

**Statistical Analysis Plan (SAP)**

**PROTOCOL 3082B2-313-WW**

**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**

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**Prepared by:** PPD [REDACTED]

**Modified by:** PPD [REDACTED], PPD [REDACTED], PPD [REDACTED]

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## OVERVIEW AND SUMMARY OF CHANGES TO PLANNED ANALYSES FOR THE FINAL CSR

### OVERVIEW

Version 5.0 of this statistical analysis plan (SAP) incorporates updates resulting from Protocol Amendments 5 (A5) through the current Amendment 10 (A10) (including a 2017 Protocol Administrative Change Letter). Text taken directly from the protocol appears in *italics*. Major updates include a shortened duration for Segment 1 for the on-demand (OD) cohort to 6 months duration from 12 months (Amendment 7 [A7]), removal of incremental recovery assessment at visit 7 and consequently the analysis of k-value (incremental) recovery over time (A7), and an increase in the upper age for the inclusion criteria from less than 6 years to less than 16 years (A10). The original planned sample sizes and the sample size re-estimation results appear in A10 and are reflected in *italics*.

A summary of changes to planned analyses for the Final clinical study report (CSR) is described in the Summary of Changes Section which immediately follows below. These changes do not appear in the body of the SAP 5.0, as they were determined after the implementation of Protocol Amendment 10. These changes include those that were implemented for either of the 2 Interim CSRs (dated 07 November 2013 and 11 April 2016), which will also be applicable for the final study report. In addition, clarification is provided regarding additional changes to analyses planned for the final study report, as a result of recent communications with the Food and Drug Administration (FDA), dated 28 January 2016 and 27 January 2017.

Two additional appendices have been added to support this SAP:

[Appendix B](#) provides a summary of changes in the conduct of the study, as per the ten protocol amendments and is included for background information.

[Appendix C](#) provides for reference the Summary of Changes to Planned Analyses implemented for both Interim clinical study reports (from CSR Section 9.8.2 in each report). Some of these changes are also relevant to the Final CSR and are referred to in the Summary of Changes Section which immediately follows below.

### SUMMARY OF CHANGES TO PLANNED ANALYSES FOR THE FINAL CSR

1. The first interim CSR presented safety, efficacy and baseline data for subjects at Site PP separately from data for subjects at other sites, due to serious breaches of GCP compliance by the investigator and study staff at Site PP pertaining to data integrity. As implemented in the second Interim CSR, in the Final CSR, safety, efficacy and baseline summary data will be presented excluding Site PP with the exception of protocol deviations, recovery/pharmacokinetic data, and inhibitor incidence, which include all sites.

2. As determined for the second Interim CSR for the study's primary endpoint analysis in the OD cohort only, a linear mixed-effects model with unstructured variance-covariance matrix provides a more robust model for the comparison of annualized bleeding rate (ABR) given the nature of the study data, while still controlling for the same factors as specified in the SAP ANOVA model. This model allows for the inclusion of all intent-to-treat (ITT) subjects with ABR data and also takes into account the correlation between the 2 within-subject measurements of ABR at each segment. Because all enrolled subjects had severe (<1%) hemophilia at baseline (ie, just one level of the factor was present and therefore not informative), hemophilia severity is not included as a factor in the model as planned. In the Final CSR, the estimates of the ABR for each regimen (segment) and for the difference as well as the corresponding two-sided 95% confidence intervals (CIs) will be reported using the linear mixed-effects model described above rather than as described in SAP [Section 3.3.1.2](#).
3. As implemented in the second Interim CSR as per FDA Written Response dated 28 January 2016 (CRMTS #10042, BL 125264/1540), supportive analyses will also be performed for the ITT population for the Final CSR. A paired t-test will be used to test the within-subject change in ABR for the subjects who will be evaluated with both OD and routine prophylaxis (RP) dosing during the study. In addition, a one-sided 95% CI for the ratio of the arithmetic means for ABR during RP over the ABR during OD treatment will be calculated. Ogawa's parametric confidence interval for the ratio of two paired means<sup>1</sup> assumes the ABR is bivariate normally distributed for RP and OD treatments and will be calculated using R statistical software (version 3.2.3). If the one-sided 95% upper confidence bound is  $\leq 0.5$ , then this will confirm that the ABR during RP treatment was at least 50% lower than that observed during OD treatment.
4. In accordance with FDA correspondence dated 27 January 2017 (IND 10040/246) stating that a non-inferiority clinical margin M2 of 3 bleeds or fewer per year may be adequate, equivalence between the 2 RP regimens will be declared if the limits of the 90% two-sided confidence interval fall wholly within the interval of (-3, 3) bleeds per year, rather than protocol/SAP specified (-4, 4) (SAP [Sections 1.4.2](#) and [3.3.2.2](#)).
5. Per FDA correspondence dated 27 January 2017 (IND 10040/246), incidence rate of inhibitor development will be additionally described by number of prior exposure days at study entry. For this assessment, based on the risk of the inhibitor development according to the number of exposure days, minimally treated patients (MTPs) will include those who had accrued 20 to <50 exposure days to any FVIII replacement product prior to enrollment into Protocol B1831001. Note: Previously treated patients (PTPs) are patients who have received FVIII replacement therapy. Prior to Protocol Amendment 4, PTPs were defined for the purposes of the study as those who had accrued at least 50 exposure days (EDs) to any FVIII replacement product prior to study enrollment. To improve enrollment, in Protocol Amendment 4 (dated 15 September 2009) this number was decreased to at least 20 prior EDs for inclusion in the study. SAP [Section 3.4.2.1](#) refers to Inhibitor Development.

6. For the exploratory analysis in RP cohort subjects, to test for the presence of treatment sequence, period and carryover effects, SAP [Section 3.3.2.2](#) states that the ANOVA model will be fitted with terms for treatment sequence (AB or BA), treatment frequency (A or B), period (study segment 1 or 2), carryover and subject nested in treatment sequence. However, this model is overparameterized. Instead, the more appropriate mixed-effect model ABR=sequence period treatment, with subject as a random effect will be used to evaluate the treatment effect. Contrasts will be constructed to test if the carryover effect for each sequence is the same, and if the same, if that carryover effect is equal to zero.
7. Protocol Amendment 10 has text in section 15.2 (also appears in SAP [Section 2.2](#)) which states that the pharmacokinetic dose will be prepared from a single lot. However, multiple lots were used over the course of this study.
8. Protocol Amendment 10 has text in sections 22 and 22.6 (also appears in SAP [Section 3](#)) which indicates that both efficacy and safety will be reported separately for the 2 cohorts (OD and RP). However, only efficacy data is presented separately, and safety data is presented for all subjects combined.

