC **and** the Sponsor (*the consent form must be approved by the sponsor as well as the IRB/IEC before it can be used for the trial at that site*). Where deemed appropriate by the IRB/IEC, the subject should also sign an assent form (*the assent form must be approved by the Sponsor as well as the IRB/IEC before it can be used for the trial at that site*). Subjects who are under the legal age of consent, must have a legally acceptable representative review, approve and sign consent for the study (also see Section 29.3). The consent process must explain to the subject (and legal acceptable representative) that they may withdraw their consent/assent at any time for any reason. A note (dated and timed) must be made in the patient's medical record that the subject is participating in this study and that consent/assent was obtained. Collection of adverse events (AEs), as well as bleeds and medications, begins after the signing of the consent/assent form and completion of the medical history. Signing the consent/assent form marks the start of study participation.

15.1.2. Payment of Subjects

Subjects may be reimbursed for expenses related to study activities. Any payments must meet applicable law and regulations and be approved by the relevant IRBs/IECs.

15.1.3. Study Visit 1 (Screening Visit) - RP Cohort

Following consent/assent, subjects will undergo the following screening activities to determine if they are eligible for the study. Results from the central laboratory, designated by the Sponsor, will be used to determine eligibility as noted. Local laboratory test results will also be used to determine eligibility as noted. Screening procedures will collect the following:

- Obtain informed consent/assent.
- Demographic information, medical history (including HIV status and history of hepatitis infections), medication history (including hepatitis vaccinations), and hemophilia A history.
- Current hemophilia A treatment information (eg, prophylaxis or on-demand therapy).
- Complete physical examination including vital signs (temperature [Celsius], blood pressure, pulse, and respiration), body weight (kilograms), and height (centimeters).
- Blood sample for:
  - CD4 cell count (central laboratory) for subjects with HIV only.
  - PT or INR (central laboratory).
  - Hematology panel (see Protocol Definitions; central laboratory).
  - Serum chemistry (see Protocol Definitions; central laboratory).
  - FVIII:C (after a 72-hour FVIII washout; local and central laboratories; results from both local and central laboratories must meet inclusion criteria).
  - FVIII inhibitor (after a 72-hour FVIII washout; local and central laboratories; results from both local and central laboratories must meet inclusion criteria).
  - anti-FVIII antibody (see Protocol Definitions; collected after a 72-hour FVIII washout; frozen and sent to central laboratory for enzyme-linked immunosorbent assay [ELISA] analysis).
  - anti-CHO antibody (see Protocol Definitions; collected after a 72-hour FVIII washout; frozen and sent to central laboratory for ELISA analysis).
  - anti-TN8.2 antibody (see Protocol Definitions; collected after a 72-hour FVIII washout; frozen and sent to central laboratory for ELISA analysis).

All screening procedures that do not require a 72-hour FVIII washout may occur during the initial screening visit. Subjects will be instructed to return to the clinic following the 72-hour FVIII washout for relevant screening sample collections if the minimum 72-hour FVIII washout was not observed before the initial screening visit. If a subject experiences a bleed

during the 72-hour washout, he should be treated with his usual FVIII therapy and then have a repeat 72-hour FVIII washout before relevant screening sample collections.

FVIII:C and FVIII inhibitor testing will be performed at both the local and the central laboratories. Subjects must have FVIII:C ≤2% by both the local laboratory and the central laboratory. Subjects must have negative FVIII inhibitor tests by both the local laboratory and the central laboratory (for local laboratory, a Bethesda inhibitor titer < ULN for the laboratory performing the assay *and* is not reported to be ≥0.6 Bethesda Units [BU]/mL; for central laboratory, Bethesda inhibitor titer <0.6 BU/mL by Nijmegen assay). Once results are received, subjects who are deemed eligible will return for visit 2 (day 1) within approximately 35 days after the screening visit.

Subjects who do not meet study eligibility criteria will be considered screen failures (please refer to the Study Reference Manual for data recording instructions for screen failures). In the event that contradictory FVIII:C or FVIII inhibitor results are reported by the local and central laboratories, a subject is ineligible for the study if **either** the local or central laboratory results do not meet study eligibility criteria (eg, if a subject is ineligible for the study based on the central laboratory results for FVIII:C or FVIII inhibitor, the subject will be considered a screen failure even if the local laboratory results indicate the subject is eligible; similarly, if a subject is ineligible for the study based on the local laboratory results for FVIII:C or FVIII inhibitor, the subject will be considered a screen failure even if the central laboratory results indicate the subject is eligible).

Please refer to the Study Reference Manual for further details on the collection and shipping of all samples collected at this and other visits.

Subjects will receive the appropriate materials (ie, Subject Diary) and instructions to record any AEs, bleeds, and concomitant medication use.

15.1.4. Screening Period Activities and Randomization - RP Cohort

During the screening period (interval of up to approximately 35 days, starting from the signing of the informed consent/assent and extending up to visit 2, day 1), subjects should adhere to their usual therapies (including FVIII therapy) prescribed by the investigator. All AEs, bleeds, and medications must be recorded in the Subject Diary (issued at visit 1, Screening).

After study eligibility has been confirmed, and prior to visit 2, day 1, subjects will be randomized. Allocation of subjects to treatment assignments will be performed through an interactive voice or web-based response system. RP subjects will practice prophylaxis during both study segments and will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences (AB or BA) defining the prophylaxis regimens to be practiced for 12 months each during segments 1 and 2, respectively:

A: 45 ±5 IU/kg, administered twice per week

B: 25 ±5 IU/kg, administered every other day

For regimen A, the interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days. For regimen B, the interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc).

Randomization will be stratified by hemophilia A severity: FVIII activity <1% or 1-2% (central laboratory screening result). The randomizations will be performed as specified in the Study Reference Manual.

15.1.5. Study Visit 2 (Day 1) - Segment 1 - RP Cohort

After confirmation of eligibility, the subject will be notified by the investigator and arrange to return for visit 2 (day 1). Visit 2 (day 1) should occur within approximately 35 days after visit 1 (Screening). Only subjects who have met the eligibility criteria for the study should have visit 2 (day 1).

This visit requires a 72-hour FVIII washout. The subject should not have exogenous FVIII:C at the time of the visit. Therefore, depending on the last FVIII dose before the beginning of the FVIII washout, an interval longer than 72 hours may be needed. If a subject sustains a bleed requiring treatment during the ≥72-hour FVIII washout, the necessary treatment should be administered using the subject's usual FVIII replacement product. Once the bleed has been adequately treated, visit 2 must be rescheduled, and must be preceded by a new ≥72-hour FVIII washout.

The subject will be examined, measured for weight (kilograms), have vital signs taken (including temperature [Celsius], blood pressure, pulse, and respiration), and will have blood samples collected for:

- FVIII:C (central laboratory).
- FVIII inhibitor (central laboratory).
- anti-FVIII antibody (central laboratory).
- anti-CHO antibody (central laboratory).
- anti-TN8.2 antibody (central laboratory).

At this visit, the subject will turn in his Subject Diary. The investigator (or designee) will review the Subject Diary with the subject, and inquire about and record AEs, bleeds, and use of medications. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

15.1.5.1. Pharmacokinetic Assessment (if Applicable) - Segment 1 - RP Subject Cohort

Please refer to Section 15.2 and study flowchart 2 in Section 8 for PK-related study procedures.

15.1.5.2. Study Drug Dispensed - RP Cohort

Study drug (moroctocog alfa [AF-CC] and accessory supplies) will first be dispensed to the subject at this visit. The investigator (or designee) will provide study drug according to the subject's treatment modality, prophylaxis, and using the subject's weight recorded that day (see Study Reference Manual for guidelines of dose selection based on the subject's measured body weight; dispensed supplies also include supplies for treatment of any bleeds). RP subjects will be following the protocol-defined regimen to which they have been randomly assigned (A or B), therefore the investigator (or designee) will review the assigned regimen, and information related to regimen escalation (criteria for, and subsequent action; see Section 15.3.3) with the subject. For regimen A, the interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days. For regimen B, the interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc). All subjects will receive instructions for study drug reconstitution and administration, and the appropriate materials (ie, Subject Diary) and instructions to collect data on his home treatment (ie, infusions, bleeding events, response to infusions, etc). All instructions given to the subject will be documented in the subject's source document. Subjects may now commence treatment with study drug (moroctocog alfa [AF-CC]). For subjects who opt to participate in the PK assessment, moroctocog alfa (AF-CC) treatment should not commence until after the final PK sample collection (ie, 32 hour collection). (*NOTE*: Treatment with study drug may occur before the final PK sample collection if a subject experiences a bleeding episode during the assessment; in the event that this occurs, the bleed is to be stabilized with study drug.) Only moroctocog alfa (AF-CC) may be used for FVIII replacement therapy from this point through the remainder of the treatment phase of this study; the treatment phase starts at visit 2 (day 1) and ends at the Final Study Visit (visit 19, month 24).

15.1.6. Subject Activities Between Successive Study Visits (Visit 2 Through Visit 11), and Activities of Study Contacts 4, 6, 8, and 10 - Segment 1 - RP Cohort

Subjects will use moroctocog alfa (AF-CC) for hemophilia A treatment (protocol-defined prophylaxis [including treatment of any bleed, if necessary, during prophylaxis]). Subjects will document *all* of their infusions (dose, time of infusion, and reason) and all bleeding episodes in the Subject Diary. In addition, subjects will record the efficacy of a study drug infusion given on-demand for treatment of a bleed using a 4-point ordinal scale of "Excellent," "Good," "Moderate," and "No Response" in the Subject Diary (please refer to Section 18.1.3 for description of scale). Subjects will also document any AEs or use of concomitant medications in the Subject Diary. Subjects will save used study drug vials; used study drug vials are returned at each study visit. Approximately 4 weeks (±1 week) after study visit 3, and approximately 6 weeks (±1 week) after study visits 5, 7, and 9, respectively, the investigator (or designee) will contact the subject by telephone in order to collect information regarding the occurrence of any AEs, the use of concomitant medications, and study compliance. During these contacts, the investigator (or designee) will also review the subject's hemophilia A treatment (ie, investigator-prescribed on-demand therapy, or protocol-defined prophylaxis). The investigator (or designee) will also review information related to regimen escalation (criteria for, and subsequent action; see Section 15.3.3) with the

subject and will ensure that the criteria for regimen escalation had not been met. In addition, any change in a subject's prophylaxis regimen must be recorded; changes in the prophylaxis regimen should only occur in the event that escalation criteria are met. These study contacts, following study visits 3, 5, 7, and 9 are referred to as study contacts 4, 6, 8, and 10, respectively. (*Note*: Study contact information may be collected at an appropriately scheduled clinic visit, if the subject or the investigator prefers).

