NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	**EUropean REgistry in Children below six years of age treated with BeneFIX *EUREKIX***
Protocol number	**B1821046**
Protocol version identifier	**Amendment 2**
Date of last version of protocol	**21 Mar 2016**
EU Post Authorisation Study (PAS) register number	**ENCEPP/SDPP/3788**
Active substance	**Pharmacotherapeutic group: Antihaemorrhagic, blood coagulation factor IX; ATC code: B02BD09** **Nonacog alfa**
Medicinal product	**BeneFIX**
Product reference	**B182**
Procedure number	**EMEA/H/C/000139 or EMEA/H/C/139**
Marketing Authorisation Holder (MAH)	**Pfizer Limited**
Joint PASS	**No**

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.**
Country(-ies) of study	**ITALY; SPAIN; SWEDEN; UNITED KINGDOM.**
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
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

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Dr Liesner, B.A. in Medical Sciences Tripos M.A. M.B B.Chir MRCP/FRCP (Paed) MD MRCPath/FRCPath	Consultant Paediatric Haematologist with an interest in Haemostasis and Thrombosis Haemophilia Director Administrative Head of Haematology Laboratories and Lead Clinician in Laboratory Haematology	Great Ormond Street Hospital for Children, NHS Foundation Trust Haemophilia Centre	Great Ormond Street, London, WC1N 3JH

Country Coordinating Investigators

Name, degree(s)	Title	Affiliation	Address
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Rafael Parra (Spain), MD	Coordinator of the Hemophilia Unit	Hospital Val d' Hebrón	Passeig Vall d' Hebrón 119-129 08035 Barcelona
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3. ABSTRACT

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

Version: Amended Protocol, 21 Mar 2016

Principal Investigator: Dr LIESNER (Great Ormond Street Hospital for Children, NHS Foundation Trust Haemophilia Centre, Great Ormond Street, London, WC1N 3JH)

3.1. 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.

3.2. Research question and objectives

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

3.3. Study design

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

3.4. 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.

Due to the data collection cut off scheduled for 31st July 2016 for the existence of an additional EU registry collecting the same data, for some patients less than 12 months of prospective data may be accrued.

3.5. 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.

3.6. 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.

3.7. Sample size

A total of approximately 50 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.

3.8. Data analysis

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

3.9. Milestones

Ethic Committee Submission: October 2012
First Ethic Committee Approval: December 2012
First patient first visit: July 2013
Last patient first visit: December 2015
End of retrospective data collection period: December 2015
Interim analysis: July 2016
Last patient last visit: July 2016
Final CSR: March 2017

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	05 Sep 2012	Substantial	PASS	Include information for PASS study	Classification of the Study as a PASS
2	21 Mar 2016	Administrative	None	New template CT24 Adjustment of milestone dates	Update of CT24

5. MILESTONES

Milestone	Planned date
<Completion of feasibility assessment>	18 APR 2013
Start of data collection	12 JUL 2013
End of data collection (Last Patient Last Visit)	31 JULY 2016
<Interim Analysis>	JUNE 2016
<Registration in the EU PAS register>	09 APR 2013
Final study report	MARCH2017

6. RATIONALE AND BACKGROUND

Substitution of blood coagulation factor IX (FIX) is the treatment of choice for patients with haemophilia B.

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 Ala148 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.

Number of factor IX IU required = body weight (in kg) · desired factor IX increase (%) or (IU/dl) · reciprocal of observed recovery

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

Number of factor IX IU required = body weight (in kg) · desired factor IX increase (%) or (IU/dl) · 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 development of 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.

The 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.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. 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.