## 1. DESCRIPTION OF THE STUDY

### 1.1. Introduction

*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 ( $\leq 2\%$  of normal), spontaneous bleeding episodes may occur. Infusing patients with a concentrated formulation of the missing FVIII protein can control the bleeding. ReFacto (moroctocog alfa) is a commercially available B-Domain Deleted Recombinant FVIII. A modified manufacturing process has been developed to produce ReFacto with an albumin free cell culture (AF-CC) that eliminates the use of all human or animal-derived proteins and therefore enhances the overall viral safety for patients. This product is referred to as moroctocog alfa (AF-CC) and this nomenclature will be used through this statistical analysis plan.*

*While prophylaxis therapy with 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) prophylaxis to reduce bleed rates relative to moroctocog alfa (AF-CC) on-demand therapy, and will compare the clinical outcomes of a high- versus a low-frequency 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. Therefore, this study will also characterize the pharmacokinetics (PK) of moroctocog alfa (AF-CC) in children younger than 16 years of age.*

### 1.2. Objectives of the Study

*Primary Objective: To demonstrate that moroctocog alfa (AF-CC) prophylaxis reduces annualized bleeding rates (ABRs) relative to on-demand therapy.*

*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 characterize the PK of moroctocog alfa (AF-CC) in children younger than 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”.*

### 1.3. Design

*This 2-segment study will be conducted as a multicenter, open-label, stratified, randomized evaluation of moroctocog alfa (AF-CC) in approximately 72 pediatric subjects (<16 years of age) with moderately severe to severe hemophilia A.*



*For segment 1, all subjects will use moroctocog alfa (AF-CC) in 1 of 2 treatment settings: on-demand (OD) therapy for 6 months (OD cohort) or prophylaxis for a 12-month period (RP cohort). Subjects who practice prophylaxis will be randomized to one of two regimens. The two prophylaxis treatment regimens, each delivering approximately 90 IU/kg/week, but differing in dosing schedule, will be:*

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

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

*For segment 2, all subjects will use moroctocog alfa (AF-CC) for a 12-month period of prophylaxis treatment. Subjects who practiced on-demand therapy during segment 1 will practice prophylactic regimen B, defined above. Subjects who practiced prophylaxis during segment 1 will crossover to the other prophylactic treatment. A subset of subjects will participate in assessments for moroctocog alfa (AF-CC) PK characterization. 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) with blood sampled for FVIII activity measurements before and at 0.5, 8, 24, 28 (optional), and 32 hours after the infusion.*

**Subjects on on-demand therapy for segment 1:** *Subjects who practice on-demand therapy at the time of the screening visit may continue to practice on-demand therapy with moroctocog alfa (AF-CC) in segment 1 (6-month period). These subjects will then practice prophylaxis regimen B for their 12-month period (segment 2) of treatment.*

**Subjects on prophylaxis treatment for segment 1:** *Subjects who are not assigned to the on-demand cohort in segment 1 will practice prophylaxis with moroctocog alfa (AF-CC) for both segments of the study and will be randomized in a 1:1 ratio to 1 of 2 treatment sequences (AB or BA) for a crossover evaluation of moroctocog alfa (AF-CC). Thus, subjects who practiced prophylaxis regimen A during segment 1 will crossover to prophylactic regimen B in segment 2 and vice versa. Randomization of these subjects will also be stratified by hemophilia A severity: FVIII activity <1% or 1-2% (central laboratory screening result).*

*During prophylaxis (segment 1 and/or segment 2), a subject's treatment will be escalated to a higher intensity 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. 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.*

### **1.3.1. Description of Subject Population**

*Subjects will be selected from approximately 40 sites. A legal acceptable representative of the subject must participate in the informed consent/assent process and sign and date the informed consent/assent form before any study procedures or screening activities are performed. The following key conditions are required for enrollment in this study. (See protocol for a complete listing of inclusion and exclusion criteria).*

**Main Inclusion Criteria:**

- *Male patients with moderately severe to severe hemophilia A (FVIII:C  $\leq$ 2%) by **both** the local laboratory and the central laboratory at screening.*
- *A negative FVIII inhibitor by **both** the local laboratory and the central laboratory at screening.*
- *Age <16 years at time of screening visit (study visit 1).*
- *Previous experience of FVIII therapy ( $\geq$ 20 exposure days to any FVIII replacement product). [Protocol Amendment 4 changed this requirement from  $\geq$ 50 exposure days to  $\geq$ 20 exposure days].*

**Additional Inclusion Criteria for subjects participating in the PK assessments:**

- *Male patients with FVIII:C  $\leq$ 1% confirmed by the central laboratory at screening.*
- *Age < 16 years at time of PK assessment (study visit 2).*
- *The subject's size is sufficient to permit PK-related phlebotomy.*
- *The subject is able to comply with the PK-related procedures and required washouts.*

**Main Exclusion Criterion:**

- *A history of FVIII inhibitor (clinical or laboratory-based assessment).*

**1.3.2. Method of Treatment Assignment**

*Allocation of subjects to treatment assignments will be performed using an interactive voice or web-based response system. Assignment to treatment groups is a function of the following variables: eligibility to undergo the PK assessments and investigator-assignment based on previous FVIII treatment. Based on the study design, two subject groups (ie, cohorts), labeled for their segment 1 treatment, are included in this study: 1) OD subjects and 2) RP subjects. Subjects undergoing PK assessments could be from either cohort. See SAP [Section 1.3.3](#).*

*At the beginning of segment 1, a subset of eligible subjects will participate in the PK assessment. Also at the beginning of segment 1, the investigator can choose to assign subjects to the OD subject group if the subject was previously practicing on-demand therapy, otherwise subjects will enter the RP subject group. Thus, the OD and RP subject groups are mutually exclusive, however, all of the PK subjects will also belong to either the OD or the RP subject group.*

### 1.3.3. Description of Subject Groups

**PK Subjects:** Eligible subjects from either subject group will participate in assessments to characterize the pharmacokinetics (PK) of moroctocog alfa (AF-CC).

**OD Subjects:** Subjects who practice on-demand therapy at the time of the screening visit may continue to practice on-demand therapy with moroctocog alfa (AF-CC) in segment 1. These subjects will then practice prophylaxis regimen B using moroctocog alfa (AF-CC) for their second segment (a 12-month period) of treatment. Dropouts after randomization will not be replaced.

**RP Subjects:** Subjects who are not assigned to the on-demand cohort in segment 1 will practice prophylaxis with moroctocog alfa (AF-CC) for both segments of the study and will be randomized in a 1:1 ratio to 1 of 2 treatment sequences (AB or BA). Subjects who practiced prophylaxis regimen A during segment 1 will crossover to prophylactic regimen B in segment 2 and vice versa. Dropouts after randomization will not be replaced.

### 1.3.4. Interim Analysis

*An independent data-monitoring committee (DMC) will periodically review data from the study to ensure subject safety, 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 SAP Section 3.3. 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. See SAP Section 3.2 for more detail on analysis populations.*

### 1.4. Sample Size Determination

Approximately 72 subjects will be enrolled in this study at approximately 40 sites. Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

The study was designed to meet three objectives: the primary objective of comparing ABRs while on on-demand therapy versus prophylaxis, and the secondary objectives of comparing ABRs while on high- versus low-frequency prophylaxis and PK characterization. Twenty-four (24) subjects (the OD subject group) will contribute to the comparison of ABR in the on-demand versus prophylaxis treatment settings; 48 subjects (the RP subject group) will contribute to the comparison of ABR in the 2 prophylaxis regimens (A and B). From the total of 72 subjects, a subset of approximately 23 PK subjects (meeting specific criteria) is needed for PK assessments for the objective of PK characterization. Additional information regarding the calculation of each of these sample size estimates is provided below.