15.1.7. Study Visits 3, 5, 7, and 9 (Study Months 1, 3, 6, and 9) – Segment 1 - RP Cohort

Approximately 1, 3, 6, and 9 months after visit 2 (day 1), the subject will return to the clinic for study visits 3, 5, 7, and 9, respectively. If the study visit occurs outside of the recommended study visit window (ie, ±1 week) the reason must be documented in the subject's source document.

These visits require a 72-hour FVIII washout; thus, for subjects assigned to prophylaxis regimen B, an interruption in the every-other-day dosing frequency is required. The subject should not have exogenous FVIII:C at the time of the visit. Therefore, depending on the last FVIII dose before the beginning of the FVIII washout, an interval longer than 72 hours may be needed. If a subject sustains a bleed requiring treatment during the ≥72-hour FVIII washout, the necessary treatment should be administered using moroctocog alfa (AF-CC). Once the bleed has been adequately treated, the study visit must be rescheduled, and must be preceded by a new ≥72-hour FVIII washout.

The subject will be examined, measured for weight (kilograms), have vital signs taken (including temperature [Celsius], blood pressure, pulse, and respiration), and will have blood samples collected for:

- FVIII:C (central laboratory).
- FVIII inhibitor (central laboratory).
- anti-FVIII antibody (central laboratory).

The subject will turn in his used study drug vials, account for all study drug he has received, and turn in his Subject Diary. The investigator (or designee) will review the Subject Diary with the subject, and inquire about and record AEs, concomitant medications, or any study drug infusions for efficacy assessments. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. During the review, the investigator (or designee) will inquire about study compliance, review information related to less than expected therapeutic effect (LETE) (see Section 18.2 for criteria), and will review the subject's hemophilia A treatment (ie, protocol-defined prophylaxis). The investigator (or designee) will also review information related to regimen escalation (criteria for, and subsequent action; see Section 15.3.3) with the subject and will ensure that the criteria for regimen escalation had not been met. In addition, any change in a subject's prophylaxis regimen must be recorded;

changes in the prophylaxis regimen should only occur in the event that escalation criteria are met.

Additional study drug will be dispensed as needed, and a new Subject Diary will be issued.

15.1.8. Study Visit 11 (Study Month 12) - RP Cohort

Approximately 12 months after visit 2 (day 1), the subject will return to the clinic for study visit 11. If the study visit occurs outside of the recommended study visit window (ie, ±1 week), the reason must be documented in the subject's source document.

For RP subjects, visit 11 (month 12) marks the subject's completion of the first 12-month moroctocog alfa (AF-CC) treatment period (segment 1). Visit 11 (month 12) also marks the start of the second 12-month moroctocog alfa (AF-CC) treatment period (segment 2) for these subjects.

This visit requires a 72-hour FVIII washout; thus, for subjects assigned to prophylaxis regimen B, an interruption in the every-other-day dosing frequency is required. The subject should not have exogenous FVIII:C at the time of the visit. Therefore, depending on the last FVIII dose before the beginning of the FVIII washout, an interval longer than 72 hours may be needed. If a subject sustains a bleed requiring treatment during the ≥72-hour FVIII washout, the necessary treatment should be administered using moroctocog alfa (AF-CC). Once the bleed has been adequately treated, visit 11 must be rescheduled, and must be preceded by a new ≥72-hour FVIII washout.

The subject will be examined, measured for weight (kilograms) and height (centimeters), have vital signs taken (including temperature [Celsius], blood pressure, pulse, and respiration), and will have blood samples collected for:

- Hematology panel (see Protocol Definitions; central laboratory).
- Serum chemistry (see Protocol Definitions; central laboratory).
- FVIII:C (central laboratory).
- FVIII inhibitor (central laboratory).
- anti-FVIII antibody (central laboratory).
- anti-CHO antibody (central laboratory).
- anti-TN8.2 antibody (central laboratory).

The subjects will turn in their used study drug vials, account for all study drug received, and turn in their Subject Diary. The investigator (or designee) will review the Subject Diary with the subject, and inquire about and record AEs, concomitant medications, or any study drug infusions for efficacy assessments. In addition to the information obtained from those

sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. During the review, the investigator (or designee) will inquire about study compliance, review information related to LETE (see Section 18.2 for criteria), and will review the subject's hemophilia A treatment (ie, protocol-defined prophylaxis). The investigator (or designee) will also review information related to regimen escalation (criteria for, and subsequent action; see Section 15.3.3) with the subject and will ensure that the criteria for regimen escalation had not been met. In addition, any change, that may have occurred since the last study contact (study contact 10), in a subject's prophylaxis regimen must be recorded; changes in the prophylaxis regimen should only occur in the event that escalation criteria are met.

15.1.8.1. Start of Segment 2 - RP Cohort

RP subjects following 1 of the 2 protocol-defined regimens to which they were randomly assigned during the screening period (see Section 15.1.4), will now crossover to the other protocol-defined regimen.

The investigator (or designee) will review the assigned prophylaxis regimen, and information related to regimen escalation (criteria for, and subsequent action; see Section 15.3.3) with the subject. For regimen A, the interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days. For regimen B, the interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc). The instructions given to the subject will be documented in the subject's source document.

15.1.8.2. Study Drug Dispensed – Segment 2 - RP Cohort

Study drug (moroctocog alfa [AF-CC] and accessory supplies) will be dispensed to the subject. The investigator (or designee) will provide study drug for prophylaxis treatment (and for treatment of any bleeds) using the subject's weight recorded that day (see Study Reference Manual for guidelines of dose selection based on the subject's measured body weight). The investigator will review instructions for study drug reconstitution and administration with the subject. The subject will also receive a new Subject Diary and instructions to collect data on his home treatment (ie, infusions, bleeding events, response to infusions, etc). The instructions given to the subject will be documented in the subject's source document.

Subjects should now commence moroctocog alfa (AF-CC) prophylaxis according to the assigned regimen (A or B). RP subjects following 1 of the 2 protocol-defined regimens to which they were randomly assigned during the screening period (see Section 15.1.4), will now crossover to the other protocol-defined regimen. These subjects will follow the assigned prophylaxis regimen for a 12-month period. Only moroctocog alfa (AF-CC) study drug may be used for FVIII replacement therapy during this 12-month period (ie, through the remainder of the treatment phase of this study which ends at the Final Study Visit [visit 19, month 24]).

15.1.9. Subject Activities Between Successive Study Visits (Visit 11 Through Visit 19), and Activities of Study Contacts 12, 14, 16, and 18 - Segment 2 - RP Cohort

Subjects should adhere to their assigned moroctocog alfa (AF-CC) prophylaxis regimen. Subjects should also use study drug for the treatment of a bleed, if necessary. Subjects will document *all* their infusions (dose, time of infusion, and reason) and all bleeding episodes in the Subject Diary. In addition, subjects will record the efficacy of a study drug infusion given on-demand for treatment of a bleed using a 4-point ordinal scale of "Excellent," "Good," "Moderate," and "No Response" in the Subject Diary (please refer to Section 18.1.3 , for description of scale). Subjects will also document any AEs or use of concomitant medications in the Subject Diary. Subjects will save used study drug vials (used study drug vials are returned at each study visit). Approximately 6 weeks (±1 week) after study visits 11, 13, 15 and 17, respectively, the investigator (or designee) will contact the subject by telephone in order to collect information regarding the occurrence of any AEs, the use of concomitant medications, study compliance, and to ensure that the criteria for regimen escalation had not been met (see Section 15.3.3 for criteria and subsequent action). The investigator (or designee) will also review the subject's assigned prophylaxis regimen, and information related to regimen escalation with the subject during these contacts. Any change in a subject's prophylaxis regimen must be recorded; changes in the prophylaxis regimen should only occur in the event that escalation criteria are met. The study contacts, following visits 11, 13, 15 and 17, are referred to as study contacts 12, 14, 16, and 18, respectively. (*Note*: Study contact information may be collected at an appropriately scheduled clinic visit, if the subject or the investigator prefers).

15.1.10. Study Visits 13, 15, and 17 (Months 15, 18, and 21) - Segment 2 - RP Cohort

Approximately 15, 18, and 21 months after visit 2 (day 1), the subject will return to the clinic for study visits 13, 15, and 17, respectively. If the study visit occurs outside of the recommended study visit window (ie, ±1 week) the reason must be documented in the subject's source document.

These visits require a 72-hour FVIII washout; thus, for subjects assigned to prophylaxis regimen B, an interruption in the every-other-day dosing frequency is required. The subject should not have exogenous FVIII:C at the time of the visit. Therefore, depending on the last FVIII dose before the beginning of the FVIII washout, an interval longer than 72 hours may be needed. If a subject sustains a bleed requiring treatment during the ≥72-hour FVIII washout, the necessary treatment should be administered using moroctocog alfa (AF-CC). Once the bleed has been adequately treated, the study visit must be rescheduled, and must be preceded by a new ≥72-hour FVIII washout.

The subject will be examined, measured for weight (kilograms), have vital signs taken (including temperature [Celsius], blood pressure, pulse, and respiration), and will have blood samples collected for:

- FVIII:C (central laboratory).
- FVIII inhibitor (central laboratory).

- anti-FVIII antibody (central laboratory).

The subject will turn in his used study drug vials, account for all study drug he has received, and turn in his Subject Diary. The investigator (or designee) will review the Subject Diary with the subject, and inquire about and record AEs, concomitant medications, or any study drug infusions for efficacy assessments. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. During the review, the investigator (or designee) will inquire about study compliance, review information related to LETE (see Section 18.2 for criteria), and ensure that the criteria for regimen escalation had not been met (see Section 15.3.3 for criteria and subsequent action). The investigator (or designee) will also review the subject's assigned prophylaxis regimen, and information related to regimen escalation with the subject. Any change in a subject's prophylaxis regimen must be recorded; changes in the prophylaxis regimen should only occur in the event that escalation criteria are met.

