Non-Interventional (NI) Post-Marketing Surveillance Protocol

Study Information

Title	**Post-Marketing Surveillance To Observe Safety And Efficacy Of Xyntha Solofuse Prefilled Syringe**
Protocol Number	B1831086
Protocol Version	Amendment 5.0
Date of Latest Protocol Version	17 May 2018
Active Substance	PF-05208756
Medicinal Product	Xyntha Solofuse prefilled syringe (moroctocog alfa) (Antihemophilic factor VIII, recombinant)
Study Objective	To observe safety and efficacy of Xyntha Solofuse prefilled syringe during the post-marketing surveillance
Created by:	PPD Pfizer Pharmaceuticals Korea Ltd. Seoul, Korea

[redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse Event Monitoring
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MFDS	Ministry of Food and Drug Safety
NIS	Non-Interventional Study
PMS	Post-Marketing Surveillance
SAP	Statistical Analysis Plan
SRSD	Single Reference Safety Document

2. RESPONSIBLE PARTIES

Principal Investigator of the Protocol

Name, Degree	Title	Affiliation	Address
PPD MD	Non-Interventional Study Lead	Pfizer Pharmaceuticals Korea Ltd.	Seoul, Korea

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	February 23, 2015	Administrative amendment	Refer to the Summary of Changes	Refer to the Summary of Changes	Amended according to the supplementation request by MFDS
2	April 16, 2015	Administrative amendment	Refer to the Summary of Changes	Refer to the Summary of Changes	Rewording appropriate for the retrospective study method
3	September 24, 2015	Administrative amendment	Refer to the Summary of Changes	Refer to the Summary of Changes	Reply to MFDS inquiries and rewording
4	16 October 2017	Substantial amendment	Refer to the Summary of Changes	Refer to the Summary of Changes	Rewording to adjust the number of target patients
5	17 May 2018	Administrative amendment	Refer to the Summary of Changes	Refer to the Summary of Changes	Amended according to the supplementation request by MFDS

4. MILESTONES

Milestones	Planned Dates
Start date of data collection	02 January 2016
End date of data collection	30 September 2017
First year (1-1) periodic report (MFDS)	30 November 2014
First year (1-2) periodic report (MFDS)	30 May 2015
Second year (2-1) periodic report (MFDS)	30 November 2015
Second year (2-2) periodic report (MFDS)	30 May 2016
Third year annual report (MFDS)	30 November 2017
Re-examination report (MFDS)	29 June 2018

Abbreviation: MFDS = Ministry of Food and Drug Safety

5. RATIONALE AND BACKGROUND

Xyntha Solofuse prefilled syringe was approved on March 31, 2014 in Korea. The Xyntha Solofuse prefilled syringe is administered by intravenous infusion after reconstitution of the freeze-dried powder with the diluent (0.9% Sodium Chloride). This drug consists of the identical ingredients with the previous Xyntha injection, and the drug and the diluent are supplied within the prefilled dual-chamber syringe. As required for all new drugs approved by the Ministry of Food and Drug Safety (MFDS), information on the safety and efficacy of the new drug should be provided based on the study conducted with at least 600 study subjects who are administered this drug in the setting of routine practice for 4 years from the approval date (March 31, 2014 - March 30, 2018). This non-interventional post-marketing surveillance (PMS) study is an obligation to the MFDS. However, it is expected that about 95 subjects who received this drug should be recruited and registered as study subjects. Considering the number of subjects who meet the analysis exclusion criteria, safety and efficacy information for at least 86 subjects will be collected for all subjects who received this drug during the study period. Background information on Xyntha Solofuse prefilled syringe can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to the Xyntha Solofuse prefilled syringe in this study.

6. STUDY OBJECTIVE

This study aims to observe the safety and efficacy of the Xyntha Solofuse prefilled syringe in the setting of routine practice. The primary objective is to detect medically significant events

(factor VIII inhibitor). The secondary objective is to observe the overall efficacy and safety of the Xyntha Solofuse prefilled syringe including serious adverse events.