#### **1.4.1. Sample Size Estimation Comparing the Annualized Bleed Rates of Prophylaxis to On-Demand Therapy**

The primary objective of this study will be to demonstrate a decrease in ABR while on prophylaxis treatment compared to while on on-demand therapy. *In a previous Wyeth moroctocog alfa pediatric study, protocol 3082A1-301-WW (study 301), a reduction in the ABR was observed for subjects during their periods of prophylaxis ( $\geq 2$  infusions per week) compared to their periods of on-demand treatment (reduction of  $5.7 \pm 6.9$  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. A 40% treatment effect difference is considered to constitute a clinically significant reduction in ABR for sample size estimation. Using a paired t-test and the above assumptions, it was determined that a sample size of 18 OD subjects will provide 80% power to detect such a difference using a 2-sided alpha level of 0.05. Based upon prior recombinant FVIII clinical studies, an attrition rate of up to approximately 25% may be expected. Therefore, approximately 24 OD subjects are required to ensure that 18 are evaluable for the comparison of ABRs in the on-demand versus prophylaxis setting.*

#### **1.4.2. Sample Size Estimation Comparing High versus Low Prophylactic Dosing**

*A secondary objective is to evaluate the effect of a high versus low dosing frequency schedule on prophylactic efficacy. Data from the previously mentioned moroctocog alfa study 301 revealed an ABR of  $5.7 \pm 5.2$  ( $N=26$ ) in subjects receiving a high-frequency prophylaxis regimen (3 infusions per week) compared to an ABR of  $7.1 \pm 4.1$  ( $N=13$ ) in patients receiving a lower-frequency prophylaxis regimen (2 infusions per week). Assuming an intraclass correlation of 30% and a standard deviation of 6 bleeds per year based on the above study results, a within-subject standard deviation of 5 bleeds per year was used for sample size calculations for the comparison between the high- and low-frequency prophylaxis regimens. Given this, 36 RP subjects are needed to provide 80% power to demonstrate equivalence of the two regimens. The two regimens will be considered equivalent if the limits of the 90% two-sided confidence interval for the difference in observed mean ABRs falls wholly within the interval of  $-4$  to 4 bleeds per year. Allowing for an attrition rate of 25%, approximately 48 RP subjects should 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. See the Summary of Changes to Planned Analyses for the Final CSR (Item 4) for further discussion.*

#### **1.4.3. Sample Size for Pharmacokinetic Assessments**

Not applicable.

## 1.5. Description of Planned Study Implementation and Procedures

Three study flowcharts including procedures across the length of the study can be found in the protocol.

## 1.6. Blinding

This study is entirely open-label and does not necessitate any blinding.

## 2. ANALYSIS OF PHARMACOKINETIC ENDPOINTS

*A subset of study subjects will participate in a single PK assessment at the start of the study. For the assessment, the response to a single  $50 \pm 5$  IU/kg infusion of moroctocog alfa (AF-CC) will be evaluated. The PK assessment will occur at the beginning of the study (visit 2), before subjects initiate moroctocog alfa (AF-CC) treatment. The assessment will permit characterization of the single-dose PK properties of moroctocog alfa (AF-CC) at initial exposure.*

### 2.1. Pharmacokinetic Endpoints

*The primary PK variables will be terminal phase half-life ( $t_{1/2}$ ), incremental recovery (K-value), and clearance (CL). Secondary PK variables will include: maximum concentration (FVIII:C at 0.5 hours after study drug infusion [ $C_{0.5 \text{ hr}}$ ]), area under the curve to infinity ( $AUC_{\infty}$ ), area under the curve to last measurable concentration ( $AUC_l$ ), steady-state volume of distribution ( $V_{SS}$ ), and mean residence time (MRT).*

*Summaries for each of these variables will be reported for the PK assessment to characterize the single-dose PK of moroctocog alfa (AF-CC) at initial exposure.*

### 2.2. Actual Dose Calculation

*A single bolus of study drug at a dosage of  $50 \pm 5$  IU/kg will be administered for the PK assessment. The dose, prepared from a single lot, will be calculated based on the labeled actual potency of the study drug and the subject's actual body weight as measured on the day of study drug administration and will be documented. See Summary of Changes to Planned Analyses for the Final CSR (Item 7) for further discussion.*

### 2.3. Analysis Populations

#### 2.3.1. Evaluable Populations

PK subjects must meet the additional PK eligibility criteria, including  $\leq 1\%$  FVIII activity at screening (by central laboratory), and  $< 16$  years of age at the time of visit 2 for this analysis.

The primary analysis for PK characterization of moroctocog alfa (AF-CC) will be performed on the per-protocol population.

For the analysis of single-dose PK, this population (herein referred to as the PK-evaluable population) consists of subjects who have no major protocol violations, who supply adequate sampling for the PK assessment while in a nonbleeding state, who had adequate FVIII washout, and who do not have a confirmed FVIII inhibitor at the time of the assessment.

A  $\geq 72$ -hour washout of FVIII activity is required before all infusions. A subject with  $< 72$  hour washout of FVIII prior to PK testing may be included for the baseline assessment, if it is determined that he had negative FVIII inhibitor value and the baseline FVIII activity (T=0 pre-infusion level)  $\leq 1\%$ , before the infusion. However, this might constitute a protocol deviation and a scientific judgment should be provided for inclusion of each such subject.

If subjects are missing measurements necessary for the calculation of certain summary statistics, their data will not be used in the calculation of that statistic. However, this does not preclude the use of their data for other statistics. The number and percentage of subjects that meet the criteria for the analysis population will be summarized by treatment regimen.

#### **2.4. Data Preparation**

The sampling times that will be used in the PK calculation will be the actual sampling time recorded relative to the time of dose administration.

#### **2.5. Analysis Methods**

The factor VIII activity pharmacokinetic parameters for each PK subject will be derived from the plasma FVIII activity time data at the beginning of the study (visit 2), based on non-compartmental (NCA) methods, as specified in the protocol.

*All PK variables will be summarized by descriptive statistics (n, mean, median, standard deviation (SD), standard error (SE), minimum and maximum, coefficient of variance % (CV), geometric mean, and 95% confidence interval (CI)).*

#### **2.6. Statistical Software**

An internally developed and validated software system, eNCA version 2.2.4, or current version-will be used to perform PK analysis and statistical comparisons on PK parameters.

### **3. ANALYSIS OF SAFETY AND EFFICACY ENDPOINTS**

All data collected during the course of the study will be presented in a listing format.

*In general, descriptive statistics will summarize all efficacy and safety endpoints as appropriate. For continuous variables, number, mean, standard deviation, median, minimum, and maximum will be provided. Interquartile ranges and 95% confidence intervals may be provided where meaningful. For categorical variables, frequency and percentage will be presented for each category.*

*Safety and efficacy analyses for the OD subject 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 subject 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. See Summary of Changes to Planned Analyses for the Final CSR (Item 8) for further discussion.*

### 3.1. Baseline Demographics and Treatment Characteristics

The mean, median, standard deviation, minimum, and maximum will be reported for age (years or months, as appropriate), weight (kilograms), and height (centimeters). Number and percentage will be used to describe sex, race, ethnicity, and hemophilia severity. A summary of subject disposition (eg, completed the study, or discontinuation reasons) and time on study will be provided.

