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

Protocol Number:	B1831097
Medicinal Product:	Moroctocog alfa (AF-CC)
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Document History

Document	Version Date	Summary of Changes
Original protocol	10-April-2019	Not Applicable (N/A)
Protocol Amendment 1	16-September-2019	The following changes were made as part of Protocol Amendment 1: Removal of the word "pragmatic" from the study title. Addition of text throughout the protocol to clarify that samples taken for factor VIII (FVIII) development could be analyzed at the local laboratory or central laboratory. Modification of footnote of Table 1 (Schedule of Assessments) to clarify that at Screening, assessment for FVIII activity and inhibitor assessment will be conducted at the local laboratory and that a duplicate blood sample will be assessed by the central laboratory for confirmation of FVIII activity and inhibitor assessment. Modification of text defining immunocompromised subjects due to human immunodeficiency virus (HIV) infection in exclusion criterion #9, changing the limit of the viral load above or equal to 400,000 copies to above or equal to 100,000 copies/mL. Addition of exclusion criterion #11 to exclude subjects who have planned use of any non-study medication for the treatment of hemophilia (such as other factor replacement agents, bypassing agents, or non-factor treatments [for example, anti-tissue factor pathway inhibitors]). Addition of text clarifying that any subject using non-study medication for the treatment of hemophilia during their

		participation in the study will be withdrawn from the study, but patients who have a bleed away from the study site and are not treated by the investigator and need non-study treatment, will not be withdrawn from the study. Addition of text clarifying that subjects will be withdrawn from the study if their central laboratory result for inhibitor assessment at screening does not confirm eligibility per the local laboratory result. Addition of text to Section 5.4 to permit a dosing variance of ±5 IU/kg throughout the study in order to simplify dosing and minimizing potential waste.

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.

Abbreviations

This is a list of abbreviations used in the protocol. All of these abbreviations may or may not be used in the protocol.

Abbreviation	Term
ABR	annualized bleeding rate
AE	adverse event
AF-CC	albumin-free cell culture
ALT	alanine transaminase
AST	aspartate transaminase
BUN	blood urea nitrogen
CD4+	cluster of differentiation 4 positive
CDSCO	Central Drugs Standard Control Organization
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
DNA	deoxyribonucleic acid
EC	ethics committee
eCRF	electronic case report form
EDs	exposure days
EDP	exposure during pregnancy
EudraCT	European Clinical Trial Database
FVIII	factor VIII
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IU	international units
IV	intravenous
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
MedDRA	medical dictionary for regulatory activities
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
TFC	total factor consumption
ULN	upper limit of normal
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Background and Rationale

Hemophilia A (congenital factor VIII deficiency) is an X-linked recessive disorder caused by a congenital deficiency of coagulation factor VIII clotting activity. Patients with hemophilia A are usually treated by replacing the missing or defective factor VIII for treatment or prevention of hemorrhage.

The current protocol outlines a post-approval study to fulfill the Central Drugs Standard Control Organization (CDSCO) written request for supplementary information relating to the use of moroctocog-alfa (Albumin-free cell culture [AF-CC]) in Indian subjects with hemophilia A. The additional information will include safety and efficacy of moroctocog-alfa (AF-CC) in Indian patients with a diagnosis of congenital moderate or severe hemophilia A (factor VIII [FVIII]:C ≤5%).

Objectives and Endpoints

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 a 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.

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.

Secondary Endpoints

- Incidence of AEs;

- Incidence of SAEs;
- Annualized bleeding rate (ABR) during prophylaxis;
- Annualized total factor consumption (TFC) in international units (IU) and annualized TFC by weight (IU/kg) of moroctocog alfa (AF-CC) measured during the up to 8 weeks of treatment, by reason for infusion and total units consumed (across all reasons);
- Number of moroctocog alfa (AF-CC) infusions used to treat each bleed.

Study Design

This is a single-country, multicenter, open-label, interventional study which will be conducted in India. Subjects will be monitored according to local standard of care, which should be in accordance with the local product document (LPD).

