Protocol B1831097

A SINGLE COUNTRY, MULTICENTER, OPEN-LABEL AND NON-RANDOMIZED CLINICAL TRIAL WITH MOROCTOCOG ALFA (AF-CC) PROPHYLAXIS AND TREATMENT OF BLEEDING EPISODES IN PREVIOUSLY TREATED PATIENTS WITH MODERATE AND SEVERE HEMOPHILIA A FOR A DURATION OF 8 WEEKS

Statistical Analysis Plan
(SAP)

Version: 1

Date: **13 Nov 2019**

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 13 Nov 2019	Amendment 1, 16 Sep 2019	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B1831097. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary Objective: To study the safety of moroctocog alfa (AF-CC) when administered for prophylaxis with respect to incidence of FVIII inhibitor development.

Secondary Objectives:

- *To evaluate the incidence of adverse events (AEs) and serious adverse events (SAEs) in subjects receiving moroctocog alfa (AF-CC) prophylaxis.*
- *To evaluate the efficacy of moroctocog alfa (AF-CC) during a prophylaxis regimen.*
- *To evaluate the total annualized consumption of moroctocog alfa (AF-CC) by subjects following a prophylaxis regimen.*
- *To evaluate the efficacy of moroctocog alfa (AF-CC) for the treatment of breakthrough bleeding episodes (on-demand treatment) while following a prophylaxis regimen.*

2.2. Study Design

This is a single-country, multicenter, open-label, interventional study which will be conducted in India.

At least 50 male subjects aged ≥12 years to ≤65 years with moderate or severe hemophilia A (FVIII:C ≤5%) who have had at least 50 exposure days (EDs) to FVIII-containing products will be enrolled in the study.

The overall treatment duration for each subject will be up to 8 weeks, with up to a 4-week screening period and a subsequent post-treatment 28-day safety observation period. Subjects are requested to continue in the study until 24 EDs or a period of up to 8 weeks on moroctocog alfa (AF-CC) treatment (whichever occurs first). Subjects will be treated with a dose and regimen of prophylaxis in accordance with the local product document (*LPD*).[1]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary endpoint will be the proportion of subjects who develop FVIII inhibitor (≥0.6 BU/mL), as confirmed by central laboratory testing, during the course of the study.

- Subjects who do not have a post-baseline blood sample drawn for inhibitor testing will not be considered in the computation of the proportion.

3.2. Secondary Endpoints

3.2.1.1. Annualized Bleeding Rate During Prophylaxis

The annualized bleeding rate (ABR) during prophylaxis *will be derived for each subject by using the following formula:*

$$\text{ABR} = \frac{\text{number of bleeds}}{\text{treatment interval duration}} \times 365.25.$$

- The number of bleeds for each subject for the ABR calculation includes all new bleeds (with a unique start date and time) requiring treatment with moroctocog alfa (AF-CC) during the treatment interval duration (up to 8 weeks of treatment, or sooner, once 24 EDs are achieved). If there is more than one bleed location (eg, ankle and joint) with identical bleed start date and time, it will be treated as one bleed occurrence. Treatment interval duration is calculated as the number of days beginning on Visit 2 (“Day 1”, provided an infusion was given) up to Visit 4, this is,

- $\text{Treatment interval duration} = \text{Date of Visit 4} - \text{Date of Visit 2} + 1.$

- If a subject does not complete the study (does not achieve 24 EDs nor 8 weeks of treatment), instead of Visit 4, number of bleeds and treatment interval duration will be computed using the data from the last study visit and the corresponding date. If a subject does not receive an infusion on Visit 2, the treatment interval duration will begin on the first day an infusion was given.

- Because bleeding information is only recorded if a bleed occurs, if there are no bleeding records present for a subject in a period, this would be derived as ZERO bleeds (and therefore ABR=0). If there are days in the observation period for which data is confirmed missing (for example, from an eDiary), ABR will be calculated using non-missing days for the denominator.

3.2.1.2. Annualized Total Factor Consumption of Moroctocog Alfa (AF-CC)

The total amount in international units *(IU) infused for each moroctocog alfa (AF-CC) infusion recorded in the investigational product infusion log* case report form *(CRF) will be summed to calculate the* total factor consumption (*TFC*) *for each subject. The annualized TFC of moroctocog alfa (AF-CC) will be derived for each subject by using the following formula:*

$$\text{Annualized TFC} = \frac{\text{TFC}}{\text{treatment interval duration}} \times 365.25.$$

- In addition, for each infusion, IU/kilogram (kg) will be calculated, using the most recently recorded weight measurement, to derive the annualized TFC by weight (IU/kg).