### 3.2. Analysis Populations

#### 3.2.1. Intent-to-Treat Populations

*The intent-to-treat (ITT) population includes all subjects for whom a legal acceptable representative has signed the informed consent/assent form. Screen failures will not be included in the ITT population. All safety and efficacy analyses will be performed on the ITT population.*

*The modified Intent-to-Treat (mITT) population is the subset of ITT subjects who received at least one dose of moroctocog alfa (AF-CC). Adverse events and lab data analyses will be additionally performed on the mITT population. Analysis of the incidence of confirmed FVIII inhibitor development will also be performed on the mITT population.*

#### 3.2.2. Per-Protocol Populations

*Efficacy analyses will also be performed on per-protocol populations.*

##### 3.2.2.1. Prophylaxis to On-Demand Per-Protocol Population

For the analysis comparing moroctocog alfa (AF-CC) prophylaxis to on-demand treatment, the per protocol population (herein referred to as the PR-OD population) consists of the subset of OD subjects who have no major protocol violations (see SAP [Section 3.7.1](#)), who practice on-demand treatment exclusively during study segment 1, and who practice prophylaxis during study segment 2. An interruption in treatment due to any unplanned and required surgery will not necessarily disqualify the subject from the PR-OD population, but the time on surgery will not count towards time on treatment in either segment. If a subject requires a dose escalation, only the data from the time on the originally prescribed regimen will be used for segment 2. The first month of segment 2 prophylaxis will be considered a washout period. Analyses will be performed with and without data from the washout period in order to assess and minimize the effect of the previous treatment regimen on ABR. Note: If an OD subject develops a confirmed FVIII inhibitor, his data will be included up to the time an inhibitor is determined to be present.

##### 3.2.2.2. Prophylaxis Regimens Per-Protocol Population

For the analysis comparing the two moroctocog alfa (AF-CC) prophylaxis regimens (A and B), the per-protocol population (herein referred to as the PR<sub>A</sub>-PR<sub>B</sub> population) consists of the subset of RP subjects who have no major protocol violations (see SAP [Section 3.7.1](#)) and who practice protocol-defined prophylaxis during segment 1 and during segment 2. An interruption in treatment due to any unplanned and required surgery will not necessarily disqualify the subject from the PR<sub>A</sub>-PR<sub>B</sub> population, but the time on surgery will not count towards the time on treatment in either segment. If a subject requires a dose escalation, only

the data from the time on the originally prescribed regimen will be used. The first month of each segment will be considered a washout period. Analyses will be performed with and without data from the washout periods in order to assess and minimize the effect of the previous treatment regimen on ABR. Note: If a RP subject develops a confirmed FVIII inhibitor, his data will be included up to the time an inhibitor is determined to be present.

### 3.2.2.3. Efficacy Evaluable Population

For the descriptive analysis of moroctocog alfa (AF-CC) efficacy over the entire course of the study, the per-protocol population (herein referred to as the efficacy-evaluable population) consists of all OD and RP subjects who have no major protocol violations (see SAP [Section 3.7.1](#)), and who accrue  $\geq 50$  exposure days and/or receive moroctocog alfa (AF-CC) treatment for  $\geq 6$  months in the study.

### 3.3. Efficacy Endpoints

The efficacy analysis to test the primary objective of comparing ABRs while on on-demand therapy versus prophylaxis will be performed on the ITT population. Supportive analyses will also be run on the PR-OD population. The efficacy analysis to test the secondary objective of comparing ABRs while on high- versus low-frequency prophylaxis will be performed on the ITT population. Supportive analyses will also be run on the PR<sub>A</sub>-PR<sub>B</sub> population. All other efficacy analyses will be performed on the ITT and efficacy-evaluable population. Analyses will be adjusted for the two stratification factors of prophylaxis treatment regimen (A and B) and hemophilia severity, as appropriate.

For efficacy analyses, dose calculations will be based on the actual potency rather than the target potency. For example, an infusion of 2 vials of lot 1 with a target potency of 2000 IU each and an actual potency of 1975 IU is an actual dose of 3950 IU. Dose (IU/kg) is calculated by dividing the subject's administered dose (IU) by the subject's weight (kg) taken from the most recent visit within 3 months preceding the infusion. If this weight is missing, the weight will be taken from the most recent visit within 3 months following the infusion. If no weight is available within 3 months, the dose will be calculated based on the last available weight and it will be noted that weight was not measured within 3 months of the infusion.

Bleeds treated with study drug will be included in efficacy analyses. If FVIII replacement products, other than study drug, are used, the infusion will be counted in the number of infusions needed to treat the bleed and noted. Bleeds that do not require FVIII treatment (such as bruises, hematoma, hematuria, epistaxis) will be listed separately and not included in efficacy analyses.

Bleed locations are categorized as joint, soft tissue/muscle, or other when reported. Bleeds that occur at more than one site (eg, both elbows, hand and knee, or joint and soft tissue) will be classified into a 'multiple sites' category. Bleeds that occurred at a site that cannot be classified as joint or soft tissue/muscle, eg, hematuria, or if the bleed site is unknown or missing, will be classified into 'other' category.



Efficacy data on and subsequent to the date of inhibitor development will not be included in efficacy analyses. The date of inhibitor development is the date that the blood sample was drawn for the positive Factor VIII inhibitor assay (by the Nijmegen method) or the SAE date reported by the investigator on the AE screen, whichever is earlier.

A summary for each bleeding episode by subject, with type of bleed (spontaneous or traumatic), number of infusions needed to resolve the bleed, mean dose, total dose and response, will be provided. A subject-based analysis of total number of bleeds (spontaneous and traumatic), total number of infusions and total dose needed to treat bleeds will also be provided by subject group (OD subjects and RP subjects).

### **3.3.1. Primary Efficacy – Bleed Rate on Prophylaxis Compared to On-Demand**

Only OD subjects will be included in this analysis.

#### **3.3.1.1. Variable Definition**

To assess the efficacy of routine prophylaxis and on-demand treatment, the annualized bleed rate (ABR) or number of bleeds per year, will be derived for each subject for each treatment regimen by using the following formula:

$$\text{ABR} = \text{number of bleeds}/(\text{Days on treatment regimen}/365.25)$$

The number of bleeds for the ABR calculation includes all bleeds requiring treatment with a FVIII replacement product during the time on treatment. For segment 1 (on-demand treatment), days on treatment regimen for this calculation is defined as (date of visit 11 – date of visit 2) +1. For segment 2 (prophylaxis), days on treatment regimen for this calculation is defined as (date of visit 19 – date of visit 11). If a subject does not complete a study segment, the days on treatment ends at the last study visit. The ABR will be calculated 3 ways: 1) including all data from the ITT population (all OD subjects), 2) including all data from the PR-OD population and 3) including all data from the PR-OD population excluding the first month of segment 2 as a washout period (and allowing for an analysis of the sensitivity of ABRs to previous therapy).