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 at least 24 EDs or a period of up to 8 weeks on moroctocog alfa (AF-CC) treatment had occurred (whichever occurs first). Subjects will be treated with a dose and regimen of moroctocog alfa (AF-CC) prophylaxis in accordance with the LPD.

Study Treatments

Moroctocog alfa (AF-CC) will be administered by the investigator or a delegate at Visits 2 and 3. For administration between study visits, the product will be administered in accordance with procedures provided by their physicians. Subjects or caregivers/parents of subjects will be trained on how to administer moroctocog alfa (AF-CC) away from the study site, as applicable.

Statistical Methods

Sample Size

No formal statistical sample size computation will be performed for this study. The sample size rationale is based on the written request of the CDSCO.

At least 50 subjects will be enrolled to participate in the study.

Statistical Analyses

Efficacy Analyses

Efficacy analyses will be conducted on all subjects who receive at least one dose of moroctocog alfa (AF-CC) and have data evaluable for the efficacy assessment. The efficacy results of this study will be presented using descriptive statistics.

Safety Analyses

All safety analyses will be performed according to Pfizer Data Standards on all subjects who receive at least one dose of moroctocog alfa (AF-CC).

SCHEDULE OF ACTIVITIES

The Schedule of Activities (Table 1) provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Table 1. Schedule of Assessments

Visit Identifier	Visit 1 Screening (Screening/Baseline) (Within 28 days of Visit 2)	Visit 2 (Day 1)	Visit 3 (Day 24-32)	Visit 4 (Day 52-60)[a]	End of Study Visit (Day 80-88)[b]
Written informed consent/assent[c]	X				
Review inclusion/exclusion criteria	X				
Demographic data[d]	X				
Physical examination[e]	X	X	X	X	X
Vital signs[f]	X	X	X	X	X
Hemophilia A history[g]	X				
Medical history[h]	X				
Laboratory assessments: coagulation, hematology, biochemistry tests, factor VIII inhibitor[i]	X			X	
Documentation of testing for HIV and CD4[j]	X				
Moroctocog alfa (AF-CC) administration[k]		X	X		
Recording of AEs[l]	X	X	X	X	X
Concomitant treatments and therapies[m]	X	X	X	X	X
Subject infusion log[n]		X	X	X	

Visit Identifier	Visit 1 Screening (Screening/Baseline) (Within 28 days of Visit 2)	Visit 2 (Day 1)	Visit 3 (Day 24-32)	Visit 4 (Day 52-60)[a]	End of Study Visit (Day 80-88)[b]

AE=adverse event; CD4=cluster of differentiation 4; eCRF=electronic case report form; ED=exposure day; FVIII=factor VIII; HIV=human immunodeficiency virus.

a. Visit 4 should occur 3 (+7) days after the final dose; ie, subjects are requested to continue participation until 24 EDs or 8 weeks of treatment has been reached (whichever occurs first). As 24 EDs approaches, the timing of Visit 4 should be discussed with the subject.

b. The End of Study Visit can occur earlier if a subject achieves the requested 24 EDs sooner than 8 weeks. As the 24th ED approaches, the end of study should be discussed with the subject.

c. Signed informed consent must be obtained prior to any procedures or collection of study data.

d. Demographic data to be captured will include sex, year of birth, race and ethnicity. Age will be calculated as “year at screening visit minus birth year”.

e. As per site-specific practice.

f. Vital signs assessments should include height, weight, heart rate, blood pressure, and body temperature.

g. Record hemophilia A history, eg, date of diagnosis and severity of hemophilia A and previous use of factor VIII (prior EDs).

h. Recording of medical history will include: co-morbidities and surgical history.

i. Coagulation (with residual activity for factor FVIII), hematology, biochemistry tests will be performed by the local laboratory per local routine clinical practice. Samples for FVIII activity and inhibitor assessment will also be collected for analysis by local laboratory and central laboratory. At Screening, assessment for FVIII activity and inhibitor assessment will be conducted at the local laboratory. A duplicate blood sample will be assessed by the central laboratory for confirmation of FVIII activity and inhibitor assessment. If a subject’s central laboratory result does not confirm eligibility for Inhibitory assessment per the local laboratory result, the subject will be withdrawn from the study.