- Treatment interval duration is defined in section 3.2.1.1.

3.2.1.3. Number of Moroctocog Alfa (AF-CC) Infusions Used to Treat Each Bleed

The investigational product infusion log CRF *will be used to determine the number of investigational product infusions administered to treat a bleed. This will be calculated by adding the initial (on-demand) infusion to any subsequent (on-demand) infusions for the same bleed (same bleed start date/time).*

If there is more than one bleed location (eg, ankle and joint) with identical bleed start date and time, it will be treated as one bleed occurrence.

3.3. Other Endpoints

Not applicable.

3.4. Baseline Variables

No variable requires specific definitions for baseline. All baseline values will be collected during screening (Visit 1), within 28 days prior to Day 1 (Visit 2, first Moroctocog alfa (AF-CC) administration) of the study. The following variables will only be collected at screening: demographic data (sex, age, race, and ethnicity), hemophilia A history, and medical history.

3.5. Safety Endpoints

3.5.1. Adverse Events

Safety endpoints are the incidence of AEs and SAEs.

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes and Preferred Terms. The most recent MedDRA version at the time of analysis will be used throughout the study.

An adverse event is considered a treatment-emergent adverse event (TEAE) relative to moroctocog alfa (AF-CC) if the event started during the effective duration of treatment (from the time the subject has taken at least 1 dose of study treatment through the last subject visit).

All events that start on or after the first dosing day, but before the end of study visit, will be considered TEAEs. Any event that started prior to the first dose date will not be considered TEAE. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

Missing severity will not be imputed. AEs will be coded per Pfizer Data Reporting Standards and therefore summarized by system organ class and preferred term.

Please refer to the protocol for the schedule and investigator instructions for recording of AEs.

3.5.2. Laboratory Data

Laboratory evaluations, according to local and/or central laboratory assessment, will be conducted at Visit 1 and Visit 4.

- Hematology (local laboratory): measurement of complete blood count, including hemoglobin, hematocrit, white blood cell count and differential, and red blood cell and platelet count.

- Coagulation: FVIII activity (local laboratory and central laboratory), international normalized ratio (INR; local laboratory), and prothrombin time (PT; local laboratory).

- Biochemistry (local laboratory): aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN) , creatinine, uric acid, albumin, total protein, glucose (fasting),calcium, sodium, potassium, and chloride.

- Laboratory assessment for factor VIII inhibitor antibodies (local laboratory and central laboratory).

- Documentation of testing for HIV and CD4+ will be collected at screening for evaluation of exclusion criteria.

3.5.3. Vital Signs and Physical Examination

Vital Signs and physical examinations will be conducted at visits 1-4 and end of study visit.

- Vital signs: to include height, weight, blood pressure, heart rate, and body temperature.

- Physical examination: to include general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, breasts, abdomen, extremities, neurological, back/spinal, lymph nodes.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Population	Description
Safety	All subjects who receive at least one dose of moroctocog alfa (AF-CC).

All dosed subjects will be included in safety, and each efficacy analysis will include those with evaluable data for the corresponding endpoint. Data collected after a subject develops FVIII inhibitor (≥0.6 BU/mL), as confirmed by central laboratory testing, will not be considered evaluable for efficacy, but may be analyzed for safety.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis will be performed after the last subject completes the study or withdraws from the study (ie, after last subject last visit).

5.1. Hypotheses and Decision Rules

No hypotheses testing will be performed. All statistical analyses will be descriptive since all subjects will have received the same treatment and there are no prespecified hypotheses.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Descriptive statistics of binary data will include the number of non-missing observations and the frequency of the observed endpoint, as well as the observed proportion. When appropriate, a two-sided 90% CI for the proportion will be provided using the exact method.

5.2.2. Analyses for Continuous Endpoints

Summary tables for continuous endpoints will include the mean, standard deviation, median, minimum, and maximum of the observed value and, when appropriate, the change from baseline. The number of non-missing observations will also be included in the tables.

5.2.3. Analyses for Categorical Endpoints

In general, number of non-missing observations, frequencies, and proportions will be presented for categorical variables.

5.3. Methods to Manage Missing Data

In general, missing data will not be imputed in this study, unless specified in Section 3, where individual endpoints are discussed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Proportion of Subjects who Develop FVIII Inhibitor

- Subjects with FVIII inhibitors confirmed by the central laboratory as a titer ≥0.6 BU/mL at baseline (ie, no longer at risk for inhibitor) will not be included.