7. STUDY METHODS

7.1. Study design

In this open-label, non-comparative, observational, non-interventional, retrospective and multi-center study, post-marketing surveillance data will be collected retrospectively for up to 6 months from the initial administration day of the Xyntha Solofuse prefilled syringe injected into patients who have been administered the Xyntha Solofuse prefilled syringe (as part of routine treatment at the Korean health care canter which has certified investigators). If the study subject has not completed the 6-month treatment, relevant data should be collected based on the medical records within the 30 days after the last administration of the drug.

7.2. Setting

7.2.1. Inclusion criteria

To be eligible to enroll in this study, the study subjects will have to meet all the following inclusion criteria:

1. Hemophilia A (congenital factor VIII deficiency) patients who have been administered according to the indication of the product

    1) Control and prevention of bleeding episodes and for routine and surgical prophylaxis in patients with hemophilia A (congenital factor VIII deficiency)

    2) This drug does not contain von Willebrand factor and, therefore, is not indicated in von Willebrand's disease

2. Those who have been administered the Xyntha Solofuse prefilled syringe at least once

7.2.2. Exclusion criteria

Patients who satisfy the following criteria are not included in the study according to the local labeling:

1. Patients who have a history of hypersensitivity to the Xyntha Solofuse prefilled syringe or the ingredients of this drug.

2. Patients who have a history of hypersensitivity to hamster proteins.

3. Patients who have bleeding disorders other than hemophilia A.

4. Patients who have a history of FVIII inhibitors, or currently have or are suspected of having FVIII inhibitors. In case inhibitor titers quantified in Bethesda Units in the laboratory test results are within the normal laboratory range or at least 0.6 BU/mL. If

laboratory tests cannot be performed, the investigator will determine whether or not inhibitors exist based on the clinical assessment results that show a decrease in efficacy of the replacement of FVIII (e.g. bleeding at least once, if the replacement of anti-bleeding agents is needed to be administered, and if frequency or dosage of replacement FVIII therapy needs to be increased).

5. Use of immunomodulatory therapy. (e.g. intravenous injection of immunoglobulin, use of regular systemic corticosteroids, cyclosporine, and mediators of anti-TNF-α)

7.2.3. Study Period

As specified in the product approval issued by the Ministry of Food and Drug Safety, the study will be conducted for 4 years from the approval date of March 31, 2014 to March 30, 2018.

7.2.4. Administrationand Dosage

This drug should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.

This drug is appropriate for use in adults and children of all ages, including newborns.

Formula

Required units	=	body weight (kg)	x	desired factor VIII rise (IU/dL or normal %)	x	0.5 (IU/kg per IU/dL)

Precise monitoring of the replacement therapy by means of plasma factor VIII activity assay should be considered, particularly for surgical intervention.

Dosing for Bleeding and Surgery

In the cases 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 outline in the following table.

<Maintenance of Factor VIII Activity for Various Hemorrhagic Events>

Degree of Hemorrhage/ Type of surgical procedure	Factor VIII Level Required (% or IU/dl)	Frequency of Doses (hours) /Duration of Therapy (days)
Bleeding Early hemathrosis, minor muscle or oral bleeds	20-40	Repeat every 12 to 24 hours as necessary until resolved. At least 1 day, depending upon the severity of the bleeding episode.
Bleeding into muscles. Bleeding into the oral cavity. Mild head trauma.	30-60	Repeat infusion every 12 to 24 hours for 3-4 days or until adequate local hemostasis is achieved.
Gastrointestinal bleeding. Intracranial, intra-abdominal or intrathoracic bleeding. Fractures.	60-100	Repeat infusion every 8 to 24 hours until bleeding is resolved.
Surgery Minor operation (including tooth extraction)	30-60	Repeat infusion every 12 to 24 hours for 3-4 days or until adequate local hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrionlytic therapy within 1 hour may be sufficient.
Major operation	60-100	Repeat infusion every 8 to 24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved. Then continue therapy for at least another 7 days to maintain the factor VIII activity at 30 to 60% (IU/dl)

Dosage for Prophylaxis

This drug has been administrated prophylactically in a pivotal clinical trial in adolescent and adult previously treated patients at a dose of 30 ± 5 IU/kg given 3 times weekly.

Administration

This drug is administered by intravenous (IV) infusion after reconstitution of the freeze-dried powder with the diluent (0.9% Sodium Chloride). Both the Xyntha powder and the diluent are supplied within the prefilled dual-chamber syringe.