j. Serological tests for HIV and CD4 will be performed as per local routine clinical practice. Consent for HIV testing is to be taken per local standard practice and also the information on the result must be shared only with the subject/caregiver. If a subject tests positive for HIV, assessment of CD4 will be performed.

k. Moroctocog alfa (AF-CC) will be administered by the investigator or a delegate at Visits 2 and 3. Administration between study visits will be in accordance with procedures provided by the investigator. Subjects or caregivers/parents of subjects will be trained on how to administer moroctocog alfa (AF-CC), as applicable. Based on the subject infusion log, the investigator will assess the EDs at each visit and if there were any changes in dose. All infusions and any related bleeding episode information will be recorded.

l. SAEs will be recorded from when a subject provides informed consent through to the last subject visit. AEs (serious and nonserious) should be recorded on the eCRF from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

m. All concomitant treatments and therapies should be recorded.

n. Subject infusion log dispensed at Visit 2 and reviewed at each visit (discussion with subject and documentation in source about any concomitant medications, study compliance issues, and investigational product administration). In addition, information on bleeds/infusions in the subject infusion log will be transcribed at the site into the eCRF.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Coagulation factor VIII (recombinant) (moroctocog alfa [Albumin-free cell culture (AF-CC)]), is a purified B-Domain deleted recombinant FVIII protein produced by recombinant deoxyribonucleic acid (DNA) technology. It will be marketed in India as Xynthophilia®.[1]

Moroctocog-alfa (AF-CC) is indicated in India for the control and prevention of hemorrhagic episodes and for routine and surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency or classic hemophilia).[1]

1.2. Background and Rationale

Hemophilia A (congenital factor VIII deficiency) is an X-linked recessive disorder caused by a congenital deficiency of coagulation factor VIII clotting activity. Patients with hemophilia A are usually treated by replacing the missing or defective factor VIII for treatment or prevention of hemorrhage. Xyntha (moroctocog alfa, AF-CC) first received regulatory approval on 21 February 2008 in the United States.[1] Xyntha is a trade name of moroctocog alfa (AF-CC) used in some other countries. Xynthophilia is the trade name for moroctocog alfa (AF-CC) in India. Moroctocog alfa (AF-CC) was approved for use in the European Union under the trade name ReFacto AF on 26 February 2009.[2] At present, moroctocog alfa (AF-CC) pre-filled syringe is approved in 87 countries and marketed in 53 countries.

The current protocol outlines a post-approval study to fulfill the Central Drugs Standard Control Organization (CDSCO) written request for supplementary information relating to the use of moroctocog-alfa (AF-CC) in Indian subjects with hemophilia A. The additional information will include safety and efficacy of moroctocog-alfa (AF-CC) in Indian subjects with a diagnosis of congenital moderate or severe hemophilia A (FVIII:C ≤5%).

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the local product document (LPD).[1]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

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

2.1.2. 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. Endpoints

2.2.1. 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.

2.2.2. Secondary Endpoints

- Incidence of AEs;

- Incidence of SAEs;

- Annualized bleeding rate (ABR) during prophylaxis;

- Annualized total factor consumption (TFC) in international units (IU) and annualized TFC by weight (IU/kg) of moroctocog alfa (AF-CC) measured during the up to 8 weeks of treatment, by reason for infusion and total units consumed (across all reasons);

- Number of moroctocog alfa (AF-CC) infusions used to treat each bleed.

3. 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 exposure days (EDs) or a period of up to 8 weeks on moroctocog alfa (AF-CC) treatment had occurred (whichever occurs first). Subjects will be treated with a dose and regimen of prophylaxis in accordance with the LPD.[1]

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom the protocol intervention is considered appropriate by their health care provider and consistent with the LPD.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male subjects ≥12 years to ≤65 years with a diagnosis of congenital moderate or severe hemophilia A (FVIII:C ≤5%).