#### **3.3.1.2. Analysis Method**

*The null hypothesis is that prophylactic treatment does not reduce the ABR relative to on-demand treatment. The alternative hypothesis is that prophylactic therapy results in a reduction in ABR.*

*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. The ANOVA will include factors for treatment regimen (study segment 1 or 2) and a blocking factor for hemophilia severity (<1% and [1%, 2%]). The model will also include a blocking factor for subject 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 for ABR of the ITT population will be used to test the null hypothesis; a p-value less than 0.05 will be considered statistically significant. See Summary of Changes to Planned Analyses for the Final CSR (Item 2) for further discussion.*

*Additionally, ABR will be presented as descriptive statistics (n, mean, SD, median, interquartile range, 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 (ie, segment 1, segment 2).*

### **3.3.2. Secondary Efficacy – Bleed Rate of High Frequency and Low Frequency Prophylaxis**

Only RP subjects will be included in this analysis. Each RP subject will serve as his own matched control.

#### **3.3.2.1. Variable Definition**

To assess the efficacy of routine prophylaxis, the ABR will be derived for each subject for each prophylaxis regimen by using the following formula:

$$\text{ABR} = \text{number of bleeds} / (\text{Days on treatment regimen}/365.25)$$

The number of bleeds for the ABR calculation includes all bleeds requiring treatment with a FVIII replacement product during the time on treatment. For segment 1 prophylaxis, days on treatment regimen for this calculation is defined as (date of visit 11 – date of visit 2) +1. For segment 2 prophylaxis, days on treatment regimen for this calculation is defined as (date of visit 19 – date of visit 11). If a subject does not complete a study segment, the days on treatment ends at the last study visit. The ABR will be calculated 3 ways: 1) including all data from the ITT population (all RP subjects), 2) including all data from the PR<sub>A</sub>-PR<sub>B</sub> population and 3) including all data from the PR<sub>A</sub>-PR<sub>B</sub> population except the first month of each segment (considering the first month to be a washout period and allowing for an analysis of the sensitivity of ABRs to previous therapy).

#### **3.3.2.2. Analysis Method**

*The null hypothesis is that there is a difference in ABR between the two prophylaxis regimens. The alternative hypothesis is that the two prophylaxis regimens are similar enough to be considered clinically equivalent.*

*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 and the null hypothesis rejected if the limits of the 90% CI fall wholly within the interval of (-4, 4) bleeds per year. See Summary of Changes to Planned Analyses for the Final CSR (Item 4) for further discussion.*

Additionally, an ANOVA model appropriate for the crossover design will be employed to test for the presence of treatment sequence, period and carryover effects. The ANOVA model will be fitted with terms for treatment sequence (AB or BA), treatment frequency (A or B), period (study segment 1 or 2), carryover and subject nested in treatment sequence. If one or more of the terms for treatment sequence, period or carryover are statistically significant then exploratory analyses may be prepared to help understand the nature of the effect. See Summary of Changes to Planned Analyses for the Final CSR (Item 6) for further discussion.

*ABR will also be presented as descriptive statistics (n, mean, SD, median, interquartile range, 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 frequency (ie, prophylaxis A, prophylaxis B).*

### **3.3.3. Other Efficacy Endpoints**

These analyses will be conducted on the ITT population and the efficacy-evaluable population.

The description of overall moroctocog alfa (AF-CC) efficacy will be based on the number of infusions per bleed, assessment of the response of bleed to treatment, time interval between bleed onset and prior moroctocog alfa (AF-CC) treatment, 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. Descriptive statistics will be provided for each of these endpoints; statistical hypothesis tests will not be conducted.

#### **3.3.3.1. Number of Infusions per Bleed**

*Number of study drug infusions used to treat a bleed will be summarized by bleed location, by dose (IU/kg) administered at the first infusion.*

#### **3.3.3.2. Assessment of the Response of Bleed to Treatment**

*The 4-point response (efficacy rating) for study drug-treated bleeds will be summarized. 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).*

#### **3.3.3.3. Time Between Bleed Onset and Prior Treatment**

*The time between onset of a bleed and prior moroctocog alfa (AF-CC) prophylaxis infusion will be summarized by the following categories:  $\leq 24$ ,  $>24-48$ ,  $>48-72$ , and  $>72$  hours. If the onset time of a bleed is unknown, then a default time of "00:00" will be used in calculation. The number of bleeds will be classified by the type of bleed (spontaneous or traumatic) and summarized for each subject and overall and by prophylaxis regimen (A or B).*

#### **3.3.3.4. Incidence of Prophylaxis Regimen Escalation**

The number (%) of subjects requiring prophylaxis regimen escalation during protocol-defined prophylaxis will be provided by prophylaxis regimen (A or B).

Exploratory analysis, such as a time-to-escalation analysis, may be performed to characterize the timing and frequency of dose escalation, and the total dose used as a function of the treatment frequency (A or B) to which subjects were randomized.

### 3.3.3.5. Less-Than Expected Therapeutic Effect

#### 3.3.3.5.1. Variable Definition

Criteria for LETE are evaluated by the investigator. If a potential LETE is identified, the date of the event along with information about the presence or absence of related confounding factors, which are defined in the protocol, will be recorded separately by LETE category. The three categories of LETE are defined as follows:

1. *On-Demand* – LETE occurs if the subject records two successive “No Response” ratings after 2 successive infusions, 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.
2. *Routine Prophylaxis* – LETE occurs if there is a spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose (which was not used to treat a bleed) of study drug in the absence of confounding factors.
3. *Low Recovery* – LETE occurs if, in the opinion of the investigator, lower than expected recovery is observed following injection of study drug in the absence of confounding factors.

#### 3.3.3.5.2. Analysis Methods

A potential LETE outcome is reported by the investigator and will be reviewed using the definitions above. Sites will be queried if a potential LETE is identified in the review of the data but is not reported by the investigator or if there are any discrepancies in the assessments.

LETE will be determined by assessing the potential LETE cases for presence or absence of confounding factors. Each occurrence of LETE will be listed separately by type of LETE (on-demand, routine prophylaxis and low recovery).

The number (%) of subjects reporting LETE will be summarized overall and by regimen [on-demand and prophylaxis (A or B)].

#### 3.3.3.6. Consumption of Moroctocog Alfa (AF-CC)

*For consumption of moroctocog alfa (AF-CC) per bleed, the dose for the first infusion (IU/kg) and the 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 total IU, 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).*

### **3.3.3.7. Compliance to Prophylaxis Regimen**

*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.*

As an exploratory analysis to determine the effect of non-compliance to regimen on ABR, the ANOVA model for the crossover design, described in SAP [Section 3.3.2.2](#), will be fitted with an additional factor for actual treatment frequency (as opposed to prescribed frequency). Actual treatment frequency will be calculated from the number of infusions divided by the number of weeks on treatment, including non-routine prophylaxis infusions.

## **3.4. Safety Endpoints**

Safety data will be collected during the entire course of the study starting from the time informed consent is signed. All safety data collected after informed consent/assent is obtained will be displayed in a listing format. All safety analyses will be performed on the ITT analysis population, additionally adverse events, lab data, and the incidence of inhibitor development will be performed on the mITT population.

