NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Post authorization safety surveillance registry with BeneFIX in hemophilia B patients in usual care settings
Protocol number	B1821050
Protocol version identifier	Version 2.0
Date of last version of protocol	26 July 2013
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	PF-05208755 Nonacog-alfa, Recombinant Factor IX
Medicinal product	BeneFIX®
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
BU	Bethesda Unit(s)
CRF	Case Report Form
ED	Exposure Day
eCRF	Electronic Case Report Form
FFP	Fresh Frozen Plasma
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IU	International Units
IV	Intravenous
MTP	Minimally Treated Patients
PCC	Prothrombin Complex Concentrates
PTP	Previously Treated Patients
PUP	Previously Untreated Patients
SAE	Serious Adverse Event
CFDA	State Food and Drug Administration

Term	Definition
AEM form	Adverse Event Monitoring form
Bleeding episode	Hemorrhage occurring spontaneously or due to injury at 1 or more sites.
Completed subject	Any subject who completes the registry activities through the Registry Completion Visit and who is not withdrawn early.
Cryoprecipitate	Prepared from plasma and contains fibrinogen, von Willebrand factor, factor VIII, factor XIII and fibronectin.
Exposure day	Any calendar day during which the subject receives BeneFIX or other purified human derived FIX product. This excludes FFP, PPC and cryoprecipitate.
Factor IX inhibitor (clinically significant)	Local positive inhibitor and at least one of the following observations within 4 weeks before or 4 weeks following a positive inhibitor result: 1. ≥2 events indicating a decrease in the efficacy of BeneFIX(or other AE indicating a decrease in the efficacy of the test article) 2. A need to administer alternate hemostatic products or increase the dose or dosing frequency in order to achieve sufficient efficacy
Factor IX inhibitor (local)	A local positive result using either the Bethesda assay (≥ 0.6 BU or > the upper limit of normal) or the Nijmegen modification of the Bethesda assay (≥ 0.6 BU).
Factor IX inhibitor (history of)	A history of factor IX inhibitor (clinical or laboratory-based assessment).
FIX Hypersensitivity Allergic reaction	A hypersensitivity reaction to BeneFIX with symptoms including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
Fresh Frozen Plasma	Plasma removed from whole blood that involves freezing during the preparation. It contains all coagulation factors in normal concentrations.
Incremental recovery	FIX:C at 30 minutes after infusion, [IU/dL]/[IU/kg]

Investigator	A person, with the appropriate qualifications, responsible for the conduct of the registry at a study site.
Lack of Efficacy/Lack of Effect	Lack of efficacy/effect is the failure of expected pharmacologic action or therapeutic benefit.
MTP	Patients who have received at least one ED but less than or equal to 150 documented prior Factor IX EDs (≤150 EDs).
On-demand treatment	Treatment of hemorrhages, as needed, by administering an unscheduled bolus infusion of BeneFIX to stop bleeding and control hemostasis.
Preventive treatment	Factor IX replacement therapy given before an event that could increase the risk of bleeding (e.g. surgery or exercise).
Prophylaxis	Factor IX replacement therapy administered at a routine interval such as every other day, for a prolonged period of time, to prevent occurrence of spontaneous bleeding episodes.
Prothrombin Complex Concentrates	Produced from the cryoprecipitate supernatant of plasma pools after removal of antithrombin and factor XI. Depending on the processing technique, PCCs may contain clotting factors II, IX, X and sometimes VII. To prevent activation of these factors, most PCC contain heparin. PCC may also contain the natural coagulation inhibitors protein C and protein S.
PTP	Patients who have received more than 100 documented prior Factor IX EDs (>150 EDs).
PUP	Patients who have not received any Factor IX products
Registry start date	Date the first registry subject provides informed consent.
Registry end date	Date of last contact with the last subject on the registry.
Regulation	The term regulation refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations (United States); the European Clinical Trials Directive; the