2. Documented history of at least 50 exposure days (EDs) to FVIII-containing products.

3. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative, parent(s)/legal guardian) has been informed of all pertinent aspects of the study. For minors under the age of legal consent in India, assent of the participating child needs to be documented for the age range 12 to 18 in addition to the parental informed consent.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Prior history of inhibitor to FVIII or positive inhibitor testing (≥0.6 BU/mL) during Screening. Clinical signs or symptoms of decreased response to FVIII.

2. Known hypersensitivity to the active substance or any of the excipients.

3. Known allergic reaction to hamster proteins.

4. Presence of any bleeding disorder in addition to hemophilia A.

5. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days before the current study begins and/or during study participation.

6. Planned surgery within 6 months from the start of the study.

7. Unsuitable to participate in study for any other reason as assessed by the investigator; including any disorder, except for conditions associated with hemophilia A, which in the investigator's opinion might jeopardize subject's safety or compliance with the protocol.

8. Subjects (or a legally acceptable representative) is not able to understand study documents and study procedure.

9. Immunocompromised subjects due to human immunodeficiency virus (HIV) infection (defined as viral load above or equal to 100,000 copies/mL; and for HIV+ subjects: cluster of differentiation 4 positive (CD4+) lymphocyte count below or equal to 200/µL). HIV status and CD4+ lymphocyte count results may be obtained at screening or from available medical records; results must be not older than 6 months prior to screening.

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, subjects who have been previously enrolled into the study, or subjects who are Pfizer employees directly involved in the conduct of the study.

11. Planned use of any non-study medication for treatment of hemophilia (eg, other factor replacement agents, bypassing agents, or non-factor treatments [such as anti-tissue factor pathway inhibitors]).

4.3. Randomization Criteria

Not applicable as this is a single-arm, non-randomized study.

4.4. Life Style Guidelines

Not applicable.

5. STUDY INTERVENTION

5.1. Allocation to Intervention/Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

The investigator will assign subject identification numbers sequentially to the subjects as they are screened for the study. This identification number will be retained throughout the study. A subject number must never be reassigned or reused for any reason. The investigator must maintain a log linking the subject number to the subject's name.

5.2. Drug Supplies

5.2.1. Dosage Form(s) and Packaging

Moroctocog alfa (AF-CC) is a freeze-dried lyophilized powder for reconstitution in a single-use vial. Investigational product will be provided by Pfizer as white to off-white lyophilized powder which will be clear to slightly opalescent, colorless solution upon reconstitution with sterile 0.9% sodium chloride solution provided in the kit for intravenous injection.

The label attached to each moroctocog alfa (AF-CC) vial and diluent container minimally states the product name and amount, potency (drug only), lot number, directions for storage, and name of manufacturer (the diluent may not have all this information). Labels may contain other information, such as expiry date, as required by local regulatory guidelines.

CCI

[redacted]

5.3. Preparation and Dispensing

Pfizer will provide the investigators with a sufficient amount of moroctocog alfa (AF-CC). Once moroctocog alfa (AF-CC) is dispensed to a subject it must not be re-dispensed to another subject. The product should be prepared, reconstituted, and used in accordance with procedures provided by their physicians. For instructions, subjects should follow the recommendations in the Administration and Reconstitution sections of the local product document (LPD). At each visit before Visit 4, the subject should receive a sufficient quantity of investigational product in order to last until their next visit. Further information on moroctocog alfa (AF-CC) will be provided in the Investigational Product Manual.

5.4. Administration

Moroctocog alfa (AF-CC) will be administered by the investigator or a delegate at Visits 2 and 3. For administration between study visits, the product will be administered in accordance with procedures provided by their physicians. Subjects or caregivers/parents of subjects will be trained on how to administer moroctocog alfa (AF-CC) away from the study site, as applicable.

Prophylaxis:

Moroctocog alfa (AF-CC) should be administered prophylactically in previously treated patients at a dose of 30 ± 5 IU/kg given 3 times weekly in accordance with the LPD.[1]

On-Demand Treatment:

The amount to be administered and the frequency of administration should always be tailored to the clinical effectiveness in individual subjects.

In the case of the following hemorrhagic events, consideration should be given to maintaining the factor VIII activity at or above the plasma levels (in % of normal or in IU/dL) for the indicated period, as outlined in Table 2.