### **3.4.1. Adverse Events and Allergic Reactions**

#### **3.4.1.1. Variable Definitions**

Safety endpoints are adverse events (AEs) and include AEs that are allergic reactions.

Adverse events (including allergic reactions) with onset or worsening after the first dose of moroctocog alfa (AF-CC) administration are considered treatment emergent adverse events (TEAEs). This study does not collect onset time of AEs. Therefore an AE with a start date on the same day of the study drug administration will be counted as a TEAE unless there is further information to support that the AE occurred prior to the study drug administration.

#### **3.4.1.2. Analysis Methods**

The number (%) of subjects who experienced TEAEs will be reviewed and summarized by relatedness to the study drug and by maximum severity grade. Descriptive statistics (number and frequency) will be provided for all adverse event summaries. No hypothesis testing will be carried out.

### **3.4.2. Other Safety Endpoints**

For change from baseline calculations, the closest non-missing value collected before the first dose of moroctocog alfa (AF-CC) will be considered baseline.

Normal ranges of the laboratory tests provided by the central lab and local labs will be used to flag abnormal test results.

*Patient serum samples will be collected and tested for the development of antibodies both neutralizing and nonneutralizing to moroctocog alfa (AF-CC), using a validated ELISA.*

### **3.4.2.1. Inhibitor Development**

*Incidence of FVIII inhibitors to moroctocog alfa (AF-CC) will be monitored throughout the duration of this study. A subject will be considered to have developed a confirmed positive inhibitor if he has a titer of  $\geq 0.6$  Bethesda Units (BU)/mL in a sample assayed at the central laboratory using the Nijmegen assay. The occurrence of an inhibitor will be reported as an SAE. This determination will be based on the mITT population. See Summary of Changes to Planned Analyses for the Final CSR (Item 5) for further discussion.*

### **3.4.2.2. Laboratory Test Results**

Abnormal lab test results will be presented. The significance of the mean change from baseline for all subjects for each of the serum chemistry and hematology assays will be assessed clinically and the 95% confidence interval of the mean change at each visit will be presented. Out-of-range results will be listed separately.

### **3.4.2.3. Concomitant Medications**

Any use of concomitant medications will be listed by subject. Bleeding episodes treated with replacement products other than test article will be listed separately from bleeds treated with test article as well as in the concomitant medication listing.

### **3.4.2.4. Vital Signs**

Vital signs and physical examinations will be listed for each visit. Changes from baseline to any subsequent visit will be assessed clinically.

## **3.5. Missing Data**

Missing data will be reported as such and no imputation will be made unless otherwise specified. The proportion of data that is missing for key variables will be presented if appropriate. The study will diligently collect all the data as planned. If any pattern of missing data is identified, extra effort will be made to ensure that the analysis is not affected by the circumstances.

## **3.6. Analysis Data Sets**

There will be analysis data sets created for use in the analysis.

## **3.7. Description of Study Deviations**

### **3.7.1. Major Protocol Violations**

The following are the criteria for the major protocol violations:

- Inclusion or exclusion criteria not met and not exempted;
- Frequent (per clinical judgment) use of nonstudy FVIII concentrates during the study;
- Routine, concomitant treatment with prohibited immunomodulating drugs;
- The use of other investigational agents during the study;

- Frequent (per clinical judgment) use of drugs with antiplatelet activity (eg, aspirin);
- Routinely noncompliant with protocol-specified procedures.

Subjects with major protocol violations should be removed from study per the medical monitor's discretion. Protocol violations or deviations will be listed in the study report.

### **3.8. Multicenter Handling**

Because relatively small numbers of subjects will be enrolled at each site, no test of homogeneity across sites will be performed. Data will be pooled from all sites for analysis.

### **3.9. Subgroup Analysis**

No subgroup analyses are planned other than those described in [Section 2.3](#) and [Section 3.2](#).

### **3.10. Statistical Software**

SAS v9.1.3 (or current version) will be used to perform all efficacy and safety analyses.

## **REFERENCES**

1. J. Ogawa (1983): On the confidence bounds of the ratio of the means of a bivariate normal distribution. *Ann. Inst. Statist. Math.*, 35, 41-48.

## **APPENDIX A: SUBJECT NARRATIVES**

Subject narratives will be available for the categories established according the International Conference on Harmonisation (ICH) guidelines. A narrative will be provided for subjects who met 1 or more of the following criteria:

- Serious adverse events;
- Death;
- Inhibitor development;
- Less-than expected therapeutic effect;
- Discontinuation due to an adverse event.



**APPENDIX B: CHANGES IN THE CONDUCT OF THE STUDY**

The original protocol dated 09 March 2007 has been amended 10 times.

**Amendment 1** (dated 12 June 2007), implemented the following changes:

- The objectives of the study were amended. “To demonstrate that ReFacto AF® prophylaxis reduces annualized bleeding rates relative to on-demand therapy” replaced “To characterize the PK of ReFacto AF in children younger than 6 years of age” as the primary objective of the study. Accordingly, “To characterize the PK of ReFacto AF in children younger than 6 years of age” became a secondary objective of the study.
- The title was revised to reflect the new order of objectives.
- PK eligibility criteria were added to the inclusion criteria. Subjects had to meet additional eligibility criteria to participate in the PK assessments, in contrast to the previous design of inviting all study subjects, regardless of eligibility.
- The duration of each treatment period (Segments 1 and 2) was lengthened from 9 months per treatment period to 12 months per treatment period. As a result, an additional study visit, and telephone contact were added to each study segment. Therefore, the total duration of study participation changed from 20 months to 26 months.
- The total blood volume collected during the entire study was recalculated to accommodate for the utilization of pediatric size collection tubes, and to reflect the additional 2 study visits.
- Additional details regarding the statistical methods by which the study hypotheses will be tested were included in the protocol. The efficacy analyses were to be performed on the ITT population, in addition to the PP population.
- Provided additional clarification on the signs of a significant spontaneous bleed.
- Provided additional information regarding the drug safety monitoring board (DSMB), and a brief description of the type of information each member reviews as part of their safety review.
- The statistical discussions were reordered to discuss safety followed by efficacy, then PK.
- A statement was added to the randomization section identifying the system used to perform subject randomization.

**Amendment 2** (dated 27 August 2007) implemented the following changes:

- The study design was revised to support the primary objective.
- The existing prophylaxis regimen escalation algorithm was enhanced by defining the dose and frequency of the first escalation regimen.

- Minor revisions were made to the 4-point On-Demand Hemostasis Efficacy rating scale.
- Definition of LETE in the OD setting was aligned with the revised efficacy rating scale.
- The term significant spontaneous bleed was clarified to indicate that the loss of function could be ‘transient or persistent’.
- The protocol definition of serum chemistry with the analytes being tested at the central laboratory (eg, phosphate was updated to phosphorus).
- Footnotes of Study Flow Chart 1: Study Procedures with the protocol-specified visit descriptions were aligned.
- Clarified that the subject's diary should be reviewed for information related to LETE at each study visit.
- It was clarified that consenting PK-eligible subjects will be enrolled sequentially into the PK portion of the study until the specified number of subjects have been enrolled.
- The total blood volume to be collected during the entire study was reduced due to the increased utilization of lower volume collection tubes.
- The description of the blocking factors used in the statistical analysis of the primary objective was updated so that they are aligned with the new study design referred to in bullet 1.
- • The description of a hemophilia event was clarified.