8. RESEARCH METHODS

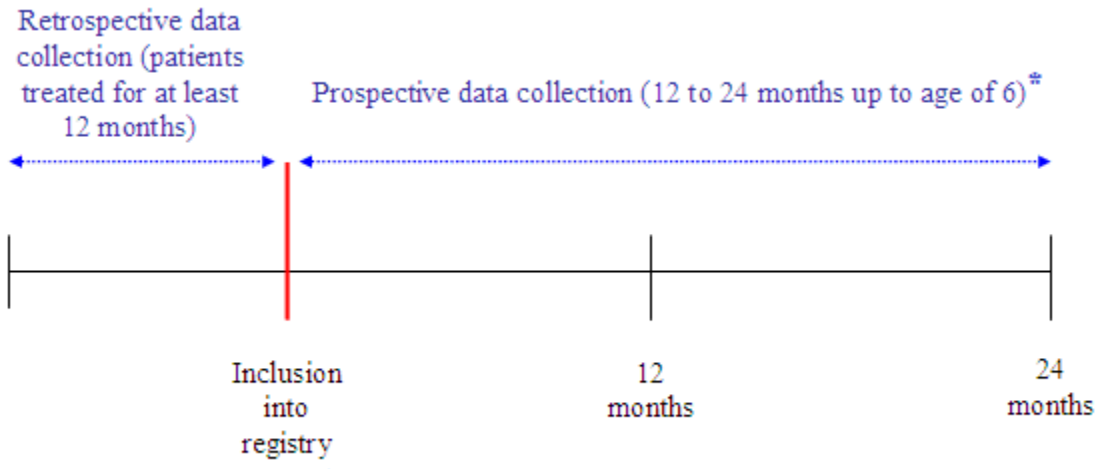
8.1. Study design

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 consecutive 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.

Regarding the prospective phase, the data collection cut off has been scheduled for 31st July 2016, for this reason it may happen that for some patients less than 12 months will be accrued. The last visit performed before 31st July 2016, following clinical practice, will be collected in e-CRF.



*All the visits performed following clinical practice by 31st July 2016, will be collected in e-CRF.

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

8.2. Setting

Approximately 50 subjects will be part of this Registry from approximately 25 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.

Regarding the prospective phase, the data collection cut off has been scheduled for 31st July 2016, for this reason it may happen that for some patients less than 12 months will be

accrued. The last visit performed before 31st July 2016, following clinical practice, will be collected in e-CRF.

The use and dosage for BeneFIX will be based on 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.

8.2.1. 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 consecutive 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.

  Regarding the prospective phase, the data collection cut off has been scheduled for 31st July 2016, for this reason it may happen that for some patients less than 12 months will be accrued. The last visit performed before 31st July 2016, following clinical practice, will be collected in e-CRF.

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.

8.2.2. 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.

8.3. Variables

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):

<u>Demographics:</u>

- 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 8.7.2.3.
- Lack of effect, defined as the failure of expected pharmacologic action or therapeutic benefit

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Safety data

- All AEs and SAEs related to Benefix during treatment
- Events of special interest
  - Inhibitor development
  - Allergic reaction
  - Thrombotic event
  - RBC agglutination in tubing or syringe
  - Low recovery
- As bleeding events in haemophilia are part of the underlying disease they are not reported as adverse events unless they fulfill the definition of LETE (Less than Expected Therapeutic Effect)

- **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 see section 10):

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 8.7.2.3.
- 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
- As bleeding events in haemophilia are part of the underlying disease they are not reported as adverse events unless they fulfill the definition

of LETE (Less than Expected Therapeutic Effect)

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.

8.4. Data sources

Source data to be reviewed during this study will include, but is not restricted to: patient's medical file and original laboratory test. All key data must be recorded in the patient's hospital notes. To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representative of the European Medicine Agency (EMA), and other national authorities and local health authorities where the study is being conducted, the Sponsor and representatives, and the IRB/IEC for each study site. The investigator will permit authorized representatives of the sponsor, the respective national or local health authorities, and auditors to inspect facilities and records relevant to this study. Auditors, IRB/IEC and/or regulatory inspectors will also have access to the CRFs and source documents

8.4.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term 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. After all data has been entered on the eCRF, data entry is closed by the user's electronic signature (user's login and password). 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.

8.4.2. 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.

8.5. Study size

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. Fifty patients will be included in this study.

8.6. Data management

Once the electronic CRF is built, the clinical data manager (and other parties as appropriate) conducts User Acceptance Testing (UAT). The tester enters data into the electronic CRF and record whether it functions as intended.

Most of the expected variables, derivations, range checks and consistency checks will be built in the CRF system, but some checks need to be programmed separately for technical reasons.

Manual queries based on edit checks programmed and manual review listings will be raised by the Clinical Data Manager in the data entry application.

Transfer of data for statistical analysis from the CRF system to datasets will be done using an export program created in SAS®.

All electronic data files delivered will be password protected. Information about the password will be sent separately to the Sponsor.