Table 2 can be used to guide dosing in bleeding events and surgery.

Table 2. Maintenance of Factor VIII Activity for Various Hemorrhagic Events

Type of Hemorrhage	Factor VIII Level Required (% or IU/dL)	Frequency of Doses (h)/ Duration of Therapy (d)
Minor		
Early hemarthrosis, superficial muscle or soft tissue and oral bleeds.	20-40	Repeat every 12 to 24 hours as necessary until resolved. At least 1 day, depending upon the severity of the hemorrhage.
Moderate		
Hemorrhages into muscles. Mild head trauma capitus. Minor operations including tooth extraction. Hemorrhages into the oral cavity.	30-60	Repeat infusion every 12-24 hours for 3- 4 days or until adequate hemostasis is achieved. For tooth extraction a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient.
Major		
Gastrointestinal bleeding. Intracranial, intraabdominal or intrathoracic hemorrhages. Fractures. Major operations.	60-100	Repeat infusion every 8-24 hours until threat is resolved or in the case of surgery, until adequate local hemostasis is achieved, then continue therapy for at least another 7 days.

Source: LPD.[1]
IU=international unit; LPD=local product document.

In the interest of simplifying dosing and minimizing potential waste, a dosing variance of ±5 IU/kg is permitted throughout the study.

5.5. Drug Storage

The investigator, or an approved representative, eg, study coordinator, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Moroctocog alfa (AF-CC) should be stored in its original container and in accordance with the storage conditions stated on the label. The reconstituted solution of moroctocog alfa (AF-CC) may be stored at room temperature prior to infusion. The reconstituted solution of moroctocog alfa (AF-CC) does not contain preservative and should be infused within 3 hours after reconstitution.

Storage conditions stated in SRSD (ie, LPD) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study, on all business days. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions.

Site staff will instruct subjects (or caregivers if applicable) on storage requirements for take home medications including how to report temperature excursions.

5.6. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. When investigational product is taken home by the subject, any unused products must be returned to the investigator by the subject at Visit 4.

All used and unused vials of moroctocog alfa (AF-CC) and unused diluent syringes will be used for investigational product accountability. Used diluent syringes will not be returned to the study center for test article accountability due to the potential risk of blood contamination. Therefore, each returned used moroctocog alfa (AF-CC) vial indirectly accounts for a diluent syringe used by the subject. The investigator can use a 1:1 ratio of used drug vials to account for used diluent syringes. The investigator uses this information to maintain an accurate and complete moroctocog alfa (AF-CC) investigational product accountability log.

Administration of moroctocog alfa (AF-CC) by subjects or their caregivers away from the study site should be captured in the Subject Infusion Log.

The monitor will review drug accountability during routine monitoring visits. Drug accountability will be done at all study visits after Day 1 until Visit 4. Any discrepancies must be investigated and their resolution documented. At the completion or termination of the study, a final drug accountability review and reconciliation must be performed. Any discrepancies that cannot be reconciled must be documented in writing in the study file.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

The use of permitted concomitant medication must be in accordance with the study drug label. The use of concomitant treatments will be recorded throughout the study.

6. STUDY PROCEDURES

6.1. Screening – Visit 1 (within 28 Days prior to Day 1)

The following information and assessments will be collected and documented at screening for each subject:

- Obtain written informed consent/assent;
- Review of eligibility criteria (as described in Sections 4.1 and 4.2).;

- Demographic data (sex, year of birth, race and ethnicity); age will be calculated as "year at screening visit minus birth year";
- Physical examination;
- Vital signs (height, weight, heart rate, blood pressure, and body temperature);
- Record hemophilia A history (date of diagnosis and severity of hemophilia A and previous factor VIII use [prior EDs]);
- Medical history (including co-morbidities and surgical history);
- Laboratory assessments (coagulation [with residual activity for factor VIII], hematology, and biochemistry (via local laboratory) and blood samples drawn for factor VIII activity and inhibitor testing (via local laboratory and central laboratory). At Screening, assessment for FVIII activity and inhibitor assessment will be conducted at the local laboratory. A duplicate blood sample will be assessed by the central laboratory for confirmation of FVIII activity and inhibitor assessment. If a subject's central laboratory result does not confirm eligibility for Inhibitory assessment per the local laboratory result, the subject will be withdrawn from the study.
- Documentation of testing for HIV (for HIV+ subjects: cluster of differentiation 4 [CD4] viral load);
- Recording of SAEs;
- Concomitant treatments and therapies.