**Amendment 3** (dated 22 January 2009) implemented the following changes:

- The definition of B-domain deleted recombinant FVIII was updated.
- “ReFacto AF” (or “ReFacto Albumin Free”) was changed into “moroctocog alfa (AF-CC)”.
- Clearance was changed from a secondary to a primary PK variable.
- Test article storage was changed from 1 month to 3 months due to new stability data and clarification regarding storage conditions.
- Clarification of statistical analysis of PK data.

**Amendment 4** (dated 15 September 2009) implemented the following changes:

- Definition of PTPs was changed to those who had accrued  $\geq 20$  EDs to any FVIII replacement product (from 50 EDs) and hence the inclusion criterion for the number of EDs required at study entry was lowered to 20 (from 50) to improve recruitment.

- The clinical experience section of the protocol was updated with revised wording to reflect completion of Study 311.
- Clarified that moroctocog alfa (AF-CC) is not approved for administration by continuous infusion and in case of unscheduled surgery, the drug should be used in the manner in which it has been approved.

**Amendment 5** (dated 20 July 2010) implemented the following changes:

- Change in sponsor Name from Wyeth to Pfizer and administration related changes such as sponsor/investigator signature, due to acquisition of Wyeth by Pfizer.
- Administrative changes to transition from legacy Wyeth protocol amendment process to Pfizer process.
- Addition of the recording process for bleed events that are SAEs.
- Change in the SAE reporting process.
- Revised duration of study from 3.5 years to 5.5 years (or 66 months) due to enrollment projections.
- As a result of the June 2010 E-DMC meeting, the conditions by which a subject can participate in the study in the OD arm were modified to allow them to continue to practice OD therapy with moroctocog alfa (AF-CC), if determined to be appropriate in the medical judgment of the investigator and consented to by the subject's legally authorized representative.
- Clarification to ensure that an SAE of inhibitor development had the serious criteria of being "medically important".

**Amendment 6** (dated 10 March 2011) implemented the following changes:

- All emergency contact information (including that of the Physician Clinician and the Regional Medical Monitors) was deleted from the protocol in order to align with the Pfizer protocol template; instead all contact information was maintained in the Study Reference Manual.
- Revised the Final Contact (Visit 20) visit window to align with the Pfizer SAE reporting requirements; must report SAEs up to at least 28 days after the Final Study Visit (Visit 19).
- Deleted references to Subject Master Log, a legacy Wyeth form that is no longer used under Pfizer procedures.

- Added the word “sponsor’s” to clarify that the clinician referred to is the 1 on the study team at the sponsor for sections of the protocol pertaining to consultation regarding inclusion and exclusion criteria, concomitant medication use and unplanned surgical procedures.
- Clarification that study drug vials and all unused diluent syringes can be returned to the sponsor or destroyed at site but in the latter case drug accountability should be performed prior to destruction.
- The entire AE section was re-written to include the Pfizer Safety language which includes:
  - Addition of Pfizer definition of AE, abnormal test findings, SAE.
  - Addition of exposure during pregnancy language.
  - Addition of Hy’s Law guidance.
  - Revised SAE Reporting timeframe from 1 business day to within 24 hours of awareness of the event by the investigator, or if the AE is fatal or life-threatening the notification to Pfizer must be made immediately.
  - 28 Day Follow-up: SAEs are to be reported to the Drug Safety Unit through 28 calendar days after the last administration of the investigative product.
  - Discontinued use of legacy Wyeth Form 7443. The new consolidated Pfizer SAE Report Form will be used.
  - Discontinued use of legacy Wyeth Medication Error Incident Report Form (Form 15701). Instead medication errors are reported to the site monitor.
  - Some specific legacy Wyeth safety elements were maintained, such as the definitions for hemophilia events, events of special interest/circumstance, overdose definitions and actions, and medication error definitions and actions.
- Added an additional potential reason for a subject’s discontinuation from the study (“if the investigator believes it is not in the subject’s best interest to continue participating in the study”).

**Amendment 7** (dated 31 August 2011) implemented the following changes:

- Abbreviations and definitions (FVIII replacement, treatment groups, treatment regimens, treatment phases and washout) were updated.

- Clarification of 2 study cohorts: 1 OD and 1 RP, with differing study schedules and durations of study, and statistical analysis requirements. Segment 1 for the OD cohort was shortened to 6 months duration from 12 months. Segment 2 for the OD cohort and Segments 1 and 2 for the RP cohort remained at 12 months duration.
- Revised duration of study from 5.5 years to 8 years (or 98 months) due to enrollment projections.
- Updating of background information such as marketing status and PK experience.
- Removal of all references to PK recovery assessment.
- Change to exclusion criterion regarding surgery to allow planned minor surgery (and commensurate changes to permitted concomitant treatment and surgery sections).
- Addition of extra Study Procedures section to reflect the change in study cohorts.
- Change in PK part of study: Reduction in number of subjects required and reduction in number of samples required from each subject (optional 28 hour blood draw and removal of collection of an archive plasma sample) to reduce burden on the subject.
- Clarification that the moroctocog alfa (AF-CC) used in the study is a study drug, not a commercial product.
- Clarification that subjective assessments and decisions will be at the discretion of the caregiver/ investigator rather than the subject/caregiver/investigator, given the youth of the subjects.
- Change in terminology of DSMB to E-DMC.
- Antibodies to be tested specified in safety section of protocol due to inadvertent omission. Addition of these parameters as safety variables in statistical analysis section.
- Bioanalytical analysis of PK samples for FVIII:C to be performed by Covance rather than sponsor.
- Clarification of changes to statistical analysis to be performed.

**Amendment 8** (dated 19 October 2012) implemented the following changes:

- Abbreviations and definitions (lack of efficacy) were updated.
- If an indwelling catheter is in place, it may be used for study drug infusions, when appropriate.
- Pfizer template language regarding study drug storage requirements added.

- Clarifications added to describe actions of the E-DMC regarding their recommendations and in turn the sponsor's actions/potential actions upon receipt of those recommendations.
- Pfizer template language regarding safety updated (with reference to lack of effect).
- Added reference to "Single Reference Safety Document" to comply with regulatory requirements.
- Added the possibility that an event could be reported as Serious by the sponsor and a requirement for follow-up regardless of the investigator's assessment of causality to comply with regulatory requirements.
- Any SAE occurring any time after the active reporting period must be promptly reported to comply with Pfizer safety process.
- Clarification that drug abuse and drug dependency are to be considered AEs to comply with Pfizer safety process. Signs and symptoms resulting from a medication error were included as examples of AEs; medication error definitions and their reporting requirements were updated.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.
- Confirmed FVIII inhibitor development to be a medically important event and to be reported as an SAE to comply with Pfizer safety process.
- Stated that there were no protocol-specified SAEs. This was added to the protocol to avoid compromising the integrity of the study by potential multiple unblinding of SAEs anticipated to occur in the study population.
- Clarification of the criteria for laboratory abnormalities that require further evaluation in the context of potential cases of drug-induced liver injury and addition of PT to laboratory tests to be repeated.
- Exposure in utero language updated to reflect regulatory guidance.
- The need to for immediate notification in the event of serious breaches of GCP was added.