Patients administered Xyntha Solofuse prefilled syringe 250 IU, 500 IU, 1000 IU, 2000 IU, or 3000 IU at least once in the routine practice will be observed. All the enrolled subjects

should meet the general prescription criteria of Xyntha Solofuse prefilled syringe according to the local product document, and should be included in this study based on the judgment of the investigator.

7.2.5. Study Procedures

The investigator collects data on the Xyntha Solofuse prefilled syringe retrospectively by recording the data in the case report form from the initial administration day up to 6 months from patients who have been administered the Xyntha Solofuse prefilled syringe at least once or are scheduled to be administered the Xyntha Solofuse prefilled syringe.

This study does not have scheduled visit dates because it is not an interventional study. Safety data will be collected at each visit. If a study subject experiences bleeding episodes during the up to 6-month observation period, the clinical response to the treatment required for each bleeding episode will be evaluated.

7.2.5.1. Basic Information

The following information will be recorded on the case report form for each study subject:

1. State (age and sex) of the study subject
2. History of hemophilia A
    1) Duration of disease
    2) Previous exposure to plasma-derived factor VIII
    3) Personal history of allergic reactions to factor VIII products (within 12 months)
    4) Family history of hemophilia A
    5) Family history of factor VIII inhibitors
    6) Family history of allergic reactions to factor VIII products (within 12 months)
    7) Severity
3. Medical History
    1) Past history and present illness
4. Concomitant Drug/Therapy
    1) Drug administered concomitantly with Xyntha Solofuse prefilled syringe
    2) Therapy given concomitantly with Xyntha Solofuse prefilled syringe infusion

5. Administration conditions of Xyntha Solofuse prefilled syringe

    1) Prophylactic Therapy

    2) Administration conditions of Xyntha Solofuse prefilled syringe (on-demand treatment: surgery and bleeding)

6. Laboratory tests: Blood test, biochemistry test (including inhibitors), urinalysis

7. Study site code: Enter the assigned code number.

8. Department code name: Enter the assigned code number.

9. Study subject ID: The investigator will sequentially assign each subject a subject identification number, a 4-digit number. Pfizer will allocate the total number of cases that need to be collected to each study site at the time of signing the contract with each site.

10. Signature of the investigator: The contracted investigator must sign the case report form after reviewing it.

7.2.5.2. Concomitant Therapy

With regard to all the concomitant therapies, the name, dosage, route of administration, period and treatment purpose should be recorded in the case report form of each study subject.

7.2.5.3. Safety and Efficacy Data

Please refer to Section 7.3 for safety and efficacy data collection.

7.3. Variables

7.3.1. Safety Variables

This study will investigate clinical nature, incidence rates, duration, severity, discontinuation due to adverse events, results and possible causality of adverse events.

7.3.2. Safety Evaluation

7.3.2.1. Definition of adverse events

Adverse events are all the undesirable medical incidents that occur in the study subjects who are administered the drug. Such incidents do not necessarily have causality with the therapy or use of the drug. Examples of adverse events include but are not limited to the following:

- Abnormal test results (see the following for the case where abnormal test results are considered as adverse events.)
- Clinically significant symptoms and signs

- Changes in physical examination findings
- Hypersensitivity reactions
- Progress/deterioration of underlying diseases
- Lack of Efficacy
- Drug abuse
- Drug dependency

Also, drugs may include signs or symptoms due to the following:

- Drug overdose
- Discontinuation of drug administration
- Drug misuse
- Off-label use
- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure during breastfeeding
- Medication error
- Occupational exposure

Abnormal test findings

The following is the criteria for deciding whether or not abnormal objective test results should be reported as adverse events:

- If the test result is related to the accompanying symptoms, and/or;
- If the test result requires separate diagnostic examinations or medical/surgical interventions, and/or;
- If the test result causes changes to study dosage or discontinuation of the study, significant additional concomitant drug therapy or other therapy, and/or;
- If the investigator or the sponsor considers the test result as an adverse event.

Abnormal test values that simply repeat and do not correspond to any of the above conditions are not adverse events. All the abnormal test results that are distinguished as errors do not have to be reported as adverse events.