Additional study drug will be dispensed as needed, and a new Subject Diary will be issued.

15.1.11. Final Study Visit (Visit 19, Month 24) - Segment 2 – RP Cohort

Approximately 24 months after visit 2 (day 1), RP subjects will return to the clinic for study visit 19 (month 24). If the study visit occurs outside of the recommended study visit window (ie, ±1 week), the reason must be documented in the subject's source document.

Visit 19 is the Final Study Visit; it coincides with the subject's completion of the second 12-month treatment period (segment 2), and marks the conclusion of the treatment phase of the study. At the conclusion of the treatment phase, subjects will resume their usual FVIII replacement therapy and will not use study drug.

This visit requires a 72-hour FVIII washout. The subject should not have exogenous FVIII:C at the time of the visit. Therefore, depending on the last FVIII dose before the beginning of the FVIII washout, an interval longer than 72 hours may be needed. If a subject sustains a bleed requiring treatment during the ≥72-hour FVIII washout, the necessary treatment should be administered using moroctocog alfa (AF-CC). Once the bleed has been adequately treated, visit 19 must be rescheduled, and must be preceded by a new ≥72-hour FVIII washout.

The subject will be examined, measured for weight (kilograms), have vital signs taken (including temperature [Celsius], blood pressure, pulse, and respiration), and will have blood samples collected for:

- CD4 cell count (central laboratory).
- Hematology panel (see Protocol Definitions; central laboratory).
- Serum chemistry (see Protocol Definitions; central laboratory).
- FVIII:C (central laboratory).

- FVIII inhibitor (central laboratory).
- anti-FVIII antibody (central laboratory).
- anti-CHO antibody (central laboratory).
- anti-TN8.2 antibody (central laboratory).

The subject will turn in all study drug vials (**used and unused**) and all unused diluent, account for all study drug he has received, and turn in his Subject Diary. The investigator (or designee) will review the Subject Diary with the subject, and inquire about and record AEs, concomitant medications, or any study drug infusions for efficacy assessments. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. During the review, the investigator (or designee) will also inquire about study compliance, and review information related to LETE (see Section 18.2 for criteria). Any change, that may have occurred since the last study contact (study contact 18), in a subject's prophylaxis regimen must be recorded; changes in the prophylaxis regimen should only occur in the event that escalation criteria are met (see Section 15.3.3 for criteria).

At the end of visit 19, the subject makes an appointment for a Final Study Contact (visit 20) that must occur at least 28 days (+10 days) after the Final Study Visit (visit 19).

15.1.12. Final Study Contact (Visit 20) – RP Cohort

At least 28 days (+10 days) after the Final Study Visit (visit 19), the investigator (or designee) will contact the subject by telephone in order to collect information regarding the occurrence of any AEs and the use of medications. In addition, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology. Completion of this telephone contact concludes the subject's participation in the study. (*Note*: Final study contact information may be collected at an appropriately scheduled clinic visit, if the subject or the investigator prefers).

15.2. Study Procedures for Pharmacokinetic Assessment

Please also refer to study Flowchart 2 in Section 8, for an overview of PK-related study procedures.

Some subjects will participate in a PK assessment. This is optional for subjects who are <16 years of age at the time of visit 2, who meet the additional PK eligibility criteria outlined in Section 12.1, and who enroll at a study site participating in the PK assessments. Consenting, PK-eligible subjects will be enrolled sequentially into the PK portion of the study. Thus, if applicable, subjects will begin activities for the PK assessment as described below (also refer to Section 8). Subjects must be in a nonbleeding state for this assessment.

The procedures for visit 2, detailed previously in Section 15.1.5 for RP subjects (ie, examination and collection of weight, vital signs, AEs, medications, and blood samples), should occur within 2 hours before study drug administration for PK assessment. In addition to the blood sample collections, subjects participating in the PK assessment will also have a blood sample collected, within 2 hours before study drug administration, for:

- Hematology panel (see Protocol Definitions; central laboratory).

An intravenous (IV) catheter (temporary) will be inserted in 1 arm for the purpose of collecting blood samples for the PK assessment. The catheter may be removed as needed. Unless the infusion is administered through a central catheter, blood samples must be drawn from the arm contralateral to the arm in which the infusion is administered. If an indwelling catheter (eg, Port-A-Cath®) is in place, it may be used for the infusion only. In no case may blood samples be obtained via the catheter through which the study drug was administered.

Heparin should not be used to flush indwelling catheters during PK study drug administration or PK sampling.

The subject will receive a single 50 ±5 IU/kg, rounded to the nearest vial, intravenous (IV) infusion of moroctocog alfa (AF-CC), given over no more than 2 minutes. The time of study drug reconstitution will be recorded. The dose, prepared from a single lot, will be calculated based on the subject's actual body weight as measured that day (see Study Reference Manual for specific guidelines for PK dose based on the subject's measured body weight). The start and stop time of the infusion will be recorded. The residual volume of dose remaining in the tubing, if any, should be immediately flushed into the subject as described in the Study Reference Manual. Time 0 is the time when the study drug infusion begins.

Blood samples for FVIII:C determinations, to be used for PK analysis, will be drawn at 0.5 hours (±3 minutes), 8 hours (±48 minutes), 24 hours (±1 hour), 28 hours (±1 hour), and 32 hours (±1 hour) after the start of the study drug infusion (refer to study flow chart in Section 8). The blood sample to be drawn at 28 hours is optional. The exact times of the actual PK sample blood draws will be recorded in the source documents. All samples collected during the PK assessment must be prepared and identified in the manner described in the Study Reference Manual.

Just before (ie, within approximately 20 minutes of) the 0.5 and 24-hour PK sample collection times, vital signs (including temperature [Celsius], blood pressure, pulse, and respiration) will be collected.

Any AEs and concomitant medications should be recorded throughout the PK assessment in the subject's source document.

If a subject experiences a bleeding episode during the PK assessment, the subject is to be stabilized with study drug. The samples collected should be processed as directed.

15.3. Procedures Following Early Termination or Other Potential Events

15.3.1. Early Termination

Subjects who are withdrawn or who voluntarily withdraw from the study subsequent to the screening period will have an accelerated Final Study Visit. At this accelerated visit, all data specified for the Final Study Visit (see Section 15.1.11 for RP subjects) will be collected. The accelerated Final Study Visit should occur, if possible, within 7 days after a subject's last infusion of study drug. A Final Study Contact should occur at least 28 days after the accelerated Final Study Visit, as described in Section 15.1.12 for RP subjects.

15.3.2. Factor VIII Inhibitor Development

For the purposes of this study, a subject will be considered to have developed a FVIII inhibitor after receiving study drug if he has an inhibitor titer of ≥0.6 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay; these criteria define a *confirmed* FVIII inhibitor for this study. In the event that a subject develops a confirmed FVIII inhibitor, the investigator will contact the Sponsor. The Sponsor and the investigator will determine whether the subject will remain in the study or be withdrawn from the study. Subjects withdrawn from the study will complete the procedures of the Final Study Visit and Final Study Contact as described in Section 15.1.11 and 15.1.12 for RP subjects. In addition to the Final Study Visit procedures described in Section 15.1.11 for RP subjects, subjects with a confirmed FVIII inhibitor should be rechallenged, unless medically contraindicated, with a single moroctocog alfa (AF-CC) infusion of 50 ±5 IU/kg at the Final Study Visit, following the 72-hour FVIII washout required for this visit (see Study Reference Manual for instructions regarding study drug reconstitution, administration, and data recording).

All blood sample collections required at the Final Study Visit (see Section 15.1.11 for RP subjects), as well as the physical examination and collections of weight and vital signs, will occur before the moroctocog alfa (AF-CC) infusion for rechallenge. A blood sample will be collected at 0.5 hours (±3 minutes) after administration of the rechallenge infusion and sent to the central laboratory for FVIII: C analysis. Vital signs (including temperature [Celsius], blood pressure, pulse, and respiration) will be collected just before (ie, within approximately 20 minutes of) the 0.5-hour sample collection. Three (3) to 5 days (inclusive of a 72-hour FVIII washout if possible) after the moroctocog alfa (AF-CC) infusion for rechallenge, blood samples will be collected for FVIII:C, FVIII inhibitor, and anti-FVIII antibody testing at the central laboratory. Samples collected for the rechallenge analysis must be prepared and identified according to instructions provided in the Study Reference Manual. After at least 28 days following the Final Study Visit, the subject will complete the procedures of the Final Study Contact, as described in Section 15.1.12 for RP subjects.

NOTE: *All tests for FVIII:C and/or FVIII inhibitor performed at the local laboratory should have duplicate samples from the same phlebotomy shipped to the central laboratory for analyses*. *In cases of FVIII inhibitor development, these duplicate analyses will continue until the Final Study Contact*. Thus, a duplicate sample of all samples tested at the local laboratory for FVIII inhibitor development should also be sent to the central laboratory for confirmatory testing. Aliquots of plasma samples will be stored in a -70°C or colder freezer. See Section 17.1 for additional discussion regarding FVIII inhibitor development.

15.3.3. Regimen Escalation

During prophylaxis (segments 1 and/or 2), a subject's prophylaxis regimen will be escalated if criteria are met. The criteria for regimen escalation will be the occurrence of either of the following:

a. 2 or more spontaneous (atraumatic) bleeds into major joints (such as elbow, ankle, or knee joint) and/or into other target joints over a 4-week (28-day) period in the absence of a confirmed FVIII inhibitor.

OR

b. 3 or more spontaneous (atraumatic) bleeds (consisting of joint bleeds and/or *significant* soft tissue/muscle or other site bleeds) over a 4-week (28-day) period in the absence of a confirmed FVIII inhibitor.

Significant spontaneous bleeds are defined as those that lead to a transient or persistent loss of function.[19] The loss of function may be transient and may evidence itself by a reluctance of the subject to utilize the affected body part in usual activities be it on account of pain, associated swelling or limitation in motion. This specification is intended to prevent regimen escalation based upon clinically insignificant or minor bleeding episodes (eg, ecchymoses, epistaxis).

