Korean Post-marketing Surveillance for Xyntha Solofuse prefilled Syringe

Sponsor : Pfizer Pharmaceuticals Korea Ltd.
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Amendment Log

Version	Date	Updated by	Reason
1.0	07/Nov/2016	PPD	Initial version
1.1	20/Mar/2018	PPD	1) Clarification and scoping of analysis populations in Section 3. 2) Define the category for family history of hemophilia as parents, brothers and other in Section 6.2. 3) Addition of analysis for duration of administration, single infusion dosage and total infusion dosage of Xyntha solofuse prefilled syringe administered for the purpose of on-demand treatment in Section 6.5. 4) Separate the analysis for surgery and bleeding and define the classification of effective/not-effective in Section 6.7.

CONTENTS

1. Introduction

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. Although 600 is the assigned number of study subjects, the number of cases will be adjusted considering the actual number of enrolled subjects after the study start day. 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.

2. Study objective(s) and Others

2.1. Objectives

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.

2.2. 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.

2.3. Study Population

2.3.1. 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.

2.3.2. 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).

2.4. Sample size Considerations

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. Although 600 is the assigned number of study subjects, the number of cases will be adjusted considering the actual number of enrolled subjects after the study start day.

3. Analysis Populations

3.1. Safety Analysis Set

Safety analysis set will include study subjects who have been administered to the Xyntha Solofuse prefilled syringe at least once, and have been evaluated for a safety parameter at least once in relation to the administration.

The following cases will be excluded from the safety analysis set in the following order.

1) Subjects who have not been administrated for Xyntha solofuse prefilled syringe.
2) Subjects who have not met the inclusion/exclusion criteria.
3) Subjects who have experienced off-label use against Xyntha solofuse prefilled syringe local product document.

3.2. Efficacy Analysis Set

Efficacy analysis set will include study subjects adequate for efficacy evaluation at least once among the safety analysis set.

The following cases will be excluded from the efficacy analysis set in the following order.

1) Subjects who are excluded from the safety analysis set.
2) Subjects without efficacy assessment endpoint.
   - On-demand treatment: Responses to the injection of the Xyntha Solofuse prefilled syringe
   - Prophylactic therapy: Subjects who have experienced bleeding (overall, spontaneous)

3.3. Special Patient Population

Special patient populations will includes pediatric subjects (age<19), elderly subjects (age≥65), patients with renal or hepatic disorders, pregnant women, respectively.

3.4. Population excluded from Safety Analysis

Population excluded from safety analysis set will be accounted for as part of the subject accounting in the report. However, subjects who have not been administrated for Xyntha solofuse prefilled syringe will be excluded from this analysis set. Any adverse events reported for subjects excluded from the Safety Analysis Set will also be described.

The following cases will be included in this analysis set.

1) Subjects who have not met the inclusion/exclusion criteria.
2) Subjects who have experienced off-label use against Xyntha solofuse prefilled syringe local product document.

3.5. Subgroups Patient Population

Subgroups patients populations will be classified into the patients who have been treated previously and patients who have not been treated, and status of treatment experience previously define previous exposure to plasma-denial factor VIII.

4. Study Endpoints

4.1. Demographics and Baseline Characteristics

1) State (age and sex) of the study subjects

4.2. History of hemophilia A

1) Duration of the disease
2) Genetic mutation of factor VIII
3) Previous exposure to plasma-derived factor VIII
4) Previous used factor VIII therapy
5) Personal history of allergic reactions to factor VIII products (within 12 months)
6) Family history of hemophilia A
7) Family history of factor VIII inhibitors
8) Family history of allergic reactions to factor VIII products (within 12 months)
9) Severity

4.3. Medical History

1) Renal/hepatic disorder
2) Past/present disease status
3) Past/present disease (Status (Yes/No), past/present disease classified by 092 version of WHO-ART(World Health Organization-Adverse Reaction Terminology))

4.4. Concomitant Treatments/Therapy

1) Concomitant medication (Status (Yes/No), Level1, Level2 of concomitant medication classified by latest version of KIMS code)
2) Concomitant therapy (Status (Yes/No), Level1, Level2 of concomitant therapy classified by latest version of KIMS code)

4.5. Administrative Status for Medicinal Products

1) Single infusion dosage.
2) Total infusion dosage.