7.3.2.2. Serious Adverse Events

Serious adverse events or serious adverse drug reactions are undesirable medical incidents as follows:

- If a death is caused;
- If it is life-threatening (risk of an immediate death);
- If hospitalization or extended duration of hospitalization is required;
- If persistent or significant disability or malfunction is induced (substantial disruption in the ability to conduct normal life functions);
- If congenital anomalies/birth defects are induced.

If lack of efficacy is related to any serious adverse event, the lack of efficacy should be reported as an adverse event.

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

Examples of such events include allergic bronchospasm requiring intensive care in the emergency room or at home, blood dyscrasia or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Hospitalization

Hospitalization is defined as all initial admission to the hospital or health facility equivalent to the hospital (including admission for less than 24 hours) or extended duration of the existing hospitalization. Hospitalization also includes the transition to the acute/intensive care unit within the hospital (e.g. from psychiatry to the internal medicine ward, from the internal medicine ward to the cardiovascular disease intensive care unit, or from neurology to the tuberculosis unit). Emergency room visits do not necessarily mean hospitalization, but the event that causes the emergency room visit should be evaluated for its medical significance.

When adverse medical events do not occur, hospitalization itself cannot be seen as an adverse event and should not be reported. For example, the following hospital admission involving no adverse events is not reported:

- Social hospitalization (e.g. the study subject has no place to stay)
- Administrative hospitalization (e.g. for annual periodical medical examination)

- Optional hospitalization that is not related to any sudden medical adverse events (e.g. for plastic surgery chosen by the subject)
- Hospitalization for observation that involves no medical adverse events
- Hospitalization to treat the existing condition that is not related to the manifestation of a new adverse event, or the deterioration in the existing condition (e.g. for complete medical examination of abnormal laboratory test results before continuing treatment)
- Hospitalization according to the protocol during the clinical trial (e.g. for the procedure required by the study protocol)

7.3.2.3. Collection of Adverse Event Data

All the adverse events observed in the post-marketing surveillance or reported voluntarily are recorded, regardless of the dose groups (if applicable) or suspicion of the causal relationship with Xyntha Solofuse prefilled syringe, on the adverse event report page of the case report form (CRF) as follows:

For all the adverse events, the investigator must collect adequate data both to determine outcomes of the adverse events and to assess whether or not the adverse events meet the criteria for the serious adverse event that should be reported immediately to Pfizer or its representative (see Section “Serious Adverse Events”). For all the adverse events, the investigator must collect sufficient data to determine the causality. The investigator should determine the causality of the adverse events. For the adverse events that have a causal relationship with Xyntha Solofuse prefilled syringe, follow-ups by the investigator are required until the event or its sequela resolves or stabilizes at a level acceptable to the investigator, and until it corresponds with Pfizer’s opinion on that assessment.

7.3.2.4. Laboratory Test Data

Laboratory tests do not have to be conducted because this study is a non-interventional study. After the investigator conducts laboratory tests for diagnosis and monitoring by methods of general medical practice, the results can be collected. First, indicate whether the test was conducted by marking with either “Not tested” or “Tested”.

- Test Items: Record the items for which abnormal test measurements have been found.

- Normal value range (unit): Record the normal range of the relevant institution with the unit for each item entered.

- Date of Test: Record in the order of year/month/day.

- Pre-dose/post-dose: Record the test measurements.

If “Tested” is marked, check “Yes”, “No” or “Not tested during drug administration” to indicate if there has been a clinically significant abnormality after drug administration

compared to before drug administration. If "Yes" is checked, record details for the following items:

See Section 7.3.2.1 to decide if the clinically significant abnormality should be reported as an adverse event. If it meets the pertinent criteria, it should be recorded in the adverse event section of the case report form.

7.3.3. Efficacy variables

- On-demand treatment

- Responses to all the injection of the Xyntha Solofuse prefilled syringe used to treat bleeding (4 point scale: excellent, good, moderate, and no response)

- Number of observations of less than expected therapeutic effect (LETE) (LETE: "no response" rated after each infusion of 2 consecutive infusions within 24 hours after on-demand treatment)

- In case of bleeding: The number of infusions of Xyntha Solofuse prefilled syringes used to treat each new bleeding episode is rated.