The investigator will review these criteria with the subject/caregiver at the time study drug is first dispensed for protocol-assigned prophylaxis treatment, during telephone contacts, and at study visits. In the event that any of the criteria for regimen escalation are met, the subject/caregiver must contact the investigator as soon as possible, and the investigator will confirm that the subject has met criteria. The subject's treatment will be escalated to a higher intensity prophylaxis regimen comprised of the most intensive components of both regimens A and B: **45 ±5 IU/kg, administered every other day**. The investigator will provide the subject/caregiver with instructions for the new, more intense prophylaxis regimen. The subject will now follow the protocol-assigned regimen escalation, and arrangements for adequate study drug supplies will be made. Further prophylaxis regimen escalations will be prescribed by the investigator with each recurrence of escalation criteria. The subject will follow the assigned regimen(s) until the respective 12-month period of prophylaxis with study drug has been completed (segment 1 or 2); the 12-month period is inclusive of treatment time on all the prophylaxis regimens assigned during the respective study segment.

15.3.4. Unplanned, Required Surgery

As indicated, major surgery or orthopedic surgery planned to occur within the period following signing of the consent/assent form to the Final Study Contact (ie, during the course of this study) is an exclusion criterion for this study and only *required* minor surgery, or major/orthopedic surgical procedures which were unplanned at the time of signing the consent/assent form, may be allowed during the course of this study.

- Major surgical intervention- surgery involving open abdominal, intracranial and orthopedic procedures, including synovectomies and liver biopsies. Retroperitoneal,

thoracic, pharyngeal, retropharyngeal and invasive dental procedures involving complicated extractions are also considered major surgery. For other major surgeries contact the Sponsor's physician clinician.

- Minor surgical intervention- surgery that includes laparoscopic abdominal procedures such as laparoscopic cholecystectomies or laparoscopic appendectomies. Central venous catheter placement is also considered minor surgery. For other minor surgeries contact the Sponsor's physician clinician.

In the event that a minor surgery or an unplanned major or orthopedic surgery is required, the investigator will contact the Sponsor's clinician. The clinician will determine whether the subject will remain on the study or be withdrawn. If withdrawn, the subject should follow procedures required for all withdrawn subjects (see Section 15.3.1). Subjects who remain on the study will temporarily cease their current study drug treatment regimen (ie, investigator-prescribed on-demand therapy or protocol-assigned prophylaxis), and will instead receive study drug in bolus injection, as prescribed by the investigator, to achieve and maintain normal hemostasis through the surgical period. Administration of study drug by continuous infusion will not be allowed during surgery or during the post surgical wound healing period. Moroctocog alfa (AF-CC) study drug will be the only FVIII replacement product used during the surgical period.

The surgical period includes pre-, intra-, and postoperative periods; the surgical period begins with the administration of any preparatory study drug infusion for the surgery, and ends when the subject has recovered and is ready to resume his investigator-prescribed on-demand therapy or protocol-assigned prophylaxis with moroctocog alfa (AF-CC). The investigator should refer to the Study Reference Manual for dosing guidelines for surgery. After reviewing the dosing guidelines for surgery provided in the Study Reference Manual, the investigator will designate the appropriate study drug dose, and treatment duration for the surgical period, and should inform the Sponsor's clinician in advance. In addition to any AEs and concomitant medications (including any transfusions), the administration time and dose of all study drug infusions will be recorded during the surgical period. The subject's estimated blood loss and any nonpharmacological treatments will also be reported.

Samples for FVIII:C measurements will be collected within 15 to 30 minutes before the preoperative moroctocog alfa (AF-CC) infusion; approximately 30 minutes after completion of the preoperative infusion (and before the first surgical incision); just before any intraoperative infusion; approximately 30 minutes after completion of any intraoperative infusion; and daily during the in-hospital, postoperative period (ie, FVIII trough levels to be obtained before an infusion). The time of the collection of samples for FVIII:C measurement will be recorded as well as the time of infusion of all doses. *NOTE*: *During the surgical period, all tests for FVIII:C and/or FVIII inhibitor performed at the local laboratory should have duplicate samples from the same phlebotomy shipped to the central laboratory for analyses*.

Subjects will resume study drug treatment, as prescribed by their investigator (for on-demand therapy) or as defined by their protocol-assigned regimen (for prophylaxis), following the

surgical period. The surgical period will not count as time on the treatment periods of this study; as such, study visits may need to be rescheduled accordingly. For subjects whose surgical period exceeds 4 weeks, the Sponsor's clinician will be contacted to discuss the suitability of the subject's continued participation in the study.

15.4. Total Volume of Blood Collected

For each subject who participates in the study, the total volume of blood collected over the study period is detailed in the following table.

Study Participation	**Blood Volume (mL)**											
Study Visit/Contact ID	**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**Total**
RP Subject	20	13	9	9	9	9	18	9	9	9	20	134
RP Subject + PK	20	42[a]	9	9	9	9	18	9	9	9	20	163

Abbreviations: RP Subject = Routine Prophylaxis treatment during segment 1 followed by Routine Prophylaxis treatment during segment 2; RP Subject + PK = Routine Prophylaxis treatment and Pharmacokinetic Assessment during segment 1 followed by Routine Prophylaxis treatment during segment 2.

a. 42 mL total. Approximately 28 mL on day 1 of PK assessment and 14 mL on day 2 of PK Assessment (Visit 2).

16. TEST ARTICLE AND ADMINISTRATION

Study drug, moroctocog alfa (AF-CC), will be labeled according to local regulations. The Sponsor will not ship clinical supplies until a signed approval letter from the IRB/IEC has been received **and** a contractual agreement has been signed by the Sponsor and the study site.

16.1. Moroctocog alfa (AF-CC) Administration for Pharmacokinetic Assessment

A single IV infusion of study drug at a dosage of 50 ± 5 IU/kg rounded to the nearest complete vial, will be administered over no more than 2 minutes for PK assessment. The dose, prepared from a single lot, will be calculated based on the subject's actual body weight as measured on the day of study drug administration (see Study Reference Manual for specific guidelines for PK and recovery dose based on the subject's measured body weight). The time of study drug reconstitution will be recorded. The start and stop time of the infusion will be recorded.

16.2. Moroctocog alfa (AF-CC) Administration for Rechallenge

In addition to the Final Study Visit procedures described in Section 15.1.11 for RP subjects, subjects with a confirmed FVIII inhibitor should be rechallenged, unless medically contraindicated, with a single moroctocog alfa (AF-CC) study drug infusion of 50 ±5 IU/kg at the Final Study Visit, following the 72-hour FVIII washout required for this visit (see Study Reference Manual for instructions regarding study drug reconstitution, administration, and data recording).

16.3. Moroctocog alfa (AF-CC) Administration for Hemophilia A Treatment

In total, RP subjects will use moroctocog alfa (AF-CC) study drug, in an open-label manner, for a 24-month period. In segment 1, all subjects will use moroctocog alfa (AF-CC) according to 1 of 2 randomly assigned prophylactic regimens. Segment 1 for RP subjects

will be 12 months in duration. All subjects will then use moroctocog alfa (AF-CC) for prophylaxis during segment 2, as specified in Section 16.3.2. Prophylaxis subjects will cross over to the other protocol-assigned prophylaxis regimen during segment 2. During prophylaxis, subjects will also use moroctocog alfa (AF-CC), as needed, for the treatment of bleeds (ie, on-demand). See Section 16.3.1 and 16.3.2 for administration guidelines and recommendations for on-demand and prophylaxis dosing, respectively.

Moroctocog alfa (AF-CC) study drug will be administered as a bolus intravenous infusion. If an indwelling catheter (eg, Port-A-Cath®) is in place, it may be used for moroctocog alfa (AF-CC) study drug infusions, when appropriate.

16.3.1. Moroctocog alfa (AF-CC) Administration for On-Demand Treatment of Breakthrough Bleeds

All bleeding episodes will be treated (on-demand) at the discretion of the caregiver/investigator. Treatment guidelines, based on current recommendations for on-demand treatment with the licensed product Xyntha®, are provided in Appendix 1. A subject's specific circumstances should be considered when determining a specific dose. The dose will be prepared using the actual potency on the label of the study drug to be administered and the subject's most recent actual body weight as measured during the study.

16.3.2. Moroctocog alfa (AF-CC) Administration for Prophylaxis

Subjects will be advised to routinely administer the prophylaxis dose in the morning, in advance of their day's activities. The dose will be prepared using the actual potency on the label of the study drug to be administered and the subject's most recent actual body weight as measured during the study. See Study Reference Manual for guidelines of dose selection based on the subject's measured body weight.

Subjects will use moroctocog alfa (AF-CC) for prophylaxis according to the assigned regimen, A or B:

A: 45 ±5 IU/kg, administered twice per week

B: 25 ±5 IU/kg, administered every other day

For regimen A, the interval between prophylactic infusions should be 3 to 4 days, and should not exceed 4 days. For regimen B, the interval between prophylactic infusions should be approximately 48 hours (eg, an appropriate dosing schedule for Regimen B is as follows Monday, Wednesday, Friday, Sunday, Tuesday, Thursday, Saturday, Monday…etc).

The dosage and dosing frequency of these regimens are consistent with ReFacto and moroctocog alfa (AF-CC) clinical data, and with recommendations for prophylactic dosing in the literature.[3,12,19,20,21] (See Study Reference Manual for specific dose selections for regimens A and B based on the subject's measured body weight). A subject's treatment will be escalated to a more intensive prophylaxis regimen (45 ±5 IU/kg, administered every other day, initially, and if dose escalation criteria are met while on this more intensive regimen the subsequent regimen escalation will be investigator-designated) if criteria justifying regimen

escalation are met (see Section 15.3.3). Guidance for prophylaxis treatment is offered in the investigator's brochure.

16.4. Formulation, Packaging, and Labeling

The study drug, moroctocog alfa (AF-CC), is formulated as a sterile, nonpyrogenic, lyophilized powder preparation for IV injection. Study drug will be available in single-use vials containing the labeled amount of actual FVIII activity (IU). Each vial of study drug contains nominally 250 IU, 500 IU, 1000 IU, or 2000 IU per vial.

16.5. Storage and Stability

Moroctocog alfa (AF-CC) as packaged: Study drug should be stored under refrigeration at a temperature of 2 °C to 8 °C (36 °F to 46 °F). It is stable for up to 3 months at 25 °C. The product should not be returned to refrigeration once it has been stored at 25 °C. Freezing of diluent or study drug should be avoided to prevent damage. The study drug should be stored to protect from light. Study drug should not be used after the expiry date on the label.

Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the study drug must be quarantined and not used until the Sponsor provides documentation of permission to use the study drug.

Moroctocog alfa (AF-CC) after reconstitution: The reconstituted moroctocog alfa (AF-CC) solution does not contain a preservative and should be used within 3 hours after reconstitution. The reconstituted solution should not be refrigerated.

16.6. Preparation

The investigator (or designee) should follow specific reconstitution and administration procedures detailed in the Study Reference Manual for study drug preparation during the study. Caregivers should follow the specific reconstitution and administration procedures provided by the investigator during the study.

16.7. Drug Accountability

The US Food and Drug Administration (FDA) and other regulatory agencies require accounting for the disposition of all investigational drugs received by each study site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the drug was administered. The investigator is responsible for the accounting for all unused study drug and diluent and all used study drug. (*NOTE*: Used diluent syringes will not be returned for test article accountability due to the potential risk of blood contamination. Therefore, each returned study drug vial indirectly accounts for each diluent syringe used by the subject). Study drug may not be given to nonstudy patients under any circumstances.

Supplies will be shipped to the study site at appropriate intervals, depending on subject accrual. The site will use the Dispensing and Inventory Record provided by the Sponsor to document study drug disposition. This record must be maintained either in the pharmacy or in another area approved by the Sponsor's monitor. Drug accountability will be reviewed by a monitor during routine monitoring visits and interim drug returns will be performed as needed. Each time a dose is prepared (for the PK assessment) or vials are dispensed for a subject, the following information must be recorded: the subject's study number, the number of vials dispensed, the date dispensed, the number of the lot from which the dose was prepared, and the initials of the person preparing the dose. The doses prepared for subjects at the study site for the PK assessment will be documented on a worksheet to be kept at the study site.

The investigator (or designee) will instruct each subject or parent/legal acceptable representative to whom drug is dispensed, to return used study drug vials at each study visit, and to return all study drug vials (used and unused) and all unused diluent syringes at the Final Study Visit.

At the termination of the study, a final drug accountability review and reconciliation must be completed and any discrepancies must be investigated and their resolution documented.

All used and unused study drug vials and all unused diluent syringes may be returned to the Sponsor. Alternatively, all used and unused study drug vials and unused diluent syringes may be destroyed at site, per the local requirements, after the site and Sponsor have performed drug accountability.

16.8. Subject Compliance

The investigator or the Sponsor's clinician may withdraw a subject if he or she decides that a subject's noncompliance is damaging to the study or the subject's best interests. No predetermined percentage of missing vials or data will define a subject as "noncompliant." The final study report will document and report the impact of extensive noncompliance on study conclusions. Vial counts, Subject Diaries, and verbal information will be used to determine subject compliance. Subjects who are withdrawn for noncompliance or any other reason will have an accelerated Final Study Visit. All data specified in Section 15.1.11 for RP subjects will be collected. The Final Study Visit for subjects who are withdrawn or withdraw, if possible, should occur within 7 days after their last infusion of study drug. A Final Study Contact should also occur at least 28 days after the Final Study Visit, as described in Section 15.1.12 for RP subjects.

17. SAFETY

The Sponsor may stop the study for any reason; the reason for study cessation will be documented.

This study will use an External Data Monitoring Committee (E-DMC). The E-DMC will periodically review data from the study to ensure subject safety according to the Charter. The E-DMC includes physicians experienced in the management of hemophilia who are not investigators in the study, including at least one who is also experienced in the treatment of

children with hemophilia. The E-DMC also includes a statistician experienced in the review of clinical trials. The schedule of the E-DMC review will be determined by the E-DMC with review intervals of approximately every 6 months. Additional meetings may be held at the discretion of the E-DMC or upon request by the Sponsor. The E-DMC members will be provided demography data, safety data inclusive of inhibitor formation data, laboratory data including factor VIII inhibitor assay results, and relevant efficacy data, in advance of the meetings. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

Safety variables in the study are listed in Section 22.1. The following describes the collection of safety data for 1 of these variables in greater detail.

17.1. Factor VIII Inhibitors

For the purposes of this study, a subject will be considered to have developed a FVIII inhibitor after receiving study drug if he has a titer of ≥0.6 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay; these criteria define a *confirmed* FVIII inhibitor for this study. Confirmed FVIII inhibitors will be further categorized as low titer or high titer. Low-titer inhibitors are defined as those inhibitors with titers between 0.6 to <5 BU/mL in a sample assayed at the central laboratory using the Nijmegen assay. High-titer inhibitors are defined as those inhibitors with a titer of ≥5 BU/mL assayed at the central laboratory using the Nijmegen assay. If a FVIII inhibitor resolves (by the Nijmegen assay at the central laboratory) at or before a subject's final assessment it will be further classified as transient.

Investigators must report all FVIII inhibitors in the same expedited manner as outlined for serious adverse events (SAEs; see Section 26.13.1). The Sponsor will report all confirmed FVIII inhibitors to regulatory authorities in the same manner as unexpected, related SAEs.

If a subject has a local laboratory assay that is considered positive for FVIII inhibitor by the investigator in spite of a negative central laboratory result, or the investigator considers the subject to have developed a FVIII inhibitor for other reasons based on clinical grounds (although all suspected FVIII inhibitors should also be supported by laboratory evidence; the investigator may perform additional laboratory tests for FVIII inhibitor as appropriate in his medical judgment), then the finding will be reported in the manner of and recorded as an SAE. Reports or assays received by the Sponsor, which are suggestive of a FVIII inhibitor, will be confirmed by the study's central laboratory before communication with regulatory authorities. In addition, for purposes of the analyses of this study, any FVIII inhibitor report not confirmed by the central laboratory (ie, sample did not have a titer of ≥0.6 BU/mL by the Nijmegen assay) will count as an SAE, but will not count as a FVIII inhibitor.

In the event that subjects develop a confirmed FVIII inhibitor, the investigator will contact the Sponsor. The Sponsor and the investigator will determine whether the subject will remain in the study or be withdrawn from the study. Subjects withdrawn from the study will complete the procedures of the Final Study Visit and Final Study Contact as described in Sections 15.1.11 and 15.1.12.

FVIII inhibitor development is a safety variable for this study. The incidence of FVIII inhibitor (ie, number of subjects with confirmed FVIII inhibitor development) will be reported.

17.2. Antibodies to Moroctocog alfa (AF-CC) Components

Patient serum samples will be collected and tested for the development of antibodies (both neutralizing and nonneutralizing) to moroctocog alfa (AF-CC), antibodies to CHO cell proteins derived from the cell line used in manufacture of moroctocog alfa (AF-CC), and antibodies to TN8.2, the affinity ligand used in purification of moroctocog alfa (AF-CC), using a validated ELISA.

18. EFFICACY

Specific efficacy variables for this study are listed in Section 22.2. The following describes the collection of some variables in detail.

18.1. Bleeding

The incidence of bleeding treated with FVIII replacement infusion(s) will be obtained from Subject Diaries and medical records. Where relevant, investigators (or designee) and monitors will ensure that there is consistency between the subject's medical record and/or Subject Diaries and the electronic case report forms (eCRFs). Such bleeding episodes will not be reported as AEs although the concomitant events associated with a bleed may be reported as an AE if appropriate (eg, a fracture). In the rare instance in which a bleeding episode also meets the criteria for a Serious Adverse Event, then the bleeding episode should be recorded as an AE. Only bleeding episodes that are considered serious and meet the SAE criteria should be listed on the AE case report form (CRF) page. If the bleeding episode qualifies as an SAE and is treated with study drug, then in addition to recording the bleed event on the AE eCRF, the bleed event should also be recorded on the Bleed log as there is information captured on the Bleed log that is not captured on the AE eCRF (eg, infusion information and response to study drug).

Both spontaneous bleeding episodes and traumatic bleeding episodes will be collected.

18.1.1. Types of Bleeding

For the purposes of this study, a bleed treated with study drug will be classified as either spontaneous or traumatic. The subject's diary or medical record will serve as the source document for bleeding episodes while on study. Investigators (or designee) and/or monitors will review the Subject Diary and medical records to assist in classification if necessary. The criteria for spontaneous and traumatic bleeds are described below.

Spontaneous Bleeding Episodes: Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is *no known* contributing factor such as definite trauma, antecedent "strenuous" activity, or "overuse". The determination of "strenuous" or "overuse" is at the discretion of the subject/caregiver/investigator. For example, if a subject were to wake up in the morning and note he was bleeding, a "spontaneous" bleed would be recorded. Target joints can have spontaneous bleeding episodes. Incidences of spontaneous

bleeding episodes define regimen escalation criteria during prophylaxis (see Section 15.3.3). For this purpose, spontaneous bleeds are further categorized as "*significant*". *Significant spontaneous bleeds* are defined as those that lead to a transient or persistent loss of function (see Section 15.3.3).

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

18.1.2. Location of Bleeds

For the purposes of this study, when subjects report a bleed treated with study drug, the location of the bleed should be recorded in the Subject Diary or medical record. Bleeds will be reported as occurring in 1 of the following locations: joint, muscle/soft tissue, or other. Each individual location of multiple-site bleeds will be reported. For joint bleeds, the specific joint will be reported. Parameters to identify joint bleeds include: pain on joint motion, limitation of motion, and visible swelling of joint.

18.1.3. Treatment of Bleeds

Typically, a bleed would be treated with an (on-demand) infusion of study drug. The specific treatment with study drug is at the discretion of the subject/caregiver/investigator but all doses and infusions of study drug will be recorded and reported.

The subject/caregiver/investigator will assess efficacy of study drug in treating a bleed by recording their assessments of efficacy through the use of the 4-point On-Demand Hemostasis Efficacy Rating Scale, described below. The 4-point response scale for on-demand treatment of a bleeding episode, is defined as follows:

- *Excellent*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.

- *Good*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.

  or,

  Definite pain relief and/or improvement in signs of bleeding starting after 8 hours following the infusion, with no additional infusion administered.

- *Moderate*: Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.

- *No Response*: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.

18.2. Less Than Expected Therapeutic Effect

All bleed and study drug infusion response data will be reported and analyzed (see Sections 22.2 and 22.5.3). The following text describes criteria defining a specific subset of these data that will also be reported and referred to "Less than expected therapeutic effect".