3) Duration of administration

4.6. Safety Endpoints

1) The incidence and number with 95% confidence Interval for all adverse events/adverse drug reactions investigated within 6 months from initial administration after at least 1 dose of Xyntha solofuse prefilled syringe (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)
   ① Severity
   ② Action taken
   ③ Seriousness
   ④ Outcome
   ⑤ Causality assessment
2) Laboratory Test
   ① Blood test(Hemoglobin, Hematocrit, RBC, WBC, Platelet Count, ESR, CRP)
   ② Biochemical test(AST(SGOT), ALT(SGPT), ALP, BUN, Creatinine, Factor VIII Inhibition Factor Hemoglobin)
   ③ Urine examination(Protein/Albumin, Glucose/Sugar, Hemoglobin/Blood)

4.7. Efficacy Endpoints

1) On-demand treatment
   ① Responses to all the injection of the Xyntha Solofuse prefilled syringe used to treat bleeding (4 point scale: excellent, good, moderate, and no response)
      - 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.
   ② Number of observations of less than expected therapeutic effect (LETE)
      - If the response to treatment of Xyntha solofuse prefilled syringe assess "no

response" after each infusion of 2 consecutive infusions within 24 hours after on-demand treatment, LETE will be calculated once, if it assess "no response" after each infusion of 3 consecutive infusion within 24 hour, LETE will be calculated twice

③ In case of bleeding: The number of infusions of Xyntha Solofuse prefilled syringes used to treat each new bleeding episode will be rated.

④ Mean infusion dosage

2) Prophylactic Therapy

① Percentage of the study subjects who have experienced bleeding (overall, spontaneous)

② Annualized Bleeding Rates (ABRs)

③ Number of observations of less than expected therapeutic effect (LETE)

- If atypical bleeding occur within 48 hours after administration of the Xyntha Solofuse Prefilled Syringe by dosage for the prevention of bleeding (spontaneous/atraumatic), LETE will be calculated once.

④ Mean infusion dosage

⑤ Total factor consumption (Total infusion dosage)

5. General Consideration

5.1. Analysis Principles

Statistical analysis will be conducted after database is locked and performed using SAS software version 9.4 according to this statistical analysis plan. If statistical analysis methods are changed, it will be described in the final study report.

Continuous variables will be summarized by the descriptive statistics (n, mean, median, SD (standard deviation), minimum, and maximum). Categorical variables will be presented in the frequency distribution table (n, %).

In case of statistical hypothesis testing, two-sided test will be conducted under 5% significance level and the p-value of each test result will be presented in the summary table.

6. Statistical Analyses

6.1. Demographic and Baseline Characteristics (frequency and percentage)

1) Sex (Male, Female)

2) Age (< 30 years, 30 ~ 39 years, 40 ~ 49 years, 50 ~ 59 years, ≥ 60 years)

6.2. Hemophilia A history factor analysis

1) Descriptive statistics (n, mean, median, SD, minimum and maximum)

① Duration of the disease (Year)

2) Frequency statistics (frequency and percentage)
   ① Genetic mutation of factor VIII (Yes, No, Unknown)
   ② Previous exposure to plasma-derived factor VIII (Yes, No, Unknown)
   ③ Previous used factor VIII therapy (Yes, No)
   ④ Personal history of allergic reactions to factor VIII products (Yes, No)
   ⑤ Family history of hemophilia A [Yes (Parents, Brothers, Other), No]
   ⑥ Family history of factor VIII inhibitors (Yes, No)
   ⑦ Family history of allergic reactions to factor VIII products (Yes, No)
   ⑧ Severity (Mild, Moderate, Severe, Unknown)

6.3. Medical History

1) Frequency and percentage for renal/hepatic status (Yes, No) will be presented.
2) Past/present disease
   ① Past disease, present disease depending on time will be analyzed, respectively.
   ② Frequency and percentage for past/present disease status will be presented and past/present disease classified by 092 version of WHO-ART in detail will be presented in each frequency and percentage.

6.4. Concomitant Treatments/Therapy

1) Concomitant medication status (Yes, No) will be presented in frequency and percentage and concomitant medication classified by 092 version of WHO-ART in detail will be presented in n, percentage and frequency.
2) Concomitant therapy status (Yes, No) will be presented in frequency and percentage and concomitant therapy classified by 092 version of WHO-ART in detail will be presented in n, percentage and frequency.