- Mean infusion dosage

- Prophylactic Therapy

- Percentage of the study subjects who have experienced bleeding (overall, spontaneous)
- Annualized bleeding rates (ABRs)
- Number of observations of less than expected therapeutic effect (LETE)

  (LETE: Atypical bleeding occurring within 48 hours after administration of the Xyntha Solofuse Prefilled Syringe by dosage for the prevention of bleeding (spontaneous/atraumatic))

- Mean infusion dosage

- Total factor consumption

- If the data are adequate, sub-analysis can be performed for each factor that is considered to affect the efficacy.

7.3.4. Efficacy Evaluation

<u>On-demand treatment (surgery and bleeding)</u>

The study subjects (or caregivers) will be given a general explanation on keeping a diary during the routine treatment situation for the purpose of clinical use. The investigator prepares medical data based on the diary written by the patient. The case report form will

be prepared based on these. For efficacy, data rated on a 4-point rating scale of "excellent", "good", "moderate" or "no response" will be collected retrospectively based on the criteria below:

- *Excellent*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered. Point = 1.
- *Good*: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.

  Or,

  Definite pain relief and/or improvement in signs of bleeding starting after 8 hours after an infusion, with no additional infusion administered. Point = 2.
- *Moderate*: Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode. Point = 3.
- *No Response*: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens. Point = 4.

For efficacy of each infusion of the Xyntha Solofuse prefilled syringe in on-demand treatment, data rated 24 hours after the infusion or immediately before the next infusion are collected retrospectively.

Prophylactic Therapy

The study subjects (or caregivers) will be given a general explanation on keeping a diary during the routine treatment situation for the purpose of clinical use. The investigator prepares medical data based on the diary written by the patient. The case report form will be prepared based on these. Rating data of details on atypical bleeding occurring within 48 hours from administration of the Xyntha Solofuse prefilled syringe by dosage for the prevention of bleeding (spontaneous/atraumatic) are rated and collected retrospectively. (Namely, "occurred" or "not occurred" and the number of bleeding episodes if "occurred").

7.4. Data Sources

7.4.1. Case report forms

The investigator will review the source documents and complete the electronic CRF for each study subject included. The completed original CRFs are the sole property of Pfizer and shall not be made available in any form to third parties, except for the authorized representatives of Pfizer or the appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs, and must ensure accuracy, authenticity/originality, attributability, completeness, consistency, legibility, timeliness (contemporaneity), sustainability, and availability upon request. The CRFs must be signed by

the investigator or an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries on the CRFs must be dated, initialed and explained (if necessary) and should not obscure the original entries.

In most cases, the source document is the hospital or doctor's study subject chart. In this case, data collected on the CRFs must match the data in this chart.

7.4.2. Record Retention

To enable evaluations and/or audits from the regulatory authorities or Pfizer, the investigator should agree to keep records, including the identity of all participating subject subjects (sufficient information associated with records, e.g. CRFs and hospital records), copy of all CRFs, SAE forms, records such as source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondences (e.g. letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the local regulations, or as specified in the Clinical Study Agreement (whichever is longer).

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g. retirement, transfer), Pfizer should be notified beforehand. The study records must be transferred to a representative approved by Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements are met.

7.5. Study Size

The calculation of sample size is not applicable for this study. At least 600 study subjects will be enrolled in this study to meet the MFDS requirements. In this study, 14 sites conduct complete enumeration study data collection for more than 86 subjects who administered this drug during study period .

7.6. Data Management

CRF data collected by the investigator will be entered into the clinical database. Validation will be performed after comparison of the double data entry. All missing data or data for review will be reported on a query sheet for further validation at the study site. Any data modifications will be recorded.

Adverse events will be coded using the World Health Organization - Adverse Reaction Terminology. Medical history will be coded using the classification of the Statistics Korea, and concomitant drugs coded using www.kimsonline.co.kr provided by KIMS Co. Ltd.

Statistical analysis will be carried out using SAS software version 9.2 or above.

7.7. Data Analysis

7.7.1. Evaluation parameters

1) Case parameters

- Descriptive analysis will be performed regarding the total number of collected CRFs, the number of safety evaluation subjects, the number of efficacy evaluation subjects, the number of discontinued cases and their reasons.