"Less than expected therapeutic effect" (LETE) is an efficacy variable of this study. LETE can occur in 3 specific circumstances. *All* types of LETE in aggregate and individually will be summarized as part of the efficacy information collected in this study. The following criteria define LETE.

Less than Expected Therapeutic Effect in the On-Demand Setting

LETE occurs in the on-demand setting if the subject records 2 successive "*No Response*" ratings after 2 successive study drug infusions, respectively. The infusions must have been administered within 24 hours (≤24 hours) of each other for treatment of the same bleeding event in the absence of confounding factors (described below). Therefore, LETE in the on-demand setting is based on the *response* to treatment of a bleed. The only confounding factors are as follows:

- Known presence or subsequent identification of a FVIII inhibitor.
- Known inadequate dose for the type and/or severity of bleed in the opinion of the investigator.
- Delay of greater than 4 hours between onset of bleed to infusion.
- Delay of greater than 24 hours before administration of a follow-up infusion.
- Known compromised study drug.
- Faulty administration of study drug.
- The subject has an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (eg, kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs).

For the purposes of this study, LETE in the on-demand setting will be summarized only from eCRFs. In the absence of identified confounding factors, monitors will query a site if 2 "*No Response*" ratings occur for 2 infusions which are given within 24 hours (≤24 hours) for the same bleed and LETE is not noted.

Less than Expected Therapeutic Effect in the Prophylaxis Setting

LETE occurs in the prophylaxis setting if there is a *spontaneous* bleed within 48 hours (≤ 48 hours) after a regularly scheduled prophylactic dose of study drug (which was not used to treat a bleed) in the absence of confounding factors. Therefore, LETE in the prophylaxis setting is the *occurrence* of a bleed. The only confounding factors are as follows:

- Known presence or subsequent identification of a FVIII inhibitor.
- Known inadequate prophylactic dose (ie, a dose less than that prescribed in subject's regimen).
- Known lack of adherence to the prescribed prophylaxis regimen.
- Bleed occurs in a target joint identified at the start of the study.
- Known compromised study drug.
- Faulty administration of study drug.
- The subject has an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (eg, kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs).

For the purposes of this study, LETE in the prophylaxis setting will be summarized only from eCRFs. In the absence of identified confounding factors, monitors will query a site if a spontaneous bleed within 48 hours (≤48 hours) of a prophylactic dose is recorded and LETE is not noted.

Less than Expected Therapeutic Effect (Low Recovery)

LETE can also be lower than expected recovery of FVIII in the opinion of the investigator following infusion of study drug in the absence of confounding factors. There are no planned recovery measurements outside the PK assessment that subjects may undergo at study start. During the course of this study, additional recovery measurements should be done only for assessment of a possible FVIII inhibitor. (*NOTE*: *During the treatment phase of the study, all tests for FVIII:C and/or FVIII inhibitor performed at the local laboratory should have duplicate samples from the same phlebotomy shipped to the central laboratory for analyses.)* Therefore, LETE (Low Recovery) can happen only if a recovery measurement is performed for clinical management of a subject and an inhibitor is not confirmed by the central laboratory. The only confounding factors for low recovery are as follows:

- Known presence or subsequent identification of a FVIII inhibitor.
- Known compromised study drug.
- Faulty administration of study drug.

19. PHARMACOKINETICS

19.1. Pharmacokinetic Analysis

FVIII:C will be analyzed by a central laboratory using a one-stage method (mnemonic CB-0052). Using a sample volume of 0.5 mL, the range of quantitation is 0.0100-0.8300 IU/mL. The upper limit of quantitation is slightly variable and depends upon the potency of the lot of calibrator. Stability of the samples has been shown for 3 freeze/thaw cycles. The coefficient of variations for precision of the calibrators in method development was less than 12.4% and the accuracy ranged between 89 and 115% of the expected amount.[22]

19.2. Pharmacokinetic Methods

The plasma FVIII activity (FVIII: C)-versus-time curves after administration of moroctocog alfa (AF-CC) will be characterized, using standard noncompartmental methods. FVIII:C at 0.5 hours after the start of study drug infusion ($C_{0.5\ hr}$) will be directly determined from the observed FVIII:C data. The terminal-phase disposition (elimination) rate constant (λ_z) will be estimated by regression of the terminal log-linear phase of the FVIII:C-versus-time curve. The terminal phase half-life ($t_{½}$) will be calculated as:

$$t_{½} = \ln 2 / \lambda_z$$

The areas under the FVIII:C-versus-time curves (AUC_t) and under the moment curve ($AUMC_t$) to last measurable activity (C_t) will be calculated using the trapezoidal method.

The area under the curve from 0 to infinity (AUC_∞) will be estimated as:

$$AUC_\infty = AUC_t + C_t / \lambda_z$$

Similarly, area under the moment curve from 0 to infinity ($AUMC_\infty$) will be estimated as:

$$AUMC_\infty = AUMC_t + [(C_t \times t) / \lambda_z] + [C_t / (\lambda_z)^2]$$

where, t is the time corresponding to the last measurable C_t.

The clearance (CL) will be calculated as:

$$CL = Dose/AUC_\infty$$

where, Dose = IU/kg of study drug administered.

The mean residence time (MRT) will be calculated as:

$$MRT = AUMC_\infty/AUC_\infty - TI/2$$

where, TI is the duration of infusion.

The volume of distribution at steady state (V_{ss}) will be calculated as:

$$V_{ss} = CL \times MRT.$$

Incremental recovery, is estimated using the following formula:

$$\text{Incremental recovery} = (C_{0.5\ hr}-C_0)/\text{Dose}$$

where,

C_0 = FVIII:C at time 0 (time before start of study drug infusion)

Dose = IU/kg of study drug administered.

The FVIII:C concentrations measured in this study may be combined with similar data from other studies to perform a population pharmacokinetic analysis using nonlinear mixed effects modeling (NONMEM).

20. PHARMACODYNAMICS

There are no planned pharmacodynamic evaluations.

21. LABORATORY DETERMINATIONS

Samples for required assays may be collected according to the procedures at the clinical trial study site. Samples taken for the central laboratory will be collected according to the schedule outlined in Section 7, 8 and 15 of this protocol. Sample collection, storage, and shipping information can be found in the Study Reference Manual supplied by the Sponsor. All clinically important abnormal laboratory test values identified after study drug administration will be followed until the condition stabilizes or until the end of the subject's participation in the study; any clinically important abnormal laboratory test value should be reported as an AE (or SAE if appropriate, see Sections 26.4 for reporting abnormal test findings as AEs and 26.13.1 for SAE criteria).

22. STATISTICS

Additional details of the analysis will be provided in the statistical analysis plan and/or the clinical study report. This may include details of missing, and if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

Safety and efficacy analyses for the OD cohort (on-demand therapy in segment 1, followed by the prescribed prophylaxis regimen in segment 2), will be done independently from the analyses for the RP cohort (randomized to follow prophylaxis regimens in both segments 1 and 2). PK characterization will be presented for all subjects (in either cohort) who provided PK data. In addition, select tables will be provided for all subjects in the study, regardless of cohort.

22.1. Safety Variables

- Incidence of AEs (by severity and by relationship to moroctocog alfa [AF-CC]).
- Incidence of confirmed FVIII inhibitor development.
- Incidence of development of antibodies to moroctocog alfa (AF-CC), CHO cell proteins, and TN8.2.

22.2. Efficacy Variables

- Annualized bleed rate (ABR).
- Number of moroctocog alfa (AF-CC) infusions per bleed.
- Response of bleed to moroctocog alfa (AF-CC) treatment (4-point scale of assessment, see Section 18.1.3).
- Time interval between bleed onset and prior moroctocog alfa (AF-CC) prophylaxis dose.
- Incidence of prophylaxis regimen escalation.
- Incidence of LETE (see Section 18.2).
- Consumption of moroctocog alfa (AF-CC).
- Compliance with assigned prophylaxis regimen.

Note: All subjective assessments will be provided by the caregiver or investigator.

22.3. Pharmacokinetic Variables

Primary variables:

- Terminal phase half-life ($t_{½}$).
- Clearance (CL).
- Incremental recovery.

Secondary PK variables:

- maximum concentration (FVIII:C at 0.5 hours after study drug infusion [$C_{0.5\ hr}$]).
- area under the curve to infinity (AUC_{∞}).
- area under the curve to last measurable concentration (AUC_t).

- steady-state volume of distribution (V_{ss}).
- mean residence time (MRT).

22.4. Subject Populations in the Analysis of Study Variables

22.4.1. Safety Variables

The safety analyses will be performed on the intent-to-treat (ITT) population. This population includes all subjects who sign the informed consent/assent form. Screen failures will not be included in the ITT population.

Analysis of the incidence of confirmed FVIII inhibitor development will be performed on the modified intent-to-treat (mITT) population. The mITT population consists of the subset of ITT subjects who received at least one dose of study drug.

22.4.2. Efficacy Variables

The efficacy analyses will be performed on the ITT population. This population includes all subjects who sign the informed consent/assent form. Screen failures will not be included in the ITT population. If a subject develops a confirmed FVIII inhibitor, his data will be included up to the time an inhibitor is determined to be present.

Efficacy analyses will also be performed on per-protocol populations. The statistical analysis plan will define per-protocol populations.

22.4.3. Pharmacokinetic Variables

All FVIII:C data will be reported. Individual pharmacokinetic analysis will be performed on all subjects for whom an adequate pharmacokinetic profile has been obtained.

22.5. Analysis of Study Variables

22.5.1. General

A discussion of the statistical methods by which the study hypotheses will be tested is provided below (see section 22.5.3). In addition, continuous variables for PK, efficacy, and safety analyses will be summarized by descriptive statistics. Categorical variables will be presented in frequency tables, with counts and percentages provided for each category. Missing data will be reported as such and no imputation will be made. Additional details of the study analyses will be provided in the statistical analysis plan.

22.5.2. Safety Variables

- The number (%) of subjects experiencing any AE will be reported. AEs will be summarized by body system and preferred term regardless of the relationship to moroctocog alfa (AF-CC). The incidence of AEs by severity and the incidence of AEs by the relatedness to moroctocog alfa (AF-CC) will also be summarized.
- The number (%) of subjects who develop a confirmed FVIII inhibitor will be reported, and categorized by inhibitor titer (ie, high or low).

22.5.3. Efficacy Variables

The annualized bleed rate (ABR) is the primary endpoint for testing the primary objective of the study, as well as for testing one of the secondary objectives of the study. ABRs will reflect the incidence of bleeds treated with FVIII replacement therapy. To avoid potential bias related to prior treatment, the first month of each protocol-defined prophylaxis treatment will serve as a washout period; ABR analyses will be performed with and without data from this washout period.

- For the primary objective of demonstrating that moroctocog alfa (AF-CC) prophylaxis reduces the ABR relative to on-demand therapy, the null hypothesis is that prophylactic treatment does not reduce the ABR relative to on-demand treatment. The alternative hypothesis is that prophylactic therapy does reduce the ABR.

- To test the hypothesis, an analysis of variance (ANOVA) will be conducted to compare the mean ABR between subjects in on-demand (segment 1) and prophylaxis (segment 2) treatment regimens. Only subjects who practice on-demand therapy with moroctocog alfa (AF-CC) during segment 1, before starting the protocol-defined moroctocog alfa (AF-CC) prophylaxis in segment 2, will be included in this analysis. The ANOVA will include factors for treatment regimen (study segment 1 or 2). The model will also include a blocking factor for subjects to ensure that the comparison of ABRs from each treatment regimen is performed on a within subject basis. The p-value for treatment regimen calculated in ABR of the ITT population will be used to test the null hypothesis; a p-value less than 0.05 will be considered significant.

- For the secondary objective of assessing the effect of a high- versus low-frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis, the null hypothesis is that there is a difference in mean ABR between the two prophylaxis regimens. The alternative hypothesis is that the two prophylaxis regimens are similar enough to be considered clinically equivalent. To test this hypothesis, the two protocol-defined prophylaxis regimens (a high- and a low-frequency dosing regimen) will be assessed in a crossover design. Only subjects who practice protocol-defined prophylaxis regimens in segment 1 and 2, respectively: the low- followed by the high-frequency dosing regimen (AB), or the high- followed by the low-frequency dosing regimen (BA) will be included in this analysis.

  The 90% 2-sided confidence interval (CI) for the mean difference in ABRs for the 2 prophylaxis regimens for ITT subjects will be constructed using the t distribution with n-1 degrees of freedom (n equals the number of subjects) to assess the equivalence of these 2 regimens. Equivalence will be demonstrated if the limits of the 90% CI fall wholly within the interval of (–4, 4) bleeds per year.

- ABR will also be presented as descriptive statistics (n, mean, SD, median, minimum, and maximum). ABRs will be summarized by bleed type (ie, spontaneous or traumatic), by bleed location (eg, joint, soft tissue/muscle), and by treatment period (ie, on-demand therapy or prophylaxis).

Additional efficacy variables:

- Number of study drug infusions used to treat a bleed will be summarized by bleed location and by dose (IU/kg) administered at the first infusion.
- The 4-point response (efficacy rating) for study drug-treated bleeds will be summarized, and any successive ratings of "*No Response*" will also be reported. The response to the first study drug infusion to treat a bleed will be tabulated by the total number of infusions needed for bleed resolution. First infusion responses will also be summarized by bleed location and by administered dose (IU/kg).
- The time between onset of a bleed and prior moroctocog alfa (AF-CC) routine prophylaxis infusion will be summarized by the following categories: ≤24, >24-48, >48-72, and >72 hours.
- The number (%) of subjects requiring prophylaxis regimen escalation during protocol-defined prophylaxis will be provided, and will be reported for each protocol-defined regimen.
- The number (%) of subjects reporting LETE (see Section 18.2) will be provided.
- For consumption of moroctocog alfa (AF-CC) per bleed, first infusion (IU/kg) and total dose (IU/kg) administered for the bleed will be summarized by bleed location (joint, soft tissue/muscle, multiple sites, and other). For consumption of moroctocog alfa (AF-CC) over time, the number of infusions, exposure days (ED), and dose (IU/kg and IU) per infusion will be summarized by reason of dosing (ie, on-demand or prophylaxis). Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided.
- Descriptive statistics will be provided to summarize subject compliance to their assigned prophylaxis regimen (dose [IU/kg] and dose frequency [number of infusions per week]). The number of infusions and the number of days (and weeks) on each assigned prophylaxis regimen will be presented for each subject.

22.5.4. Pharmacokinetic Variables

All PK variables (see Section 19.1, 22.3) will be summarized by descriptive statistics (number [n], mean, median, standard deviation [SD], standard error [SE], minimum and maximum, coefficient of variance [CV %], geometric mean, and 95% confidence intervals [CI]).

Graphic exploration of potential relationships between age, weight, body-surface area and body mass index and CL, Vss, $t_{½}$ and incremental recovery will be performed.

22.6. Interim Analysis and Report

An independent E-DMC will periodically review data from the study to ensure subject safety, with review intervals of approximately every 6 months. See Section 17 for more information regarding the E-DMC.

Prior to study completion, selected (safety, efficacy and/or PK) data from this study may be summarized and reported to regulatory authorities to support regulatory submissions or requests. The analyses for these summaries would be based on descriptive statistics.

Per discussions with the FDA, a final report for the OD cohort will be submitted comparing prophylaxis efficacy and safety versus on-demand therapy according to section 3.3 of the statistical analysis plan. Additionally, after approximately 38 evaluable RP subjects, who practiced prophylaxis for both segment 1 and segment 2, complete the study, a final report for the RP cohort will be submitted.

22.7. Statistical Power and Sample Size Considerations

The sample size of each cohort of the study is based on the statistical comparison of ABR between the first and second segments. Data from a previous ReFacto PUP study (Wyeth protocol 3082A1-301-WW) guided assumptions for the sample size estimates for objectives of this study. Additional information regarding each of these sample size estimates is provided below.

In the completed ReFacto 3082A1-301-WW PUP study, a reduction in the ABR was observed for subjects during their periods of prophylaxis (≥2 infusions per week) compared to their periods of on-demand therapy (reduction of 5.7 ± 6.9 bleeds per year, [11.85 to 6.15 bleeds per year], ABR decrease of 48%, N=39). Based upon this experience, a more conservative decrease in ABR of 40% (corresponding to a mean change of 4.75 bleeds per year) and a standard deviation of 7 were selected for use in power calculations for the comparison of ABRs in the on-demand versus prophylaxis setting for this study (see Section 22.4.2 for description of statistical analysis). A sample size of 18 OD subjects who practice on-demand therapy in segment 1, followed by prophylaxis in segment 2, provides 80% power to detect such a difference using a 2-sided alpha level of 0.05. Due to an expected attrition rate of up to 25%, approximately 24 OD subjects, who practice on-demand therapy during segment 1, were planned to be enrolled to ensure that 18 are evaluable for the comparison of ABRs in the on-demand versus prophylaxis setting. Because enrollment into the OD cohort has been closed, all available data will be analyzed.

For the RP cohort, the comparison of high- versus low-frequency prophylaxis dosing schedules, a subset analysis of data from the completed ReFacto PUP study (Wyeth protocol 3082A1-301-WW) revealed an ABR of 5.7 ±5.2 (N=26) in patients receiving a high-frequency prophylaxis regimen (3 infusions per week) compared to an ABR of 7.1 ±4.1 (N=13) in patients receiving a lower-frequency prophylaxis regimen (2 infusions per week). However, the treatment assignment was not randomized and prophylaxis regimens were not controlled in that study. To avoid selection bias and inter-patient variability affecting outcome, two protocol-defined prophylaxis regimens (a high- and a low-frequency dosing regimen) will be assessed in a crossover design. Assuming an intraclass correlation of 30% and a standard deviation of 6 bleeds per year based on this previous ReFacto PUP study, a within-subject standard deviation of 5 bleeds per year was used for sample size calculations for the comparison between the two protocol-defined prophylaxis regimens (A and B). Given this, 36 RP subjects are needed to provide 80% power to demonstrate equivalence of the two regimens (see Section 22.5.3 for description of statistical analysis).

Allowing for an attrition rate of 25%, approximately 48 RP subjects need to be enrolled to support this objective.

Based on a sample size re-estimation using data from this ongoing study, a difference of means of 1.3 bleeds per year between the two protocol-defined prophylaxis regimens (A and B) with a corresponding standard deviation of the difference of 6.5 was obtained requiring 38 subjects to provide 80% power to demonstrate equivalence of the two regimens. Allowing for an attrition rate of 30%, approximately 56 RP subjects need to be enrolled. The two prophylaxis regimens will be considered equivalent if the limits of the 2-sided 90% confidence interval for the difference in observed mean ABRs fall wholly within the interval defined by fewer than 4 bleeds per year.

23. SUBJECT IDENTIFICATION

Subjects will be numbered sequentially using the site number and their sequence number. Each subject in the study must be assigned a unique subject number and must keep that number throughout the study even if he transfers to another site. A subject who discontinues or is withdrawn (including screen failures), who reenrolls at a later time must be assigned a new subject number. A number must never be reassigned or reused for any reason. The investigator must maintain a log (see Section 12) linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the Sponsor.

24. TEST ARTICLE ACCOUNTABILITY, RECONCILIATION, AND RETURN

The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the Sponsor. All used and unused vials of study drug, and unused diluent must be returned by the subject/caregiver to the study site in the original containers. See Section 16.7 for further details.

25. RANDOMIZATION

Randomization for assignment of a treatment regimen(s) to be followed during this study will be performed during the screening period (interval of up to approximately 35 days, starting from the signing of the informed consent/assent and extending up to visit 2) after confirmation of study eligibility, and as specified in the Study Reference Manual. All subjects will practice prophylaxis for both segments of the study, will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences (AB or BA) defining the prophylaxis regimens to be practiced during segments 1 and 2, respectively: the low- followed by the high-frequency dosing regimen (AB), or the high- followed by the low-frequency dosing regimen (BA). Randomization will be stratified by hemophilia A severity: FVIII activity <1% or 1-2% (central laboratory screening result). Allocation of subjects to treatment assignments will be performed using an interactive voice or web-based response system. Dropouts after randomization will not be replaced.

26. ADVERSE EVENT REPORTING

For safety information on moroctocog alfa (AF-CC), refer to the most recent version of the Single Reference Safety Document, which for this study is the investigator's brochure.