6.5. Administrative Status for Medicinal product

1) Duration of administration, single infusion dosage and total infusion dosage of Xyntha solofuse prefilled syringe administered for the purpose of on-demand treatment will be presented by n, mean, SD, median, minimum and maximum.
2) Duration of administration, single infusion dosage and total infusion dosage of Xyntha solofuse prefilled syringe administered for the purpose of prophylactic therapy will be presented by n, mean, SD, median, minimum and maximum and total frequency of infusion will be presented frequency and percentage.

6.6. Safety Analyses

Safety analysis will be performed based on data of safety analysis set. All adverse events in CRF will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Korean 092 Version of WHO-ART distributed by Korean Ministry of Health and Welfare.

1) All adverse events occurred during or after administration of this medicinal product will be summarized by frequency and percentage (n, percentage) by categorizing as follows. Also, it will be presented in n, incidence proportion, 95% confidence interval of incidence proportion and number of events for each SOC and PT.
   ① Frequency analysis of adverse event/adverse drug reaction
   ② Frequency analysis of serious adverse event/serious adverse drug reaction
   ③ Frequency analysis of unexpected adverse event/unexpected adverse drug reaction
2) All adverse events by categorizing as follows will be presented in number of events and percentage.
   ① Occurrence status of adverse event and adverse drug reaction by its severity
      - Mild
      - Moderate
      - Severe
   ② Occurrence status of adverse event and adverse drug reaction by its action taken related with administrating this medicinal product.
      - No change
      - Dosage reduced
      - Dosage increased
      - Temporarily discontinued
      - Permanently discontinued
      - Not applicable
   ③ Occurrence status of adverse event and adverse drug reaction by other action taken
      - Therapeutic prescription
      - Other
      - No treatment
   ④ Occurrence status of adverse event and adverse drug reaction by its seriousness
      - 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.

- Important medical event: if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

⑤ Incidence of adverse event and adverse drug reaction by outcome

- Yes
- Unknown
- No (disappeared)

⑥ Occurrence status of adverse event and adverse drug reaction by its causality assessment.

- Related to this medicinal product:
  - I. Certain
  - II. Probable/likely
  - III. Possible
  - V. Conditional/unclassified
  - VI. Unassessable/unclassifiable
- Not related to this medicinal product:
  - IV. Unlikely

3) Occurrence status of adverse event by demographics and baseline characteristics

Occurrence status of adverse events will be presented in frequency and percentage and incidence proportion with 95% confidence interval based on categorical variables of demography and baseline characteristics of the patients (sex, age group, past/present disease status, renal/hepatic disorder status). To identify statistically significant difference in occurrence of adverse events among demography and baseline characteristics, Chi-square test or Fisher's exact test will be performed.

4) Occurrence status of adverse event by concomitant treatment/therapy

Occurrence of adverse events will be presented in frequency and percentage and incidence proportion of adverse events with 95% confidence interval by concomitant treatment status and concomitant therapy status. To identify statistically significant difference in occurrence of adverse events among concomitant treatment status, concomitant therapy status, Chi-square test or Fisher's exact test will be performed.

5) Analysis of factors that affect safety

Logistic regression analysis will be performed and an odds ratio with 95% confidence interval will be presented to identify the factors that affect occurrence of adverse events in demography and baseline characteristics (sex, age group, past/present disease status, renal/hepatic disorder status), or concomitant treatment status, concomitant therapy status. etc.

6) Test of difference for laboratory data before and after administration.
Laboratory data before and after administration will be presented by descriptive statistics and test of difference for laboratory data before and after administration will be performed by using paired t-test (or Wilcoxon signed-rank test). This analysis will be performed if possible.

7) Distribution for special patient populations (children (age<19), elderly (age≥65), renal disorder, hepatic disorder, pregnant woman) will be presented. Also, adverse events and adverse drug reactions collected by these groups will be presented in incidence proportion and number events of it for each SOC and PT.

8) Distribution for subgroups status (patients with prior treatment experience/patients with prior non-treatment experience) will be presented. Also, adverse events and adverse drug reactions collected by these groups will be presented in incidence proportion and number events of it for each SOC and PT.

9) Distribution for excluded safety patient groups will be presented. Also, adverse events and adverse drug reactions collected for these groups will be presented in incidence proportion and number events of it for each SOC and PT.

6.7. Efficacy Analyses

A descriptive summary will be performed for efficacy endpoint.