2) Safety parameters

- Safety parameters will be evaluated.
- The incidence of adverse events sorted by body organ and disease/symptom
- If the data is adequate, sub-analysis can be performed for each factor that is considered to affect safety.
- Clinically significant abnormalities found in laboratory tests (if conducted)

3) Efficacy variables

- On-demand treatment
  - Responses to all the injection of the Xyntha Solofuse prefilled syringe used to treat bleeding (4 point scale: excellent, good, moderate, and no response)
  - Number of observations of less than expected therapeutic effect (LETE) (LETE: “no response” rated after each infusion of 2 consecutive infusions within 24 hours after on-demand treatment)
  - In case of bleeding: The number of infusions of Xyntha Solofuse prefilled syringes used to treat each new bleeding episode is rated.
  - Mean infusion dosage
- Prophylactic Therapy
  - Percentage of the study subjects who have experienced bleeding (overall, spontaneous)
  - Annualized bleeding rates (ABRs)
  - Number of observations of less than expected therapeutic effect (LETE)

(LETE: Atypical bleeding occurring within 48 hours after administration of the Xyntha Solofuse Prefilled Syringe by dosage for the prevention of bleeding (spontaneous/atraumatic))

- Mean infusion dosage

- Total factor consumption

- If the data are adequate, sub-analysis can be performed for each factor that is considered to affect the efficacy.

7.7.2. Statistical Considerations

Descriptive statistics are conducted regarding safety and efficacy parameters. If the data are adequate, statistical analysis may be considered. As required by the regulations of the Ministry of Food and Drug Safety, periodic reports should be submitted to the MFDS every 6 months for the first 2 years, and the annual report submitted to the MFDS in the 3rd year. In the 4th year the final report should be submitted. Interim analysis will be conducted when each report is submitted.

Two different groups will be used for analysis.

- Safety analysis group: Study subjects who have been administered the Xyntha Solofuse prefilled syringe at least once, and have been evaluated for safety parameters at least once in relation to the administration.
- Efficacy analysis group: Study subjects adequate for efficacy evaluation at least once

- For analysis, each group will be classified into the subgroups of patients who have been treated previously and patients who have not been treated.

However, among the enrolled study subjects, those who meet the following conditions are excluded from analysis (analysis exclusion criteria).

1. Patients who have a history of hypersensitivity to the Xyntha Solofuse prefilled syringe or the ingredients of this drug.

2. Patients who have a history of hypersensitivity to hamster proteins.

3. Patients who have bleeding disorders other than hemophilia A.

4. Patients who have a history of FVIII inhibitors, or currently have or are suspected of having FVIII inhibitors. In case inhibitor titers quantified in Bethesda Units in the laboratory test results are within the normal laboratory range or at least 0.6 BU/mL. If laboratory tests cannot be performed, the investigator will determine whether or not inhibitors exist based on the clinical assessment results that show a decrease in efficacy of the replacement of FVIII

(e.g. bleeding at least once, if the replacement of anti-bleeding agents is needed to be administered, and if frequency or dosage of replacement FVIII therapy needs to be increased).

5. Use of immunomodulatory therapy. (e.g. intravenous injection of immunoglobulin, use of regular systemic corticosteroids, cyclosporine, and mediators of anti-TNF)

7.7.2.1. Safety Analysis

- Number and incidence of adverse events sorted by body organ, disease/symptom

- If the data are adequate, the Chi-square test(X^2-test) or the Fisher's exact test can be used for subgroup analysis.

If necessary and if the data are adequate, the pairwise comparison and/or the descriptive analysis method will be used for clinically significant abnormalities found in the laboratory tests that have been reported as adverse events.

7.7.2.2. Efficacy Analysis

A descriptive summary will be performed for efficacy endpoints.

Details about the summary and statistical analysis of the data collected in this study will be included in the statistical analysis plan (SAP), and the sponsor will date, organize and retain the SAP. The plan described in the protocol may be amended in the SAP. The definition of the primary endpoint, or important revisions to the analysis will be reflected in the protocol amendment.

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7.9. Strength and Limitations of the Study Methods

Strength:

- This is a non-interventional study to observe the safety and efficacy of the study drug under the actual condition of use.