	International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice; and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
Treatment Period	Day 0 until study completion/withdrawal

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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ABSTRACT

A Post authorization safety surveillance registry with Benefix in hemophilia B patients in usual care settings

Version of Protocol: Version 1.0

Date of Protocol: 9 July 2013

Main Author: Li Xie, Medical Affairs, China

Pablo Rendo, Clinical Affairs

- Rationale and background

Hemophilia B (congenital factor IX deficiency or Christmas disease) is an X-linked disorder caused by a congenital deficiency of coagulation factor IX clotting activity. Patients with hemophilia B are usually treated by replacing the missing or defective factor IX for treatment or prevention of hemorrhage. BeneFIX received the first regulatory approval on 11 February 1997 in the United States. Presently it is approved in 67 countries and marketed in 43 countries. Reformulated nonacog alfa was approved for use in the EU in July 2007 and since January 2011 only the reformulated version of Nonacog - alfa is being distributed worldwide. The registration trial was conducted in 2008 to support licensure in China. 35 patients with hemophilia B received BeneFIX in this study. It demonstrated that BeneFIX is an efficacious and safe treatment for adult and pediatrics Chinese PTPs and MTPs with hemophilia B. BeneFIX received regulatory approval on 10 July 2012 in China. It's indicated for Control and prophylaxis of bleeding episodes in adult and pediatric patients with hemophilia B;Surgical prophylaxis in adult and pediatric patients with hemophilia B.
A prospective Registry of hemophilia B patients will be conducted to evaluate the safety and efficacy of BeneFIX in the usual treatment of hemophilia B in China.

- Research question and objectives

The registry is to evaluate the safety and efficacy of BeneFIX in hemophilia B patients in the Chinese population.
Primary study objective is to evaluate the product medically important events (FIX inhibitor development, FIX hypersensitivity allergic reaction, thrombogenicity, lack of effect and red blood cell (RBC) agglutination) in Chinese hemophilia B patients during treatment with BeneFIX.
Secondary study objective is to evaluate the overall safety of BeneFIX, including the occurrence of serious adverse events (SAEs), and efficacy.

- Study design

This is a non-interventional, voluntary prospective registry study conducted in major hemophilia treatment centers in China. The registry will enroll Chinese patients of all severities with Hemophilia B. Patients will undergo a screening review prior to enrollment. Enrolled subjects will be treated with intravenous infusions of BeneFIX at a dose and frequency prescribed by the subject's treating physician in accordance with the BeneFIX label and will be adjusted solely according to medical and therapeutic necessity. The registry study will capture observations that will be used for evaluating recombinant FIX replacement product safety, including: subject demographics, medical history, hemophilia history and medications. Safety assessments, treatment data and any laboratory-based FIX inhibitor determinations will be collected at all visits. It is recommended that all subjects in this registry study will be followed for a minimum of 6 months and participation in this registry study will conclude after 12 months.

- Population - "Population" includes the setting and study population

This registry plans to enroll any patient with Hemophilia B in China who is eligible and willing to participate in the registry.

Principle inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1) Male subjects of all ages and severity with Hemophilia B.
2) Subjects using or intending to use BeneFIX for Factor IX replacement therapy.
3) Subjects/parents/legal representatives must be able to comply with registry procedures (informed consent/assent process, clinical visits, reporting of infusion and bleed data, reporting of adverse events, etc).
4) Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Principle exclusion criteria:

Patients meeting any of the following criteria will not be included in the registry study:

1) Presence of any bleeding disorder in addition to hemophilia B.
2) Treatment with immunomodulatory therapy (e.g., intravenous immunoglobulin [IVIg], routine systemic corticosteroids, cyclosporins, anti-TNF agents).
3) Treatment with any investigational agent or device within 30 days prior to the Enrollment Visit.
4) Subjects with a past history of, or current factor IX inhibitor. For laboratory-based assessments, any Bethesda inhibitor titer greater than the laboratory's normal range or $\geq$0.6 BU/mL.
5) Known hypersensitivity to hamster protein.
6) Any condition(s) that compromises ability to collect registry-related observations or that poses a contraindication to registry participation (these conditions include, but are not limited to, inadequate medical history to assure registry eligibility; expectation of poor compliance in provision of observations for registry-related documentation).
7) Unwilling or unable to follow the terms of the registry study.

- Variables

Baseline data is including Demographic data , Medical history, Medication history and Hemophilia History.

Treatment Data Collection (Day 0 to 12 months/Early Withdrawal) is including Exposure days, bleed, infusion and response data will be collected throughout the treatment period on the subject diaries. The efficacy outcomes data will be:

- Annualized bleeding rates (ABR) in subjects receiving treatment with BeneFIX,
- The responses to all on-demand treatment with BeneFIX for all bleeds (4 point scale of assessment),
- Number of BeneFIX infusions to treat each new bleed
- Number of spontaneous/non traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX

Safety data collected throughout the treatment period will consist of all AE and SAE data, including product-related medically important adverse events (inhibitor development, FIX hypersensitivity allergic reactions, thrombogenicity, lack of effect and red cell agglutination)

- Data sources

Registry study data will be recorded by a physician/nurse in the medical records, through subject interview and subject diaries, and in the Case Report Forms (CRF).

- Study size

The registry study will be conducted in hospitals and clinics in China. Since the number of potential subjects is unknown, the study is not designed based on sample size considerations

- Data analysis

The results of this study will be presented using descriptive statistics. The primary analysis will be performed on all subjects who receive at least one dose of BeneFIX. The reasons for discontinuation of BeneFIX therapy will be described. Subgroup analysis will be done by several sub-populations, and the details will be in the SAP.

- *Milestones*

Milestone	Planned date
Completion of feasibility assessment.	23 Sep 13
Start of data collection	22 Feb 2014

End of data collection	14 Jul 2016
Study progress report 1	11 Mar 2014, 11 Mar 2015, 11 Mar 2016
Interim report 1	11 Mar 2015, 11 Mar 2016
Registration in the EU PAS register	17 Dec 2013
Final study report	12 Dec 2016

3. AMENDMENTS AND UPDATES

There is no protocol amendment.

4. MILESTONES

Milestone	Planned date
Completion of feasibility assessment.	23 Sep 13
Start of data collection	22 Feb 2014
End of data collection	14 Jul 2016
Study progress report 1	11 Mar 2014, 11 Mar 2015, 11 Mar 2016
Interim report 1	11 Mar 2015, 11 Mar 2016
Registration in the EU PAS register	17 Dec 2013
Final study report	12 Dec 2016

5. RATIONALE AND BACKGROUND

Hemophilia B (congenital factor IX deficiency or Christmas disease) is an X-linked disorder caused by a congenital deficiency of coagulation factor IX clotting activity. Patients with hemophilia B are usually treated by replacing the missing or defective factor IX for treatment or prevention of hemorrhage. Pfizer has initiated a clinical development program to support the approval of BeneFIX for the control and prevention of hemorrhagic episodes and for surgical prophylaxis in patients with hemophilia B. The clinical development program is comprised of 8 completed clinical studies. Four (4) global studies of the BeneFIX development program supported the original licensure. The other 4 studies (3 global studies and 1 conducted in Japan) were conducted after the initial licensure of BeneFIX. In total, 213 patients with hemophilia B

have received BeneFIX in these studies. Overall, the results of the clinical development program demonstrate that BeneFIX is an efficacious treatment that provides clinical benefit and has an acceptable safety profile in patients with hemophilia B.

In 2007, BeneFIX was reformulated to decrease the occurrence of red blood cell (RBC) agglutination in the syringe or tubing. The reformulation involved no changes to the active ingredient (recombinant FIX protein), but included a change in the diluent (from sterile water to 0.234% sodium chloride [NaCl]). The active recombinant Factor IX in reformulated nonacog alfa is identical to that in original nonacog alfa.

BeneFIX received the first regulatory approval on 11 February 1997 in the United States. Presently it is approved in 67 countries and marketed in 43 countries. Reformulated nonacog alfa was approved for use in the EU in July 2007 and since January 2011 only the reformulated version of nonacog alfa is being distributed, worldwide.

It is estimated that 8,288 patients have been exposed to nonacog alfa since the product was first approved.

BeneFIX has the important advantage over plasma-derived FIX concentrates of being free from the risk of containing blood-borne pathogens because it is not derived from human or animal proteins.

All patients, including previously treated patients (PTPs), minimally treated patients (MTPs) and newborns, infants and very young children, who may present as previously untreated patients (PUPs), with hemophilia B may require FIX replacement treatments for various bleeding events, preventive infusions or a prophylaxis regimen. It is well-known that young children, especially those naïve to FIX, are at greater risk for developing neutralizing antibodies (inhibitors). In addition, they may have altered responses to replacement therapy compared with older hemophilia B patients. While factors such as clinical severity, genetic mutations, exposure intensity and inherent immunoresponse heterogeneity may be risk factors for inhibitor safety issues, it is also important to ensure that these are not specifically related to different FIX replacement products.

Since the introduction of BeneFIX in the United States and in the EU, there have been a total of 136 reports of possible systemic allergic reactions. There have been 56 reports of inhibitor formation.

To evaluate the safety and efficacy of BeneFIX in the usual treatment of hemophilia B in China, a prospective Registry of all severities of patients that are being treated or scheduled to be treated with BeneFIX will be conducted. All Chinese patients of all severities who begin or have begun treatment with BeneFIX for hemophilia B will be eligible for the Registry. These patients must consent to the review and release of their medical records from the time of initiation of BeneFIX therapy through to their conclusion of participation in the study.

The most recent version of the BeneFIX investigator's brochure (IB) provides a summary of findings from clinical studies that are relevant to this registry. Additionally, this document also provides a summary of the known and potential risks and benefits, if any, to human patients.

6. RESEARCH QUESTION AND OBJECTIVES

The registry is to evaluate the safety and efficacy of BeneFIX in hemophilia B patients in the Chinese population.
Primary study objective is to evaluate the product medically important events (FIX inhibitor development, FIX hypersensitivity allergic reaction, thrombogenicity, lack of effect and red blood cell (RBC) agglutination) in Chinese hemophilia B patients during treatment with BeneFIX.
Secondary study objective is to evaluate the overall safety of BeneFIX, including the occurrence of serious adverse events (SAEs) and efficacy

7. RESEARCH METHODS

7.1. Study design

This is a non-interventional, voluntary prospective registry study conducted in major hemophilia treatment centers in China. The registry will enroll Chinese patients with Hemophilia B of all severities. Patients will undergo a screening review prior to enrollment. Enrolled subjects will be treated with intravenous infusions of BeneFIX at a dose and frequency prescribed by the subject's treating physician in accordance with the BeneFIX label and will be adjusted solely according to medical and therapeutic necessity. The registry study will capture observations that will be used for evaluating recombinant FIX replacement product safety, including: subject demographics, medical history, hemophilia history and medications. Safety assessments, treatment data and any laboratory-based FIX inhibitor determinations will be collected at all visits. It is recommended that all subjects in this registry study will be followed for a minimum of 6 months and participation in this registry study will conclude after 12 months.

7.2. Setting

7.2.1Registry study population

The subject/parent/legal representative and physician's decision to use BeneFIX must be independent of registry participation and determined prior to discussions regarding the registry and obtaining informed consent for participation.
This registry plans to enroll any patient with Hemophilia B in China who is eligible and willing to participate in the registry. Subject enrollment at given centers may vary based on the capabilities of each center. Subjects withdrawn from the registry will not be replaced, regardless of the reason for withdrawal. The registry will be open to enrollment from Registry start date until July 2015.

7.2.2 Approximate Duration of Subject Participation

The frequency of the registry study visits may be conducted following the local standard of care, however, the sponsor recommends that registry study visits be conducted at a minimum of 6 months after the enrollment baseline visit (Day 0) with an additional visit at 12 months after Day 0. A Follow-up Call is to be conducted at least 28 calendar (+10 days) after the Final/Early Termination visit in order to collect information on the occurrence of adverse events and concomitant medications.

7.2.3 Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Male subjects of all ages and severity with Hemophilia B.

2. Subjects using or intending to use BeneFIX for Factor IX replacement therapy.

3. Subjects/parents/legal representatives must be able to comply with registry procedures (informed consent/assent process, clinical visits, reporting of infusion and bleed data, reporting of adverse events, etc).

4. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

7.2.4 Exclusion criteria

Patients meeting any of the following criteria will not be included in the registry study:

1. Presence of any bleeding disorder in addition to hemophilia B.

2. Treatment with immunomodulatory therapy (e.g., intravenous immunoglobulin [IVIg], routine systemic corticosteroids, cyclosporins, anti-TNF agents).

3. Treatment with any investigational agent or device within 30 days prior to the Enrollment Visit.

4. Subjects with a past history of, or current factor IX inhibitor. For laboratory-based assessments, any Bethesda inhibitor titer greater than the laboratory's normal range or $\geq$0.6 BU/mL.

5. Known hypersensitivity to hamster protein.

6. Any condition(s) that compromises ability to collect registry-related observations or that poses a contraindication to registry participation (these conditions include, but are not limited

to, inadequate medical history to assure registry eligibility; expectation of poor compliance in provision of observations for registry-related documentation).

7. Unwilling or unable to follow the terms of the registry study.

7.2.5 Prohibited Concomitant Medication

Treatment with PCC, FFP or any other coagulation products other than BeneFIX is prohibited throughout the registry study unless clinically indicated.

7.3 Study procedures

A written, Pfizer and institutional review board (IRB)/independent ethics committee (IEC)-approved, informed consent/assent (as appropriate) must be obtained before initiating study procedures.

Informed consent must be obtained from the legal representative of the child or adolescent in accordance with local law before assent is sought. An assent should be obtained from all subjects that have an intellectual age of 7 years or more. All potential pediatric subjects should be informed to the fullest and most appropriate extent possible about the study, in language and terms they are able to understand.

If a subject signed assent for a study, a consent must be signed once the subject turns legal age, based on local requirements.

The eligibility of the subject will be evaluated. After inclusion of the subject and after obtaining written informed consent (prior to any registry-related procedure being performed) from the subject's parents/caregiver/legal representative and assent, if applicable, the investigator or site staff will enter the subject data into source documents and into an electronic Case Report Form (eCRF).

Following the baseline data collection (Day 0), the visits to collect registry study data are at the discretion of the investigator and may follow the local usual standard of care, however, the sponsor recommends safety, treatment data and FIX inhibitor assessments at 6 month intervals at a minimum during the 1 year of participation in the registry. A Follow-up Call is to be conducted at least 28 calendar (+10 days) after the Final/Early Termination visit in order to collect information on the occurrence of adverse events and concomitant medications.

7.4. Variables

7.4.1 Baseline Data Collection (Day 0)
Baseline data including:

- Demographic data
  date of birth, height, weight, race and ethnicity

- Medical history

  Immunization and viral infections (HIV, vaccination hepatitis A/B, hepatitis A/B/C)
- Medication history

  Concomitant diseases and medications including factor IX and other factor IX-containing blood products
- Hemophilia History
  1. Date of the diagnosis of hemophilia B
  2. Age of first exposure to PCC, FFP or any other coagulation factor products
  3. Disease severity
  4. Genetic mutation (if available)
  5. Inhibitor history
  6. FIX hypersensitivity allergic reactions
  7. Family history of hemophilia and inhibitor
  8. Approximate number of exposure days to Factor IX products (e.g. plasma-derived FIX or BeneFIX) that the patient has experienced.
  9. Treatment [prophylaxis regimen (dose and frequency) or on-demand treatment] at the time of enrollment

7.4.2 Treatment Data Collection (Day 0 to 12 months/Early Withdrawal)

All data will be collected in the CRF. This data will be collected following Day 0 though the Registry Completion/Early Withdrawal Visit.

1. Exposure days, bleed, infusion and response data will be collected throughout the treatment period on the subject diaries.

2. The efficacy outcomes data will be:

   - Annualized bleeding rates (ABR) in subjects receiving treatment with BeneFIX,
   - The responses to all on-demand treatment with BeneFIX for all bleeds (4 point scale of assessment),
   - Number of BeneFIX infusions to treat each new bleed
   - Number of spontaneous/non traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX

7.4.3 Safety Data Collection (Day 0 to 12 months/Early Withdrawal)

Safety data collected throughout the treatment period (Day 0 to 12 months/Early Withdrawal) will consist of:

- All AE and SAE data, including product-related medically important adverse events (inhibitor development, FIX hypersensitivity allergic reactions, thrombogenicity, lack of effect and red cell agglutination,). This data will be reported on the appropriate CRF and AEM forms during treatment with BeneFIX.

- Laboratory results determining the presence of FIX inhibitor antibodies by the Bethesda assay or Nijmegen modification of the Betheseda assay are recommended to be collected for subjects at all study visits.

- Changes in concomitant diseases or medicinal therapy

    1. Medicinal concomitant therapy

- FIX activity and recovery values, if available and assessed at routine clinic visits.

7.5. Data sources

Investigator will first record the study data in source documents, such medical records through subject's scheduled visits. Investigator or the delegate will then enter the study data as well as subject's diary data onto the eCRFs in the Electronic Data Collection (EDC) system.

7.6. Study size

The registry study will be conducted in hospitals and clinics in China. Since the number of potential subjects is unknown, the study is not designed based on sample size considerations.

7.7. Data management

Datalabs is the Electronic Data Collection (EDC) system for the study. The statistical software is Statistical Analysis System(SAS).

The investigator is responsible to collect study data, including the eCRF data, laboratory data and the subject's diary data, via the EDC system in a timely manner and to ensure the integrity, accuracy, and completeness of the data.

The investigator should keep accurate records of: identity of all subjects (sufficient information to link the patients to the corresponding study data), serious adverse event forms, all related source documentation, details of treatment disposition, as well as relevant correspondence details (e.g. letters, emails, meeting minutes, telephone call reports). The investigator record retention period should comply with 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, relocation), Pfizer should be 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. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

7.8. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

A statistical sample size calculation will not be performed for this study. Because all eligible and willing-to-participate subjects will be enrolled in the study and no statistical hypotheses are tested.

All safety and efficacy analyses, except the analysis for Annualized Bleeding Rates(ABR),will be performed on all subjects who receive at least one dose of BeneFIX. ABR analysis will be performed on subjects who participated in prophylaxis period for at least 6 months.

The primary safety outcomes to be reported will be development of clinically significant FIX inhibitors, FIX hypersensitivity allergic reactions, thrombogenicity, lack of effect and red cell agglutination.
Secondary safety outcomes include the frequency of adverse events and serious adverse events, etc.

Secondary efficacy outcomes will be:

- Annualized bleeding rates (ABR) in subjects receiving treatment with BeneFIX,
- The responses to all on-demand treatment with BeneFIX for all bleeds (4 point scale of assessment),
- Number of BeneFIX infusions to treat each new bleed,
- Number of spontaneous/non traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX.

The efficacy results of this study will be presented using descriptive statistics. The following descriptive statistics will be used:

- For numeric endpoints: sample size, mean, standard deviation, median, minimum and maximum;
- For categorical endpoints: count and percentage.

Safety data will be tabulated and listed according to Pfizer’s standard reporting algorithms. The reasons for discontinuation of BeneFIX therapy will be described.

Subgroup analysis will be done by several sub-populations.

Additional details of the analysis will be provided in the statistical analysis plan and/or the clinical study report. This information may include details of missing and, if applicable, unused and spurious data. Deviations from the statistical plan will be reported in the clinical study report.

7.9. Quality control

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the investigator's brochure, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these site visits, information recorded in the CRFs is verified against source documents.

7.10. Other aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1 Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

8.2 Patient withdrawal

Patients 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 or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

For patients that are withdrawn from the study prior to the 12 month visit, the treatment and safety data are to be collected at that visit and it is recommended to collect a FIX Inhibitor sample that is analyzed at the local laboratory. A Follow-up Call is to be conducted at least 28 calendar (+10 days) after the Final/Early Termination visit in order to collect information on the occurrence of adverse events and concomitant medications. If the patient 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.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

9MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1 Adverse Event Reporting

9.1.1 Adverse Events

All observed or volunteered adverse events regardless of treatment group (if applicable) or suspected causal relationship to BeneFIX will be recorded on the adverse event page(s) of the case report form (CRF) as follows.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to BeneFIX follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

9.1.2 Reporting Period

For non-serious and serious adverse events, the reporting period to Pfizer or its designated representative begins from the time of the patient's first dosing in the observational period as per study design through and including 28 calendar days after the last administration of the study drug within the observational period. If the investigator becomes aware of a SAE that is considered related to study drug occurring at any other time after completion of the study, the SAE is also reportable.

9.1.3 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including infant and toddler formulas [hereinafter "pediatric formulas"]) or medical device. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;

- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

9.1.4 Hemophilia Events

Hemophilia events are a subset of AEs that are related to the condition of hemophilia or are directly the consequences of bleeding events. Hemophilia events that require hospitalizations or meet other SAE criteria (defined below) should be reported as SAEs. If there is any doubt whether the information constitutes an AE, the information is treated as an AE for the purposes of this protocol.

9.1.5 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

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

9.2 Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

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. However, 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, the important medical event should be reported as serious.

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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

The following events must be considered medically important and have the same reporting requirements as SAEs:

- FIX inhibitor development
- FIX hypersensitivity allergic reaction
- Thrombogenicity

- Lack of effect
- Red blood cell agglutination

9.2.1 Hospitalization

Adverse events reported from studies associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. 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, neurological floor to a tuberculosis unit).

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

9.2.2 Causality Assessment

The investigator’s assessment of causality must be provided for all adverse events (serious and non-serious). The investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that BeneFIX caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether BeneFIX caused the event, then the event will be handled as related to BeneFIX for reporting purposes. If the investigator’s causality assessment is unknown but not related to BeneFIX this should be clearly documented in the CRF.

9.2.3 Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) BeneFIX or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to BeneFIX (maternal exposure).

2. A male has been exposed, either due to treatment or environmental exposure to BeneFIX prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE/SAE.

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with BeneFIX the investigator must submit this information to Pfizer within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero report.

For clinical studies conducted in pregnant women, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the clinical database. In such instances only EIUs associated with a SAE are to be reported.

9.2.4 Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE :

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

9.3 Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events.

If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

9.3.1 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure during breast feeding and medication error cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes 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 serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event 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 and illnesses must be provided. In the case of a patient

death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.4 Single reference safety document

The safety document will be used in this study is the BeneFIX® Local Product Document approved by CFDA.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.
The results are posted in a tabular format called Basic Results. Since BeneFIX was already approved by FDA in 1997, Pfizer posts results within one year of the primary outcome completion date (PCD).
Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

11 REFERENCES

Package Insert: BeneFIX® Locally Approved Prescribing Information. Pfizer China. 2012.