1) On-demand treatment (surgery)
   ① The best responses to all the injection of the Xyntha Solofuse prefilled syringe used to treat bleeding (4 point scale: excellent, good, moderate, and no response) will be presented in frequency and percentage.
   ② Number of observations of less than expected therapeutic effect (LETE) will be presented by n, mean, SD, median, minimum and maximum or frequency and percentage.
   ③ Mean infusion dosage will be presented by n, mean, SD, median, minimum and maximum.

2) On-demand treatment (bleeding)
   ① The best responses to all the injection of the Xyntha Solofuse prefilled syringe used to treat bleeding (4 point scale: excellent, good, moderate, and no response) will be presented in frequency and percentage.
   ② Number of observations of less than expected therapeutic effect (LETE) will be presented by n, mean, SD, median, minimum and maximum or frequency and percentage.
   ③ The number of infusions of Xyntha Solofuse prefilled syringes used to treat each new bleeding episode is descriptive statistics of medication treatment duration will be presented in n, mean, SD, median, minimum and maximum or frequency and

percentage.

④ Mean infusion dosage will be presented by n, mean, SD, median, minimum and maximum.

3) Prophylactic Therapy

① Subjects who have experienced bleeding (overall, spontaneous) will be presented in frequency and percentage.

② Annualized Bleeding Rates (ABRs)

The annualized bleeding rate is the incidence rate of bleeding per year. Since the follow up period for each patient is 6 months (= 0.5 year), the ABR is calculated as follows.

N=Number of patients who received prophylactic treatment.

X=Number of patients who have bleeding among the patients included in the patients who received prophylactic treatment

$$\text{ABRs} = \frac{\text{X}}{\text{N} \times 0.5}$$

③ Number of observations of less than expected therapeutic effect (LETE) will be presented by n, mean, SD, median, minimum and maximum or frequency and percent.

④ Mean infusion dosage will be presented by descriptive statistics as n, mean, SD, median, minimum and maximum.

⑤ Total factor consumption (total infusion dosage) will be presented by descriptive statistics as n, mean, SD, median, minimum and maximum.

4) Overall efficacy assessment will be classified as effective/not-effective as follows, presented in frequency and percentage of it.

① On-demand treatment

- [Effective]: Subjects with whom the best responses 'Excellent' or 'Good' or 'Moderate'.
- [Not-effective]: Subjects with whom the best responses 'No response'.

② Prophylactic Therapy

- [Effective]: Subjects who haven't experienced any atypical bleeding within 48 hours after administration of the Xyntha Solofuse Prefilled Syringe.
- [Not-effective]: Subjects who have experienced at least once atypical bleeding within 48 hours after administration of the Xyntha Solofuse Prefilled Syringe.

5) Efficacy assessment by demographics and baseline characteristics

Classified overall assessment (effective/not-effective) will be presented in frequency and percentage based on categorical variables of demography and baseline characteristics (sex, age group, past/present disease status, renal/hepatic disorder status). To identify statistically significant difference of frequency distribution of classified overall assessment (effective/not-effective) among demography and baseline characteristics, Chi-square test or Fisher's exact

test will be performed.

6) Efficacy assessment by concomitant treatment (Concomitant Treatments/Therapy status)
Classified overall assessment (effective/not-effective) will be presented in frequency and percentage for concomitant treatment status (Concomitant Treatments/Therapy status). To identify statistically significant difference of frequency distribution of classified overall assessment (effective/not-effective) among concomitant treatment status, concomitant therapy status, Chi-square test or Fisher's exact test will be performed.

7) Analysis of factors that affect efficacy
Logistic regression analysis of multivariate analysis will be performed and presented an odds ratio with 95% confidence interval to identify the factors that affect classified overall assessment (effective/not-effective) in demography and baseline characteristics of the patients (sex, age group, past/present disease status, renal/hepatic disorder status), or concomitant treatment status, concomitant therapy status, etc.

7. Reporting Principles

All results of analysis will be reported table and graph to assist the understanding for the study results. Continuous variables will be summarized by descriptive statistics (n, mean, SD, median, minimum and maximum) and categorical variables will be presented in frequency and percentage (n, %). Summary statistics including n, mean, SD, median, minimum and maximum, frequency, etc will be reported to two decimal places using rounding off.

The p-values through the statistical test will be reported to four decimal place and if p-values smaller than 0.0001 will be written as '<0.0001'.