For the management of activities described in the Statistical Analysis Plan, will be used the statistical software SAS 9.4.

8.7. 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.

8.7.1. 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. Fifty patients will be included in this registry.

8.7.2. 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 8.7.2.3.
- Lack of effect, defined as the failure of expected pharmacologic action or therapeutic benefit

8.7.2.1. 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.

8.7.2.2. 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.

8.7.2.3. 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).

8.7.2.4. 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.

8.7.2.5. 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.

8.7.3. 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.

8.7.4. 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.

8.8. Quality control

The Sponsor or representative's monitor is responsible for verifying the CRF at regular intervals throughout the study to verify the adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. 100% of the data entered into the eCRF is to be verified against the source data at the site. Manual queries based on edit checks programmed and manual review listings will be raised by the Clinical Data Manager in the data entry application.

Queries will be resolved by the Investigator or his authorized designee in the data entry application. The Investigator is responsible for resolving and signing these queries.

8.9. Limitations of the research methods

8.9.1. Investigational site selection

The voluntary participation of physicians constitutes a selection bias observed for this type of study. Investigational sites will be recruited within a representative list of the country's centres in terms of size, care management system and practices.

8.9.2. Patients selection

This constitutes another potential selection bias classically associated with NI studies. Voluntary or involuntary selection of patients in a study by investigators is inevitable, but this bias can be limited by systematic attempts of the investigators to enroll patients in the study.

8.9.3. Patients lost to follow-up

The pragmatic nature of this study (which involves non-intervention on usual patient management practices) complicates the collection of follow-up data and may increase the number of patients lost to follow-up.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. 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.

The assent form is foreseen for this study for children between 6 and 8 years old. It will be administered to the subjects according to the local regulation and after IRB/IEC approval.

9.2. 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 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 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.

9.3. 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.

9.4. 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 Guidelines for 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 Practices for Outcomes Research 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 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.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. ADVERSE EVENT REPORTING IN THE PROSPECTIVE SETTING

For the definitions of safety events see 10.3

The table below summarizes the requirements for recording safety events on the eCRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section “Definitions of safety events”.

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	Inhibitor development Less than expected therapeutic effect (LETE) Allergic reactions Thrombogenicity Medication errors/product confusion
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Medication errors/product confusion

As bleeding events in haemophilia are part of the underlying disease they are not reported as adverse events unless they fulfill the definition of LETE (Less than Expected Therapeutic Effect)

For each AE, 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 SAE (see section "Serious Adverse Events" below)

Safety events listed in the right column of the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. 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. Any information relevant to 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.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of *BeneFIX* or the time of the patient's informed consent if s/he is already exposed to *BeneFIX*, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to *BeneFIX*, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to *BeneFIX*, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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 s/he cannot determine whether *BeneFIX* caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that *BeneFIX* did not cause the event, this should be clearly documented on the eCRF and the NIS AEM Report Form.

10.2. ADVERSE EVENT REPORTING IN THE RETROSPECTIVE SETTING

For the definitions of safety events see 10.3

This study uses existing health care databases, in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual.

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to BeneFIX that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.
The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to BeneFIX that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of BeneFIX must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

As bleeding events in haemophilia are part of the underlying disease they are not reported as adverse events unless they fulfill the definition of LETE (Less than Expected Therapeutic Effect)

10.3. DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. 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 (see below for circumstances in which an abnormal test finding constitutes an adverse event);

- 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;
- Occupational exposure.

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.

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 (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. 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.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization;

however, an event leading to an emergency room visit should be assessed for medical importance.

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)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

<u>Exposure during pregnancy</u>

An exposure during pregnancy (EDP) occurs if:

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

   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).

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 and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with BeneFIX, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to BeneFIX in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

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 (e.g., 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 (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, 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 (e.g., 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.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.4. Single reference safety document

The SmPC will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. 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.

11.2. 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.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., 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 a Pfizer product, Pfizer should be informed immediately.

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

12. 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

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

If there is no document to be listed, delete the table and write “None”.

Number	Document reference number	Date	Title
1	Version 1.0	09 Nov 2012	CRF
2	V 21 Oct 2012	21 Oct 2012	Non Interventional Informed

			Consent Pediatric Study
3	V 21 Oct 2012	21 Oct 2012	EUREKIX Child Assent form (6 to 8 years)_21102012

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.