6.2. Study Period

6.2.1. Visit 2 (Day 1)

The following information and assessments will be collected and documented for each subject:

- Physical examination;
- Vital signs (weight, heart rate, blood pressure, and body temperature);
- Moroctocog alfa (AF-CC) administration by the investigator or delegate (administration between study visits will be in accordance with procedures provided by the investigator. Subjects or caregivers/parents of subjects will be trained on how to administer moroctocog alfa [AF-CC], as applicable);
- Recording of AEs;

- Concomitant treatments and therapies;

- Dispensing of Subject Infusion Log and instruct on its use (discussion with subject and documentation in source about any concomitant medications, study compliance issues, and investigational product administration. In addition, information on bleeds/infusions will be transcribed into the electronic CRF [eCRF]).

6.2.2. Visit 3 (Day 24-32)

The following information and assessments will be collected and documented for each subject:

- Physical examination;

- Vital signs (weight, heart rate, blood pressure, and body temperature);

- Moroctocog alfa (AF-CC) administration by the investigator or delegate (administration between study visits will be in accordance with procedures provided by the investigator. Subjects or caregivers/parents of subjects will be trained on how to administer moroctocog alfa [AF-CC], as applicable);

- Recording of AEs;

- Concomitant treatments and therapies;

- Review of Subject Infusion Log and transcription of bleeds/infusions data into the eCRF.

6.2.3. Visit 4 (Day 52-60, or earlier)

It should be noted that this visit will occur between Day 52 and Day 60 or earlier and should occur 3 (+7) days after the final dose of moroctocog alfa (AF-CC) (if the requested number of EDs are reached [24 EDs or 8 weeks of treatment, whichever occurs first]). As 24 ED approaches, the timing of Visit 4 should be discussed with the subject.

The following information and assessments will be collected and documented for each subject:

- Physical examination;

- Vital signs (weight, heart rate, blood pressure, and body temperature);

- Laboratory assessments (coagulation [with residual activity for factor VIII], hematology, and biochemistry (via local laboratory) and blood samples drawn for factor VIII activity and inhibitor testing (via local laboratory and central laboratory);

- Recording of AEs;
- Concomitant treatments and therapies;
- Review of Subject Infusion Log and transcription of bleeds/infusions data into the eCRF.

6.3. End of Study Visit (Day 80-88 or earlier)

It should be noted that this visit will occur between approximately Day 80 and Day 88 or earlier if the requested number of EDs is reached (24 EDs before Day 60). As the 24th ED approaches, the end of study should be discussed with the subject. The following information and assessments will be collected and documented for each subject:

- Physical examination;
- Vital signs (weight, heart rate, blood pressure, and body temperature);
- Recording of AEs;
- Concomitant treatments and therapies;

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator. Any subject who uses non-study medication for the treatment of hemophilia (eg, other factor replacement agents, bypassing agents, or non-factor treatments [such as anti-tissue factor pathway inhibitors]) will be considered to have a protocol violation and will be withdrawn from the study. The exception to this would be for subjects who require non-study treatment for a bleed away from the study site. This would be considered a protocol deviation rather than a protocol violation that would not require withdrawal from the study.

Subjects will be withdrawn from the study if their central laboratory result for inhibitor assessment at screening does not confirm eligibility per the local laboratory result.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. If possible, subjects who withdraw from the study, and who do not withdraw consent, should be requested to return to the study center to have the procedures listed under Visit 4 completed. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that protocol required assessments and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol required assessment cannot be performed, the investigator will document the reason for the missed assessment and any corrective and preventative actions which s/he has taken to ensure that required processes are adhered to as soon as possible. These will be documented as protocol deviations. The study team must be informed of these incidents in a timely manner. The assessments described in this section will be performed at times defined in the schedule of assessments (Table 1) and Section 6 of this protocol.