- The number of subjects who develop inhibitors (numerator) will include all subjects where the blood sample collection for positive inhibitor occurred after the first dose of study drug, regardless of how many on-study EDs had accrued at the time of sample collection. The number of subjects at risk (denominator) will include all subjects that received at least one dose of study drug and had at least one post-baseline assessment performed.

- The analysis will consist of the following descriptive statistics: number of non-missing observations, frequency and observed proportion of subjects for which FVIII inhibitors were detected at Visit 4. A two-sided 90% CI for the corresponding proportion will be computed using the exact method (Section 5.2.1).

6.2. Secondary Endpoint(s)

6.2.1. Annualized Bleeding Rate During Prophylaxis

- The analysis will consist of the following descriptive statistics: mean, standard deviation, median, minimum, and maximum observed ABR, as well as the number of non-missing observations (Section 5.2.2).

- Additionally, ABRs will be summarized by bleed type (eg, spontaneous or traumatic) and by bleed location (eg, joint, soft tissue/muscle).

6.2.2. Annualized Total Factor Consumption of Moroctocog Alfa (AF-CC)

- The analysis of annualized TFC and dose by weight (IU/kg) will consist of the following descriptive statistics: mean, standard deviation, median, minimum, and maximum observed annualized TFC, as well as the number of non-missing observations (Section 5.2.2). Summary tables by reason for infusion will also be presented.

6.2.3. Number of Moroctocog Alfa (AF-CC) Infusions Used to Treat Each Bleed

- Summary statistics will be reported using the number of infusions as a continuous variable, and will include the mean, standard deviation, median, minimum, and maximum of the observed number of infusions (Section 5.2.2). Additionally, this endpoint will be summarized as a categorical variable with categories 1, 2, 3, 4, or >4 infusions needed to treat the blead (Section 5.2.3). Frequency tables will be provided, in which the numerator used for the computation of proportions will be the number of bleeds falling into each category and the denominator will be the total number of new bleeds across all subjects. The number of subjects contributing data (ie, the number of subjects with any new bleed) for the analysis will also be reported.

6.3. Other Endpoints

Not applicable.

6.4. Subset Analyses

No subset analyses are planned for this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Descriptive statistics will be used to summarize the following variables: sex, age (year at screening visit – birth year), age group (pediatric: 12 to < 18 years and adult: 18 to ≤65 years), race, ethnicity, hemophilia A history, and medical history.

6.5.2. Study Conduct and Subject Disposition

The number and percentage of subjects in the Safety Analysis Set, completing the study, prematurely discontinuing the study, and the reason for subject discontinuation, will be summarized.

6.5.3. Study Treatment Exposure

Infusion data will be listed for each subject. A summary of moroctocog alfa (AF-CC) consumption, by primary reason for infusion and across all reasons, will include summary statistics on total units (IU) per subject (TFC), range of infusion (IU) (minimum, maximum), dose (IU) per infusion, number of infusions per subject, and EDs on study per subject.

6.5.4. Concomitant Medications and Nondrug Treatments

Descriptive summaries of concomitant medications and treatments will be reported. Summary tables will include all drug and nondrug treatments taken during the effective duration of study treatment, whether or not they were recorded at Baseline.

6.6. Safety Summaries and Analyses

All safety summaries and analyses will be performed using the Safety Analysis Set.

6.6.1. Adverse Events

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. Adverse event reporting details have been described in the protocol Section 8.

6.6.2. Laboratory Data

Additional laboratory tests other than assessment for factor VIII inhibitor antibodies will be presented in a summary table for all subjects including sample size, mean, standard deviation, median, minimum, and maximum.

6.6.3. Vital Signs and Physical Examination

Descriptive statistics of observed values and change from baseline for vital signs at each visit, including height (cm), weight (kg), blood pressure (mmHg), heart rate (beats/min), and body temperature (°F), as well as abnormal findings from physical examination, will be presented.

7. INTERIM ANALYSES

No formal interim analysis is planned for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or to support clinical development.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. Moroctocog alfa (AF-CC) LPDXYN042018.

9. APPENDICES

List of Abbreviations

Abbreviation	Term
ABR	Annualized bleeding rate
AE	Adverse event
AF-CC	Albumin-free cell culture
ALT	Alanine transaminase
AST	Aspartate transaminase
BU	Bethesda units
BUN	Blood urea nitrogen
CD4+	Cluster of differentiation 4 positive
CI	Confidence interval
CRF	Case report form
Eds	Exposure days
FAS	Full analysis set
FVIII	Factor VIII
HIV	Human immunodeficiency virus
INR	International normalized ratio
IU	International units
LPD	Local product document
N/A	Not applicable
PT	Prothrombin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TFC	Total factor consumption