Limitations:

- This is a study mandated by the regulatory authority to maintain approval.

- SAP and the number of study subjects to be enrolled will be decided, not by specific diseases and/or characteristics of the drug, but by the guidelines for the re-examination of new drugs etc. by the Ministry of Food and Drug Safety.

7.10. Other Aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1. Subject information and consent

Although the written consent form (for the use of personal information) does not need to be obtained due to the unidentifiable records collected in this study, all the parties guarantee the protection of personal information of the study subjects, and the names of the subjects shall not be included in any Pfizer forms, reports, publications, or other public materials except when the law requires. For the delivery of materials, Pfizer will maintain the highest level of confidentiality and protection of the study subjects' personal information.

8.2. Subject Withdrawal

Not applicable

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be submitted to the MFDS prior to the study. The ethical consideration in this study will be evaluated by the IRB/IEC in each study site prior to the study, if the site has the approval procedures for the PMS study according to the standard operating procedure of each study site.

It is the responsibility of the investigator to obtain prospective approval for the study protocol, protocol amendments, and other relevant documents, if applicable, by the IRB/IEC. All correspondences with the IRB/IEC should be retained in the investigator file. The copy of the IRB/IEC approval letters should be forwarded to Pfizer or the Pfizer representative.

8.4. Ethical Conduct of the Study

This study will be conducted in accordance with the legal and regulatory requirements, scientific purpose, value and rigor, and will follow the generally accepted research practices described in the guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice guidelines issued by the International Epidemiological Association (IEA), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines, and Korea PMS regulations and/or guidelines.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

This study generally uses the existing medical database that is unlikely to connect a particular product to medical incidents of an individual (in other words, to identify potential connections).

Also, this study protocol requires the review of unstructured data at the level of the study subjects. Unstructured data refer to original medical materials including text-centered

explanations and medical records, descriptive images from the doctor, visual explanations on medical information such as a nerve scan, X-ray or the description section of the database. The reviewer is responsible for reporting all adverse events, which appear in the reviewed information (as defined by the study period and subject group specified in the protocol), clearly attributed to Pfizer products. Clear attribution is not inferred from the temporal relationship between drug administration and adverse events, but should be based on the clear causal statement of the medical provider, which connects drug administration and adverse events.

The requirements for reporting safety incidents using the non-interventional study (NIS) adverse event monitoring (AEM) report form to Pfizer Safety are as follows:

- All serious adverse events and non-serious adverse events, which appear in the reviewed information, clearly attributed to all Pfizer drugs should be recorded in the case report form, and should be reported using the NIS AEM report form to Pfizer Safety within 24 hours of recognition.

- Scenarios related to drug exposure such as exposure during pregnancy, exposure during breastfeeding, medication errors, overdose, misuse, extravasation, lack of efficacy and occupational exposure related to the use of Pfizer products should be reported within 24 hours to Pfizer Safety using the NIS AEM report form.

For these safety incidents clearly attributed or related to the use of Pfizer products, the data collected in the medical record constitute all clinical information known to be related to such adverse events. No follow-ups are conducted for relevant adverse events.

All the study staff will complete "*Your Responsibility for Reporting: Safety, Performance and Quality Monitoring of Pfizer Products (in multiple languages)*" and the Pfizer requirement for supplementary training on their responsibility to report. These trainings are provided for all the study staff before the start of the study. For all training, training completion records include the "Certificate of Training Completion" (signed by the attendee) and should be kept in the retrievable form. The copy of all signed certificates of training completion should be offered to Pfizer.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For the first 2 years, 6-month reports are submitted to the MFDS (i.e. Reports 1-1, 1-2, 2-1, and 2-2). Thereafter, data collected in the 3rd year are reported to the MFDS annually. The final study report (i.e. re-examination report) is submitted to the MFDS in the 4th year, including all data collected during the entire study period (see Section 4).

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g. clinical hold) by an applicable jurisdictive authority in each region of the world, or if the investigator becomes aware of any new information which may influence the evaluation of the benefits and risks of the Xyntha Solofuse prefilled syringe, it should be reported to Pfizer immediately.

In addition, the investigator must inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the subjects against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

11. REFERENCES

1. Xyntha Solofuse prefilled syringe local product document

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable