# NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

## EUropean REgistry in Children below six years of age treated with BeneFIX *EUREKIX*

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| **Compound Number:** | B182 |
| **Compound Name:** | BeneFIX |
| **Study Number:** | B1821046 |
| **EU Post-Authorisation Study (PAS) registration number** | ENCEPP/SDPP/3788 |
| **Version and Date:** | Amended Protocol<br>15 April 2013 |

# ABSTRACT

## EUropean REgistry in Children below six years of age treated with BeneFIX - *EUREKIX*

Version: Amended Protocol, 15 April 2013

Principal Investigator: XXX (add name and affiliation)

### Rationale and background

BeneFIX is indicated for the treatment and prophylaxis of bleeding episodes in patients with haemophilia B (congenital coagulation factor IX deficiency). Whilst clinical trial data in adult patients treated with BeneFIX is available for a relatively large number of patients, data in paediatric patients below 6 years of age is limited to date.

A clinical study in 25 subjects below 6 years of age (Study 3030A1-301-WW) has demonstrated the safety and efficacy of rFIX in this age group. Due to small patient numbers in haemophilia B, registries appear to be a valuable tool to assess safety and efficacy in routine clinical settings.

### Research question and objectives

The objective of this non-interventional study is to assess safety and efficacy of patients below 6 years of age treated with BeneFIX in the routine clinical setting.

### Study design

This is a two phase, non-interventional, multicenter trial including a retrospective (Phase I) and/or prospective (Phase II) data collection period.

### Study population

Patients are eligible to take part in the retrospective data collection if they have been treated with BeneFIX for at least 12 months at an age below 6 years and are at time of consent not older than 8 years. Patients are eligible to participate in the prospective part of the study if they are able to accrue at least 12 months of data in the study before reaching the age of 6 years. The maximum time of prospective observation is 24 months.

### Data sources

Data will be collected from the patient's treatment records and from their treatment diaries. All data collected have been assessed in routine clinical practice. Due to the non-interventional nature of this study, no additional visits or procedures are requested for the study.

### Variables

Patient baseline demographic data and disease/treatment history will be collected. In addition to this, determinants for safety (i.e. all adverse, serious adverse events and events of special interest) as well as for efficacy (i.e. number of bleeding episodes, number of infusions to stop a bleeding episode, efficacy assessment etc.) will be recorded.

### Sample size

A total of 100 patients will be enrolled in this study. Given the rarity of the disease and the focus on a specific subcohort of patients, this is considered to be a substantial number of patients that will significantly enlarge the knowledge of BeneFIX in the age group below 6 years.

### Data analysis

Data will be analysed descriptively. No hypothesis testing will be performed.

### Milestones

Ethic Committee Submission: October 2012

First Ethic Committee Approval: November 2012

First patient first visit: December 2012

Last patient first visit: December 2013

End of retrospective data collection period: June 2013

Interim analysis: October 2013

Last patient last visit: December 2015

Final CSR: June 2016

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## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ABRs | Annualized Bleeding Rates |
| AEs | Adverse Events |
| CRF | Case Report Form |
| eCRF | Electronic Case Report Form |
| CSR | Clinical Study Report |
| EMA | European Medicines Agency |
| FDAAA | Food and Drug Administration Amendments Act |
| FIX | Blood coagulation factor IX |
| rFIX | Recombinant factor IX |
| GPP | Good Pharmacoepidemiology Practices |
| ICH - GCP | International Conference on Harmonisation - Good Clinical Practice |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISPE | International Society of Pharmacoepidemiology |
| ISPOR | International Society of Pharmacoeconomics and Outcomes Research |
| IU | International Unit |
| LETE | Less Than Expected Therapeutic Effect |
| LSLV | Last Subject Last Visit |
| NI | Non Interventional |
| PCD | Primary Outcome Completition Date |
| PhRMA | Pharmaceutical Research and Manufacturers Association |
| PUP | Previously Untreated Patient |
| PTP | Previously Treated Patient |
| PWS | Pharmaceutical Website Synopis |
| RBC | Red Blood Cells |
| SAEs | Serious Adverse Events |
| SmPC | Summary of Product Characteristics |
| TEAEs | Treatment-Emerging Adverse Events |
| TEHEs | Treatment-Emerging Haemophilia Events |

# 1. RATIONALE AND BACKGROUND

Substitution of blood coagulation factor IX (FIX) is the treatment of choice for patients with Haemophilia B. At present, BeneFIX® (Nonacog alfa) is the only recombinant FIX (rFIX) product marketed.

BeneFIX (Nonacog alfa) is indicated for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

BeneFIX contains recombinant coagulation factor IX (INN = nonacog alfa). Nonacog alfa is a purified protein that has 415 amino acids in a single chain. It has a primary amino acid sequence that is comparable to the $\text{Ala}^{148}$ allelic form of plasma-derived factor IX, and some post-translational modifications of the recombinant molecule are different from those of the plasma-derived molecule. Recombinant coagulation factor IX is a glycoprotein that is secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line.

The dosage and duration of the substitution therapy depends on the severity of the factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition. The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. Factor IX products rarely require to be administered more than once daily.

One International Unit (IU) of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma. Estimation of the required dose of BeneFIX can be based on the finding that one unit of factor IX activity per kg body weight is expected to increase the circulating level of factor IX, an average of 0.8 IU/dl (range from 0.4 to 1.4 IU/dl)in adolescents and adults. Pharmacokinetics must be assessed regularly in each patient and posology adjusted accordingly.

The required dosage is determined using the following formula:

$$\text{Number of factor IX IU required} = \text{body weight (in kg)} \cdot \text{desired factor IX increase (\%) or (IU/dl)} \cdot \text{reciprocal of observed recovery}$$

For a recovery 0.8 IU/dl (average increase of factor IX in adolescents and adults), the formula reads:

$$\text{Number of factor IX IU required} = \text{body weight (in kg)} \cdot \text{desired factor IX increase (\%) or (IU/dl)} \cdot \text{1.3 IU/kg}$$

During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. Individual patients may vary in their response to factor IX, achieving different levels of in vivo recovery and demonstrating different half-lives.

Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, biological testing should be performed to determine if a factor IX inhibitor is present.

For long term prophylaxis against bleeding in patients with severe haemophilia B, BeneFIX may be administered. In a clinical study for routine secondary prophylaxis the average dose for previously treated patients (PTP) was 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days. In younger patients, shorter dosage intervals or higher doses may be necessary.

For further information on BeneFIX please refer to the current version of the SmPC

Randomized controlled trials have demonstrated the efficacy and safety of BeneFIX® for prophylactic treatment, on demand treatment and surgery[1, 2, 3]

Study 3030A1-301-WW (hereinafter referenced as study 301-WW) was an open-label, single-arm, safety and efficacy study of recombinant human factor IX (rFIX, BeneFIX) in children less than 6 years of age with severe haemophilia B[4]. This study provides safety, efficacy, and pharmacokinetic data in paediatric patients. A total of 25 subjects at 19 treatment centers participated in this study. Subjects had to be less than 5 years of age (to complete the study before attainment of age 6) with severe haemophilia B (FIX:C≤1%), and with no detectable FIX inhibitor (defined as ≥0.6 Bethesda Units) or history of inhibitor. At least 6 subjects were to have had minimal (≤20 exposure days) or no prior exposure to rFIX.

rFIX was efficacious in the treatment of children less than 6 years of age with severe haemophilia B who were PTPs, MTPs, and PUPs, when rFIX was used for on-demand treatment of bleeding episodes, routine prophylaxis, and surgery. Most (89.1%) on-demand bleeding episodes were resolved with 1 or 2 infusions of rFIX. This favourable outcome was not restricted to any one bleed location, as 87.5% of joint bleeds and 88.6% of soft tissue/muscle bleeds resolved with 1 or 2 rFIX infusions. Most first infusions to treat a bleed were rated *Excellent* or *Good* (88.3%). These high ratings were associated with bleeding episodes occurring at each location site; the initial infusions used to treat the majority of joint (81.3%), soft tissue/muscle (88.6%), and multisite (100.0%) bleeding episodes were rated *Excellent* or *Good*.

The majority of bleeding episodes (61.4%) occurred >48 hours after the last rFIX dose and only 1 patient raised his prophylaxis dose regimen (from 42 IU/kg/week to 55 IU/kg/week). Four (4) patients had their on-demand regimen changed to routine prophylaxis. All 76 (100%) investigator assessments of overall response in patients treated with rFIX were rated as *Very Useful*/*Useful*.

The most frequent treatment-emergent adverse events (TEAEs) reported in this study were fever and infection (14 [56%] each); rhinitis (12, 48%); cough increased (10, 40%); vomiting (9, 36%); accidental injury (8, 32%); rash (6, 24%); and abnormal laboratory tests, diarrhea, conjunctivitis, and otitis media (3 [12%] each), which are not unexpected frequent events for this patient population. Related TEAEs were abnormal laboratory tests and rash (2 [8%] each); and allergic reaction, urticaria, FIX inhibition, local reaction to procedure, and increased cough (1 [4%] each). The mild haematomas (1 each in 2 patients) were the only related treatment-emergent haemophilia events (TEHEs).

One (1) of 25 patients (4%) had 1 severe TEAE considered related to rFIX, FIX inhibition. No patients had a severe TEHE considered related to rFIX. No life-threatening TEAEs or TEHEs considered related to rFIX were reported. In total, 1 patient had 1 SAE (FIX inhibitor). There were no serious haemophilia events.

No deaths were reported in the study.

No withdrawals due to AEs were reported in the study.

The FIX inhibitor is an event of interest; this patient also had allergic-type manifestations. There were no reports of thrombogenicity or red blood cell (RBC) agglutination in the syringe or tubing.

Regulatory authorities in Europe (EMA) increasingly request to provide sufficient and valid data on post-marketing safety and efficacy of their products[5]. A European Registry on children below six years of age treated with BeneFIX like this non-interventional trial would offer further useful data to support the safe and efficacious use of this type of treatment in children. It will be conducted according to the recommendations for improving quality and transparency of non-interventional trials.

## 1.1. PASS designation

The study is considered a Post Authorization Safety Study (PASS) per Pfizer CT34 policy because its primary objective is to collect safety data for BeneFIX in a sub-cohort of patients aged below 6 years. The obtained data will increase the overall amount of data available in this age group substantially. The PASS is not performed upon request from or as a commitment to a regulatory agency.

# 2. RESEARCH QUESTION AND OBJECTIVES

The objective of the study is to collect data in Europe regarding safety (primary endpoint) and efficacy (secondary endpoint) of treatment with rFIX (BeneFIX®) in children below 6 years of age treated in the routine clinical setting.

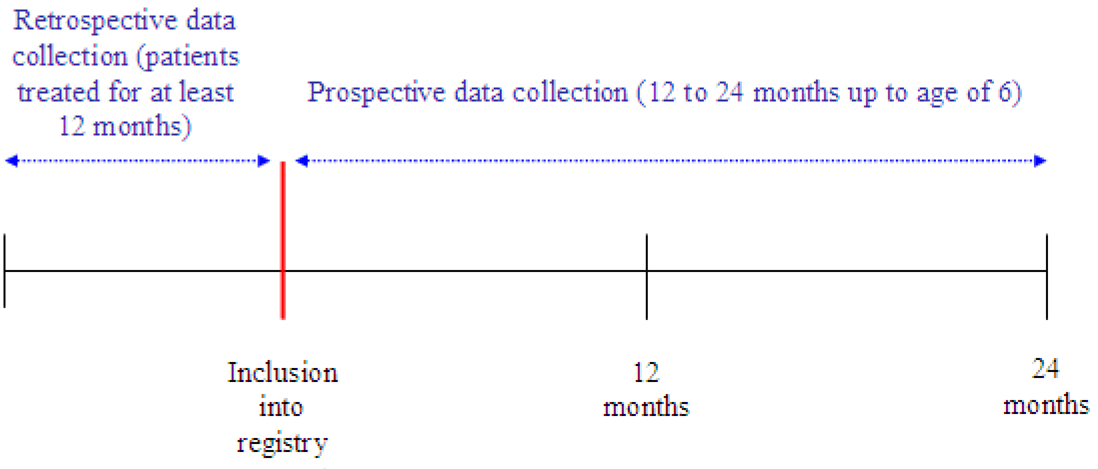
## 3. RESEARCH METHODS

### 3.1 STUDY DESIGN

This is a two phase, non-interventional, multicenter trial including a retrospective (Phase I) and/or prospective (Phase II) data collection period.

Retrospective data will be collected only if patients have been treated with BeneFIX for at least 12 months ahead of the inclusion in the study. In order to ensure consistent data quality, retrospective documentations must not cover a time period longer than 8 years ago i.e. if a patient is 8 years of age, his treatment with BeneFIX between 0-6 years of age may still be retrospectively documented.

Prospective data will be collected if patients will be able to follow 12 to 24 months of treatment with BeneFIX before they reach 6 years of age.



Participating physicians will not be influenced in their decision making and routine proceedings in any way.

### 3.2 STUDY POPULATION

100 subjects will be part of this Registry from approximately 40 sites across the European Union.

All subjects enrolled should meet the usual prescribing criteria for BeneFIX as per the local product information and should be entered into the study at the investigator's discretion.

Patients may be enrolled in both the retrospective and prospective part or in only one of the two, respectively.

Upon informed consent and when eligible for retrospective data collection, patient's charts will be assessed retrospectively for at least 12 months on treatment with BeneFIX. If the patient received treatment with BeneFIX for more than 12 months, data from the entire time period before reaching 6 years of age or inclusion in the study should be collected retrospectively.

When eligible for prospective data collection, patients' treatment outcomes will be documented prospectively for up to 24 months or until the patient reaches the age of 6 years. A minimum prospective collection period of 12 months should be attained before the patient reaches the age of 6 years.

The use and dosage recommendations for BeneFIX will take place on the basis of the approved SmPC and will be adjusted solely according to medical and therapeutic necessity. All treatment decisions follow the general clinical practice and are not influenced by this study protocol in any way.

### 3.2.1. Inclusion Criteria

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

- Patients treated with BeneFIX for at least 12 months before reaching the age of 6 years. These patients are allowed to have a maximum age of 8 years at time of inclusion.
- Patients who will be able to accrue at least 12 months in the prospective phase before reaching the age of 6 years. The treatment with BeneFIX must have been in any case decided or started ahead of the inclusion of the patient in the study

Evidence of an informed consent document prior to any trial-related procedure being performed, signed and dated by the patients' parents indicating that they (or a legally acceptable representative) have been informed of all pertinent aspects of the study.

### 3.2.2. Exclusion Criteria

Subjects presenting the following will not be included in the study:

Patients treated with a product for the treatment of haemophilia B other than BeneFIX® over the retrospective and the prospective collection period.

## 3.3 STUDY PROCEDURES

The eligibility of the patients will be evaluated. After inclusion of the patient and after obtaining written informed consent (prior to any trial-related procedure being performed) from the patients' parents (or a legally acceptable representative), the physician will enter the patient data in an electronic Case Report Form (eCRF).

The following parameters will be recorded (where available):

Demographics:

- Demographic variables (date of birth, height, weight, ethnic group)
- Regular attendance of school
- Date of onset of the treatment with BeneFIX
- Haemophilia B previous therapy
- Disease severity (including genetic mutation if identified in routine clinical practice)
- Family history
- Disease history

    Safety data

    - Inhibitor history
    - History of allergic reactions
    - Immunization and viral infections (HIV, vaccination hepatitis A/B, hepatitis A/B/C)
    - History of red blood cell agglutination in the tubing or syringe

    Concomitant diseases

    - Medicinal or non medicinal concomitant therapy

    Laboratory values

    - Previous FIX activity and recovery if available

Clinical parameters:

- Retrospective part

    Treatment Regimen for at least a 12 months period

    - Dose of FIX at the beginning of the retrospective period (treatment regimen, target value in IU/kg, amount of IU actually administered per infusion, frequency of administration)
    - Any changes to the treatment regimen incl. dose and frequency of administration over the course

of the retrospective period and reasons for this change

Efficacy data

  - Annualized bleeding rates (ABRs) for all bleeds and according to bleed location
  - Responses to the on-demand and prophylactic treatment with BeneFIX for all bleeds, respectively (4-point scale of assessment: excellent, good, moderate, no response)
  - The incidence of less-than-expected therapeutic effect (LETE) will be assessed by the investigator using the criteria listed in Section 7.2.1.
  - Lack of effect, defined as the failure of expected pharmacologic action or therapeutic benefit

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Safety data

  - All AEs and SAEs during treatment with BeneFIX
  - Events of special interest
    - Inhibitor development
    - Allergic reaction
    - Thrombotic event
    - RBC agglutination in tubing or syringe
    - Low recovery

- Prospective part (collection of the data 2-4 times a year, except for the occurrence of a serious or not serious adverse event, that should be reported within 24 hours):

  Treatment regimen at start of prospective period (time of enrolment)

  - Dose of FIX at the beginning of the prospective period (treatment regimen, target value in IU/kg, amount of IU actually administered per infusion, frequency of administration)
  - Any changes to the treatment regimen incl. dose and frequency of administration over the course

of the prospective observational period and reasons for this change

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Efficacy data

- Annualized bleeding rates (ABRs) for all bleeds and according to bleed location
- Responses to the on-demand and prophylactic treatment with BeneFIX for all bleeds, respectively (4-point scale of assessment: excellent, good, moderate, no response)
- The incidence of less-than-expected therapeutic effect (LETE) will be assessed by the investigator using the criteria listed in Section 7.2.1.
- Lack of effect, defined as the failure of expected pharmacologic action or therapeutic benefit
- Total number of days missed from work by parents/caregivers
- Total number of days when the patient was affected in daily activities due to his disease

Safety data

- All AEs and SAEs during treatment with BeneFIX
- Events of special interest
  - Inhibitor development
  - Allergic reaction
  - Thrombotic event
  - RBC agglutination in tubing or syringe
  - Low recovery

Changes in Concomitant diseases and therapy

- Medicinal or non medicinal concomitant therapy

Laboratory values

  - FIX activity and recovery if available and assessed in routine clinical visits

Subjects may withdraw from the study at any time their parents (or a legally acceptable representative) should 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 subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study, and also parents (or a legally acceptable representative) withdraw 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.

## 3.4 DATA COLLECTION AND DATA MANAGEMENT

### 3.4.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to an electronic data record.

A CRF should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts. In haemophilia patients, another source document is the patient diary from which data may be collected in this study.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### 3.4.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to 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 (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## 3.5 DATA ANALYSIS

The data collected in this study will be documented in a NI Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a NI protocol amendment.

### 3.5.1 Sample Size Calculation

A statistical sample size calculation will not be performed for this study. Since no statistical hypotheses are tested, statistical power does not need to be determined. One hundred patients will be included in this registry.

### 3.5.2 Efficacy Analysis

The efficacy of BeneFIX® will be descriptively assessed by different measurement parameters:

- Annualized bleeding rates (ABRs)
- Responses to the on-demand and prophylactic treatment with BeneFIX, respectively, for all bleeds and according to bleeding location (4-point scale of assessment: excellent, good, moderate, no response)
- The incidence of less-than-expected therapeutic effect (LETE) will be assessed by the investigator using the criteria listed in Section 3.5.2.2.
- Lack of effect, defined as the failure of expected pharmacologic action or therapeutic benefit

#### 3.5.2.1 Response Scale

In the event of a bleed in the on-demand setting (including those occurring during the prophylaxis period), the 4-point response scale for an on-demand treatment of a bleeding episode is defined as follows:

- Excellent: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.

- 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 following the infusion, with no additional infusion administered.
- 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.
- No Response: No improvement at all between infusions or during the 24 hour interval following an infusion, or condition worsens.

All subjective assessments will be provided by the subject/caregiver or investigator/qualified staff.

#### 3.5.2.2 LETE Criteria

LETE can occur in 3 specific circumstances. All types of LETE, in aggregate and individually, will be summarized as part of the efficacy information collected in this study.

The following criteria are the definitions for LETE in this study.

##### 3.5.2.2.1 Less than Expected Therapeutic Effect in the On-Demand Setting

LETE occurs in the on-demand setting if 2 successive *"No Response"* ratings are recorded after 2 successive BeneFIX drug infusions, respectively (4-point response scale follows below). The infusions must have been administered within 24 hours (≤24 hours) of each other for treatment of the same bleeding event in the absence of confounding factors (described below). Therefore, LETE in the on-demand setting is based on the response to treatment of a bleeding episode (including those occurring during the prophylaxis period). The only confounding factors are as follows:

- Known presence or subsequent identification of a FIX inhibitor;
- Known inadequate dose for the type and/or severity of bleed in the opinion of the investigator;
- Delay of greater than 4 hours between onset of bleed to infusion;

- Delay of greater than 24 hours before administration of a follow-up infusion;
- Known compromised BeneFIX;
- Faulty administration of BeneFIX;
- The subject has an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (eg, kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs).

##### 3.5.2.2.2 Less than Expected Therapeutic Effect in the Prophylaxis Setting

LETE occurs in the prophylaxis setting if there is a *spontaneous* bleed within 48 hours (≤48 hours) after a regularly scheduled prophylactic dose of BeneFIX (which was not used to treat a bleed) in the absence of confounding factors. Therefore, LETE in the prophylaxis setting is the *occurrence* of a bleed. The only confounding factors are as follows:

- Known presence or subsequent identification of a FIX inhibitor;
- Known inadequate prophylactic dose (ie, a dose less than that prescribed in subject's regimen);
- Known lack of adherence to the prescribed prophylaxis regimen;
- Bleed occurs in a target joint identified at the start of the study;
- Known compromised BeneFIX;
- Faulty administration of BeneFIX;
- The subject has an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (eg, kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs);
- Traumatic injury responsible for bleeding.

##### 3.5.2.2.3 Less than Expected Therapeutic Effect (Low Recovery)

LETE can also be lower than expected recovery of FIX in the opinion of the investigator following infusion of BeneFIX in the absence of confounding factors. The only confounding factors for low recovery are as follows:

- Known presence or subsequent identification of a FIX inhibitor;

- Known compromised BeneFIX;
- Faulty administration of BeneFIX, including inadequate dosing.

### 3.5.3 Safety Analysis

Safety will be assessed throughout the course of the study. Adverse and serious adverse events are defined according to type, onset and end, intensity, seriousness (yes/no), causal relationship with BeneFIX® therapy, outcome and any counteractive measures and are to be documented and evaluated by the investigator

Serious adverse events (SAEs) will be handled according to the current policy.

### 3.5.4 Interim Analysis

An Interim Analysis will be performed after the data collection for the retrospective part has been completed. The details of the Interim Analysis will be outlined in the Statistical Analysis Plan.

## 4. PROTECTION OF HUMAN SUBJECTS

### 4.1 Patient Information and Consent

All parties will ensure protection of subject personal data and will not include subject 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 subject 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 subject's parents, 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 subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

### 4.2. 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, eg, 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.

### 4.3. 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 such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

## 5. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

### 5.1. RETROSPECTIVE PERIOD

All observed or volunteered adverse events for which the investigator has determined that the adverse event is related to *BeneFIX* will be recorded as described on the adverse event page(s) of the case report form (CRF).

For these adverse events, the data captured in the medical chart will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

#### 5.1.1. Reporting period

For non-serious and serious adverse events, the reporting period to Pfizer or its designated representative relates to the start and end of the observational period, as described in section 3.2.

#### 5.1.2 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;
- Progression/worsening of underlying disease;
- 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;

### 5.1.3. 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.

#### 5.1.4. 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.

### 5.1.5. 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)

### 5.1.6. Causality Assessment

The reviewer of the medical chart will identify all adverse events where an investigator's assessment of causality relative to the use of *BeneFIX* (serious and non-serious) is provided in the medical chart. The reviewer of the medical chart must record those adverse events with a causal relationship to *BeneFIX* in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse event 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.

### 5.1.7. 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.

### 5.1.8. Reporting requirements

Each adverse event that in the opinion of the investigator (documented in the medical chart during this chart review) is related to *BeneFIX* is to be assessed to determine if it meets the criteria for serious adverse event.

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

### 5.1.9. Serious or Not Serious Adverse Event Reporting Requirements

If a serious or not serious adverse event occurs (documented in the medical chart during this chart review), that in the opinion of the investigator is related to *BeneFIX*, Pfizer is to be notified within 24 hours of awareness of the event by the reviewer of the medical chart, and a Non-Interventional Study Adverse Event Report Form must be completed and submitted to Pfizer Safety. 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 or not serious event reports as well as to the initial and follow-up reporting medication error cases.

For all serious or not adverse events that in the opinion of the investigator are related to *BeneFIX*, the reviewer of the medical chart is required to pursue and provide adequate clinical information describing the serious or not serious adverse events from the medical chart. All information available in the medical chart concerning the event should be reported to Pfizer in accordance with the timeframes for reporting specified above, and a Non-Interventional Study Adverse Event Report Form must be completed and submitted to Pfizer Safety. This information collected for serious or not serious adverse events is more detailed than that captured on a typical adverse event case report form. In general, this will include a description of the serious or not serious 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 data regarding concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings referenced in the medical chart should be submitted to Pfizer.

### 5.1.10. Communication of issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of *BeneFIX*, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

## 5.2. PROSPECTIVE PERIOD

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.

### 5.2.1. 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.

### 5.2.2. 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;

- Progression/worsening of underlying disease;
- 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;

### 5.2.3. 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.

### 5.2.4. 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.

### 5.2.5. 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)

### 5.2.6. 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.

### 5.2.7. 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.

### 5.2.8. 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.

### 5.2.9. Serious or Not Serious Adverse Event Reporting Requirements

If a serious or not 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 or not serious adverse event reports as well as to the initial and follow-up reporting of medication error cases.

In the rare event that the investigator does not become aware of the occurrence of a serious or not 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 or not 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 or not 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.

### 5.2.10. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of *BeneFIX,* Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

# 6. STUDY DISCLOSURE

## 6.1 Communication of results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clincaltrials.gov regardless of the reason for registration; OR
- All other studies for which the results have scientific or medical importance as determined by Pfizer.

Results are posted as follows:

- The results of all required studies (even if not previously registered to ClinicalTrials.gov) and any voluntarily registered studies are posted on ClinicalStudyResults.org in a format called a Pharmaceutical Research and Manufacturers Association (PhRMA) website synopsis (PWS), the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis.
- For studies involving products already approved in any country and applicable under FDAAA and/or state of Maine, Pfizer posts results within one year of the primary outcome completion date (PCD). For all other studies that do not involve a Pfizer product, Pfizer posts results one year from last, subject last visit (LSLV);

Primary Completion Date is defined as the date that the final subject 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.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

### 6.2. Publications by Investigators *(Optional)*

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

## 7. REFERENCES

[1] Roth DA, Kessler CM, Pasi KJ et al. Human recombinant factor IX: safety and efficacy studies in hemophilia B patients previously treated with plasma-derived factor IX concentrates. Blood 2001;98(13):3600-3606

[2] Ragni MV, Pasi KJ, White GC et al. Use of recombinant factor IX in subjects with haemophilia B undergoing surgery. Haemophilia 2002; 8(2):91-97

[3] Lambert T, Recht M, Valentino LA et al. Reformulated BeneFIX: efficacy and safety in previously treated patients with moderately severe to severe haemophilia B. Haemophilia 2007; 13(3):233-243

[4] Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. Haemophilia 2010; 16(3):460-8. Epub 2010 Jan 4

[5] EMEA/CHMP/BPWP/144552/2009