26.1. Adverse Events

All observed or volunteered adverse events (AEs) regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

26.2. Reporting Period

For SAEs, and confirmed FVIII inhibitors, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

26.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.
- Drug abuse;
- Drug dependency;

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breast feeding;
- Medication Error;
- Occupational exposure.

26.3.1. Hemophilia Events

Hemophilia Events are certain AEs that are likely to occur due to the subject's hemophilia. For example, pain, swelling, or decreased range of motion due to a bleed may be an expected consequence of hemophilia (per Section 18.1, the bleeding episode itself is not reported as an AE, unless the bleeding episode meets the criteria for a Serious Adverse Event). Investigators will be asked to determine if an AE is expected because of the subject's hemophilia. Bleeding or bruising, not due to the subject's hemophilia, will be recorded as an AE, and not a hemophilia event. Hemophilia events that require hospitalization or meet other SAE criteria should be reported as SAEs.

26.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or

- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an adverse event by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

26.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following event must be considered medically important and has the same reporting requirements as SAEs:

- Confirmed FVIII inhibitor development. For the purposes of this study, a confirmed FVIII inhibitor is a Nijmegen assay result of ≥0.6 BU/mL at the central laboratory.

26.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section 26.13.1 Serious Adverse Event Reporting Requirements).

26.5.2. Potential Cases of Drug-Induced Liver Injury (Potential Hy's Law Cases)

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (x ULN) concurrent with a total bilirubin value ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 x ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller).
- Concurrent with
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 x ULN **or** if the value reaches ≥3 x ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery,

blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

26.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

26.7. Severity Assessment

If required on the adverse event CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

26.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section 26.13 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and

CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

26.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

3. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or (pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

Additional information about pregnancy outcomes that are reported as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the Form that the subject was given this letter to provide to his partner.

26.10. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

26.11. Withdrawal Due to Adverse Events (See Also Section 27 - Subject Discontinuation or Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

26.12. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

26.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

26.13.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, or confirmed FVIII Inhibitor, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the AE CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and vaccines and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

26.13.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

26.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

26.14. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

27. SUBJECT DISCONTINUATION OR WITHDRAWAL

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, subject request, protocol violation, subject noncompliance, study termination by the Sponsor, and if the investigator believes it is not in the subject's best interest to continue participating in the study. Discontinued or withdrawn subjects will not be replaced. Subjects will be withdrawn from the study by the Sponsor if screening laboratory results performed at the central laboratory indicate the subject was not eligible for the study. This will occur even if the local laboratory results indicate the subject is eligible. Subjects will be withdrawn from the study if a FVIII inhibitor, confirmed by the central laboratory, develops during the study. Except for screen failures, when a subject discontinues or is withdrawn, the investigator will directly notify the Sponsor and, when possible, will perform the procedures indicated for the Final Study Visit and Final Study Contact, see Section 15.1.11 and 15.1.12. For subjects who are withdrawn due to confirmed FVIII inhibitor development, see Section 15.3.2 for procedures.

27.1. Reporting of Safety Issue and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) that the investigator becomes aware of.

28. STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or part of the study at any time for any reason.

If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all test article, test article containers, and other study materials to the Sponsor. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. For investigational new drug (IND) studies, the investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

29. ETHICS

29.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/ethics committee (EC). All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

29.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

29.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each

subject's numerical code to his actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject or his legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent/assent document.

30. PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the

IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved by the Sponsor and the investigator.

31. QUALITY CONTROL AND ASSURANCE

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, Sponsor personnel and the investigator review the protocol, the investigator's brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent/assent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study by visiting the study site and by contacting the study site by telephone, fax, mail, or e-mail. During these study site visits, information recorded in the eCRFs is verified against source documents.

32. DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

32.1. Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. The subject's medical record is considered to be the source document for the study unless it is information collected specifically for this study and recorded directly in the subject's Subject Diary or in eCRFs. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study. Remote data capture will be used to record and transmit data electronically to the Sponsor.

Central laboratory data will be transmitted directly to the Sponsor. There may be no prior written or electronic record for these data.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation. An updated Form 1572 will be filed with the Sponsor for any changes in the study personnel reported in the current Form 1572.

32.2. Sponsor

The eCRF data are stored in a database and processed electronically. The Sponsor clinician reviews the data for safety information. The data are reviewed for legibility, completeness, and logical consistency. Automated validation programs identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification are forwarded to the investigative site for resolution. By participating in this study, the investigator (and their designated staff) accepts responsibility for resolving questions about study data to the best of their ability.

33. SUBJECT INJURY

In general, subject to specific provisions in the Clinical Study Agreement (CSA), if a subject is injured as a direct result of a test article, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the Sponsor shall comply with such laws or regulations. Where applicable, the Sponsor has taken specific national insurance.

34. PRESTUDY DOCUMENTATION

The investigator must provide the Sponsor with the following documents BEFORE enrolling any subjects:

- Completed and signed Form 1572.
- All applicable country-specific regulatory forms.
- Current (within 2 years) signed and dated curricula vitae for the investigator, subinvestigators, and other individuals having significant investigator responsibility who are listed on the form 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC members and their qualifications, and a description of the committee's working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Fully executed CSA.
- Where applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form (Form 1572). The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The Sponsor must be notified if normal values or units of measurement change.

35. RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of (i) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

36. SAMPLE RETENTION

Samples may be used for purposes related to this research, such as repeat testing is needed. The samples will be stored for up to 15 years after the end of the study and then destroyed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

37. CLINICAL STUDY REPORT

As appropriate, an investigator will be selected to act as the signatory for the clinical study report. This investigator will be selected based on clinical experience and understanding of the product.

38. PUBLICATION OF STUDY RESULTS

38.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

38.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical

Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

39. REFERENCES

1. Eaton DL, Wood WI, Eaton D, et al. Construction and characterization of an active factor VIII variant lacking the central one-third of the molecule. Biochemistry. 1986; 25: 8343 8347.

2. Toole JJ, Pittman DD, Orr EC, Murtha P, Wasley LC, Kaufman RJ. A large region (~95 kDa) of human factor VIII is dispensable for in vitro procoagulant activity. Proc Natl Acad Sci USA. 1986; 83: 5939-5942.

3. Wyeth investigator's brochure: ReFacto (moroctocog alfa), [WAY-167652].

4. Sandberg H, Almstedt A, Brandt J, et al. Structural and functional characterization of B domain deleted recombinant factor VIII. Semin Hematol. 2001; 38(2 Suppl 4): 4-12.

5. Brinkhous K, Sandberg H, Widlund L, et al. Preclinical pharmacology of albumin-free B domain deleted recombinant factor VIII. Semin Thromb Hemost. 2002; 28(3): 269-272.

6. Kelley BD, Booth J, Tannatt M, et al. Isolation of a peptide ligand for affinity purification of factor VIII using phage display. J Chromatogr A. 2004; 1038: 121-130.

7. Kelley BD, Tannatt M, Magnusson R, Hagelberg S, Booth J. Development and validation of an affinity chromatography step using a peptide ligand for cGMP production of factor VIII. Biotechnol Bioeng. 2004; 87: 400-412.

8. Pfizer Inc. Periodic Safety Update Report #20 for moroctocog alfa AF-CC, 27 August 2013 to 26 August 2014. Collegeville, PA. 15-Oct-2014.

9. Kessler CM, Gill JC, White GC, et al. B-domain deleted recombinant factor VIII preparations are bioequivalent to a monoclonal antibody purified plasma-derived factor VIII concentrate: a randomized, three-way crossover study. Haemophilia. 2005; 11: 84 91.

10. Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. J Intern Med. 1994; 236: 391 399.

11. Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment on children with severe haemophilia. Br J Haematol. 1996; 92: 973-978.

12. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. N Engl J Med. 2007; 357;6: 535 544.

13. Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992; 232: 25-32.

14. Shapiro AD, Donfield SM, Lynn HS, et al. Defining the impact of hemophilia: the academic achievement in children with hemophilia study. Pediatrics. 2001; 108: 105 110.

15. Srivastava A, Giagrande P, Poon MC, McGraw A, Weideln J. WFH Guidelines for the management of hemophilia. Available at: http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf

16. Berntorp E, Bouyjenkov V, Brettler D. Modern treatment of haemophilia. *Bull World Health Organ*. 1995; 73:691-701.

17. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AKC. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B (Review). The Cochrane Library. 2011, Issue 9. http://www.thecochranelibrary.com

18. Aronstam A, McLellan DS, Wassef M, Mbatha PS. Effect of height and weight on the in vivo recovery of transfused factor VIII. J Clin Pathol 1982; 35:289 - 291.

19. Feldman BM, Pai M, Rivard GE, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian hemophilia primary prophylaxis study. J. Thromb Haemost. 2006; 4: 1228-1236.

20. Medical and Scientific Advisory Council (MASAC). MASAC Recommendation #117: Recommendation concerning prophylaxis (prophylactic administration of clotting factor concentrate to prevent bleeding). May 2001 [cited 2006 April]; Available from: http://www.hemophilia.org.

21. Lofqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients - a long-term follow-up. J Intern Med. 1997; 241: 395-400.

22. Gooding A. ReFacto AF: Bioanalytical analysis in human plasma and human serum in support of Wyeth Protocol 3082B2-311-WW. Wyeth Research. RPT 74903. 2008).

40. APPENDICES

Appendix 1. Guidelines for On-Demand Treatment With Moroctocog alfa (AF-CC)

Guidelines for On-Demand Treatment With Moroctocog alfa (AF-CC), Based on Current Recommendations for On-Demand Therapy With the Licensed Product Xyntha®

Type of Bleeding Episode	**FVIII Level Required** (IU/dL or % of normal)	**Frequency of Doses (hours)/** Duration of Therapy (days)
Minor Early hemarthrosis, minor muscle or oral bleeds.	20-40	Repeat infusion every 12 to 24 hours as necessary until resolved for at least 1 day, depending upon the severity of the bleeding episode.
Moderate Bleeding into muscles. Mild head trauma. Bleeding into the oral cavity.	30-60	Repeat infusion every 12 to 24 hours for 3 to 4 days, or until adequate local hemostasis is achieved.
Major Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding. Fractures.	60-100	Repeat infusion every 8 to 24 hours until bleeding is resolved