7.1. Efficacy Assessments

7.1.1. Total Factor VIII Consumption and Bleeds

Subjects/caregivers or the investigator or his/her delegate will record all moroctocog alfa (AF-CC) infusions, including each prophylaxis infusion (and dose) and those administered to treat a bleeding episode in the Subject Infusion Log. For on-demand infusions (ie, to treat a bleeding episode), the date and time that the bleeding event occurs, type/etiology of bleed (eg, spontaneous or traumatic), location of bleed, and details of each infusion (dose) administered to resolve the bleed) will be recorded.

7.2. Safety Assessments

Safety assessments throughout the study will include collection of AEs, laboratory safety testing, vital signs, and physical examination at the time points specified in (Table 1 [schedule of assessments]), but can be conducted at other time points at the investigator's discretion.

7.2.1. Laboratory Evaluations

Laboratory evaluations, according to local laboratory and/or central laboratory assessment, will be conducted at the time points specified in Table 1.

- 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).

7.2.2. Vital Signs and Physical Examination

Vital Signs and physical examinations will be conducted at the time points specified in Table 1.

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

  - Supine blood pressure should be measured, after the subject has been at rest for at least 5 minutes, using a digital or mercury sphygmomanometer with a cuff appropriate to the subject's arm girth.

- Physical examination: to include general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, breasts, abdomen, extremities, neurological, back/spinal, and lymph nodes. This will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulations.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of 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 nonserious AE 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.

8.2. Reporting Period

For SAEs, 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. AEs and 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 AEs and 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 nonserious) should be recorded on the eCRF from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

8.3. 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 breastfeeding;
- Medication error;
- Occupational exposure.

In this population, bleeding episodes are not considered AEs. Bleeding episodes should be reviewed by the investigator and those that meet the criteria of serious should be reported as an SAE.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, 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 adverse event (AE) page of the eCRFs 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 and, if applicable, any associated AE(s) are captured on an AE eCRF page (refer to the ADVERSE EVENT REPORTING section for further details).

8.5. 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 AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

An SAE 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.

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. The important medical event should be reported as serious, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes.

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.

In addition, FVIII inhibitor development (defined as a titer ≥0.6 BU/mL confirmed by central laboratory testing) will be considered an SAE.

8.7. 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 8.17).

8.8. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in AST and/or 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 values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

- Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased by 1 × ULN or ≥3 × 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 liver function test (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.

8.9. Additional Safety Information

8.9.1. Medically Important Events

For this study, the medically important events are any confirmed FVIII inhibitor development (defined as a titer ≥0.6 BU/mL confirmed by central laboratory testing). These events must be reported as SAEs.

8.10. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to 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 AE is not in itself an SAE. Examples include:

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

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned 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 noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.11. Severity Assessment

If required on the AE eCRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. 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 AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.12. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the eCRF, 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 AE; 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 Section 8.16). 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 that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.13. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy 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;

   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).

2. A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/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 a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (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 until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental 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 preprocedure 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, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs 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 SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to 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 in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.14. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

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

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.15. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legally acceptable representative. In addition, each study subject/parent/legally acceptable representative will be questioned about AEs. Bleeding episodes are not considered AEs (further details are provided in Section 8.3).

8.16. 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.

8.17. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames 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 SAEs is more detailed than that captured on the AE eCRF. In general, this will include a description of the AE 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, 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.

8.18. Nonserious Adverse Event Reporting Requirements

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

8.19. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

No formal statistical sample size computation will be performed for this study. The sample size rationale is based on the written request of the CDSCO.