**Amendment 9** (dated 29 January 2013), implemented the following changes:

- Following a request to the FDA to update the US label for moroctocog alfa (AF-CC)/Xyntha<sup>®</sup>, an interim analysis was added to support submission of aggregate PK, efficacy, and safety data from this study and other Xyntha<sup>®</sup> studies which include pediatric subjects. The following text was added "Additionally, 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."

- Text relating to FVIII inhibitors was updated to allow the investigator to perform additional laboratory tests as appropriate in his/her medical judgment.

**Amendment 10** (dated 02 October 2015) implemented 3 main changes following FDA approval of Xyntha<sup>®</sup> (moroctocog alfa [AF-CC]) in children and a change in the standard of care from on-demand to prophylactic use:

- The closure of the OD cohort and the re-estimation of sample size for the RP cohort.
- PK assessments became optional.
- Revision of inclusion criteria for subject age.

As a result of the 3 changes above, the following sections of the protocol were amended:

- The rationale for the study was updated to include the change in recommendation of the National Hemophilia Foundation (NHF), the World Federation of Hemophilia (WFH) and the WHO, all of which now endorse prophylaxis. Editorial changes were made to update references to the now-closed OD cohort accordingly and to include male children up to 16 years of age.
- The primary objective of the study was amended to state that enrollment into the OD cohort had been closed.
- A secondary objective of the study was revised to extend the PK characterization of FVIII:C to children aged  $\geq 6$  months to  $< 16$  years of age.
- The study description was updated for the closure of the OD cohort, to state that enrollment for the RP cohort was ongoing, and to revise the sample size (from 72 to 56 subjects) and age of subjects to be recruited (from  $< 6$  years to  $\geq 6$  months -  $< 16$  years). In addition, it was clarified that in the updated protocol, subjects would now be referred to by their segment 1 treatment modality, ie, OD or RP.
- Inclusion criterion 1 was amended to extend the age range of eligible subjects from  $< 6$  years at the screening visit to  $\geq 6$  months -  $< 16$  years.
- The inclusion criteria were also updated to include 3 new criteria applicable to the older eligible subjects.
- The section regarding consent/assent was updated to reflect the older age of eligible subjects: all subjects now had to review and sign a consent form. Text was added stating that subjects who were under the legal age of consent had to have a legally acceptable representative review, approve and sign consent for the study.
- The procedures for Study Visit 1 were updated to include obtaining informed consent/assent and to clarify that CD4 cell count was required for subjects with HIV only.

- The requirement for a repeat visit for subjects experiencing a bleeding episode during the PK assessment was removed. It was clarified that the dosage of a single IV infusion could be rounded to the nearest complete vial.
- The statistical discussions included a correction to the 2-sided CIs for the mean difference in ABRs for the 2 prophylaxis regimens for ITT subjects (from 95% to 90% for the secondary objective of assessing the effect of high- versus low-frequency dosing schedule).
- Section 22.6, Interim Analysis and Report, was updated to state that separate final reports would be submitted for the OD and RP cohorts.
- The number of planned evaluable RP subjects was amended from 74 to 38.
- The sample size calculation was re-estimated using data from the ongoing study; 38 subjects would be required to provide 80% power to demonstrate equivalence and approximately 56 RP subjects would need to be enrolled. The sample size calculation for the PK assessments was removed.
- A number of updates were made as a result of changing the template from legacy to current Sponsor template and industry-regulatory authority accepted norms:

An administrative change to the protocol (dated 24 February 2017), removed the following safety variable. From this date, anti-CHO antibody and anti-TN8.2 antibody blood samples were no longer to be collected during the study.

- Incidence of development of antibodies to moroctocog alfa (AF-CC), CHO cell proteins, and TN8.2.



## APPENDIX C: CHANGES IN THE PLANNED ANALYSES FROM INTERIM CSRS

Changes in the Planned Analyses were described in Section 9.8.2 within each of the 2 interim CSRs for this study.

### Interim CSR 1 (dated 07 November 2013), in support of the Pediatric 2013 sBLA

**9.8.2 Changes in the Planned Analyses:** The analyses reported in here are limited and restricted to descriptive statistics. Safety, efficacy and baseline data for subjects at Site **PP** are presented separately from data for subjects at other sites, due to serious breaches of Good Clinical Practice (GCP) compliance by the investigator and study staff at Site **PP** pertaining to data integrity. Pharmacokinetic (PK) data are objective and it is believed that interpretation of these data is not compromised by the deficiencies noted at Site **PPD**. The PK data which were collected from subjects from this site are, therefore, presented and included in the summary for the study.

### Interim CSR 2 (dated 11 April 2016), in support of the Prophylaxis 2016 sBLA

**9.8.2 Changes in the Planned Analyses:** The previous interim CSR presented safety, efficacy and baseline data for subjects at Site **PP** separately from data for subjects at other sites, due to serious breaches of GCP compliance by the investigator and study staff at Site **PP** pertaining to data integrity. In this second interim CSR, safety, efficacy and baseline summary data are presented excluding Site **PP** with the exception of protocol deviations, and inhibitor incidence, which include all sites.

As per the SAP [Section 3.3](#), efficacy data on and subsequent to the date of inhibitor development was not to be included in the efficacy analyses. However, with the exception of the following summary tables: CSR Section 14.2, Table 14.2.4.3, Table 14.2.4.4, Table 14.2.5.1, and Table 14.2.5.2, the efficacy summary tables did not exclude bleeds occurring after inhibitor development. (This has been corrected for the Final CSR).

During the programming for the primary endpoint, prior to the data snapshot and prior to analysis, it was determined that a linear mixed-effects model with unstructured variance-covariance matrix would provide a more robust model for the comparison of annualized bleeding rate (ABR) given the nature of the study data, while still controlling for the same factors as specified in the SAP ANOVA model. This model allows for the inclusion of all intent-to-treat (ITT) subjects with ABR data including the 1 subject with Segment 1 (on-demand [OD] regimen) only at the time of the data cut-off for this second interim analysis and also takes into account the correlation between the 2 within subject measurements of ABR at each segment. Because all enrolled subjects had severe (<1%) hemophilia at baseline (ie, just one level of the factor was present and therefore not informative), hemophilia severity was not included as a factor as planned. The estimates of the ABR for each regimen (segment) and for the difference as well as the corresponding two-sided 95% confidence intervals (CIs) are reported using the linear mixed-effects model.

Supportive analyses were also performed for the ITT population. A paired t-test was used to test the within-subject change in ABR for the 8 subjects who were evaluated with both OD and routine prophylaxis (RP) dosing during the study. In addition, a one-sided 95% CI for

the ratio of the arithmetic means for ABR during RP over the ABR during OD treatment was calculated using R statistical software (version 3.2.3). If the one-sided 95% upper confidence bound was  $\leq 0.5$ , then this confirmed that the ABR during RP treatment was at least 50% lower than that observed during OD treatment.