At least 50 subjects will be enrolled to participate in the study. With a sample size of 50, if FVIII inhibitors were detected, the corresponding exact two-sided 90% confidence intervals (CIs) for the proportion of subjects who developed FVIII inhibitors would be:

Observed cases	Observed rate	90% CI (%)
1	2%	(0.10, 9.14)
2	4%	(0.72, 12.06)
3	6%	(1.66, 14.78)

9.2. Data Sources

The investigator will first record the study data in source documents, such as medical records which will include treatment data, during subjects scheduled visits. Another source document will be the Subject Infusion Log from which bleeding assessment, investigational product infusion that may occur outside hospital or clinic and other information will be captured during this study. Each subject will be identified by a single number that will be maintained throughout the study. The investigator or the delegate will then enter the applicable study data and Subject Infusion Log data into the eCRFs.

9.3. Effectiveness Analysis

Efficacy analyses will be conducted on all subjects who receive at least one dose of moroctocog alfa (AF-CC) and have data evaluable for the efficacy assessment. The efficacy results of this study will be presented using descriptive statistics. The following descriptive statistics will be used:

- For continuous endpoints: sample size, mean, standard deviation, median, minimum and maximum;
- For binary or categorical endpoints: sample size, frequency and percentage (proportion).

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.

9.3.1. Analysis of Primary Endpoint

Not applicable, since all efficacy endpoints are secondary endpoints in this study.

9.3.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints assessed during this study are described in this section.

9.3.2.1. Annualized Bleeding Rate During Prophylaxis

The ABR will be derived for each subject by using the following formula:

ABR = number of bleeds/(Treatment interval duration/365.25).

The number of bleeds for each subject for the ABR calculation includes all bleeds 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). 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. Additionally, ABRs will be summarized by bleed type (eg, spontaneous or traumatic) and by bleed location (eg, joint, soft tissue/muscle).

9.3.2.2. Number of Moroctocog alfa (AF-CC) Infusions Used to Treat Each Bleed

The investigational product infusion log case report form 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.

Summary statistics will be reported using the number of infusions as a continuous variable. In addition, frequency tables will be provided for each of the categories (1, 2, 3, 4, or >4 infusions needed to treat the bleed), in which the numerator is the number of bleeds falling into each category, and the denominator is 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.

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

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

Annualized TFC = TFC / (Treatment interval duration/365.25).

In addition, for each infusion, IU/kg will be calculated, using the most recently recorded weight measurement, and annualized TFC by weight (IU/kg) will be summarized similarly, by reason for infusion, and for the total.

9.4. Analysis of Other Endpoints

Not applicable.

9.5. Safety Analysis

All safety analyses will be performed according to Pfizer Data Standards on all subjects who receive at least one dose of moroctocog alfa (AF-CC).

The primary safety endpoint is the proportion of subjects with central-laboratory-confirmed positive FVIII inhibitor, defined as ≥0.6 BU/mL, developed during the course of the study. Only subjects with a confirmed positive FVIII inhibitor will count towards the numerator of the derived proportion. The denominator will be the total number of subjects at risk for developing an inhibitor during the study, who received at least one dose of moroctocog alfa (AF-CC). The corresponding two-sided 90% CIs will be reported. Secondary safety endpoints include the occurrence of AEs and SAEs.

Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms. Additional analyses may be done for safety endpoints if needed. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.

9.6. Data Monitoring Committee

Not Applicable.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the subject's chart in the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents.

In addition, the Subject Infusion Log will be a source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed informed consent/assent documents, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Council for Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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/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.

12.2. 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), the Declaration of Helsinki (World Medical Association 1996 & 2008), and Schedule Y, Drugs and Cosmetics Act 1940 and Rules 1945.

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

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include OMITTING subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the

study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of 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 their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study subject, or his or her 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, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then 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/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 India law, they must be re-consented 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 or the 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.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues 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 ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF STUDY

13.1. End of Study in all Participating Countries

End of Study in all participating countries (India) is defined as Last Subject Last Visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all eCRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. 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), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), www.ctri.nic.in (Clinical Trials Registry -India), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov.

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

15.2. Publications by Investigators

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) 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 (other than the Study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. 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, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Moroctocog alfa (AF-CC) LPDXYN042018.

2. Commission of the European Communities. Commission decision of 26.2.2009 Amending the Marketing Authorisation for "ReFacto AF- Moroctocog Alfa", a Medicinal Product for Human Use, Granted by Decision C(1999)938.

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