# NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

## Study information

| | |
|---|---|
| **Title** | Treatment patterns and outcomes in patients treated with BeneFIX or ReFacto/ReFacto AF – A Swedish cohort study |
| **Protocol number** | B1821054 |
| **Protocol version identifier** | 1 |
| **Date of last version of protocol** | 16 June 2015 |
| **Active substance** | B02BD09 - nonacog alfa<br>B02BD02 - moroctocog alfa |
| **Medicinal product** | BeneFIX, ReFacto/ReFacto AF |
| **Research question and objectives** | The objective of this study is to describe demographic and clinical characteristics, treatment patterns and outcomes, as well as the related treatment costs in the populations of hemophilia patients treated with BeneFIX and ReFacto/ReFacto AF at the Malmö Hemophilia Center. The analyses will be carried out for the total populations and for subgroups (e.g. level of severity). |
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# 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems - Tenth Revision |
| IEC | Independent Ethics Committee |
| IHE | Swedish Institute for Health Economics |
| IRB | Institutional Review Board |
| NBHW | National Board of Health and Welfare |
| MHC | Malmö Hemophilia Center |
| MHR | Malmö Hemophilia Registry |
| NIS | Non-Interventional Study |
| PIN | Personal Identification Number |
| SAP | Statistical Analysis Plan |
| SUH | Skåne University Hospital |

## 2. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation | Address |
|---|---|---|---|
| PPD , PhD | Health Economics Manager | Medical GIP and Health & Value, Pfizer AB | Vetenskapsvägen10, S-191 90 Sollentuna, Sweden |

## 3. AMENDMENTS AND UPDATES

None

## 4. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | *01 August 2015* |
| End of data collection | *31 September2015* |
| Final study report | *31 November 2015* |
| Publication submitted | *31 December 2015* |

## 5. RATIONALE AND BACKGROUND

In Sweden nearly 950 people suffer from bleeding disorders. Of these individuals, about 900 are diagnosed with hemophilia A (insufficient production of coagulation factor VIII) and B (insufficient production of coagulation factor IX). The distribution of patients with hemophilia A and B is about 80 percent and 20 percent respectively. About 50 people are diagnosed with von Willebrand disease [1]. All these patients lack sufficient levels of a protein in the blood that impacts the coagulation process. As a result the patients have a higher risk of having a bleed as well as suffer from prolonged bleeding. Bleeding can result in severe complications, especially in joints, and could result in permanent damage such as pain and disability [2].

Patients diagnosed with coagulation disorders receive intravenous replacement treatment of the missing coagulation factor. Replacement treatment can be given prophylactically, i.e., regularly to reduce the insufficiency to prevent bleeding to occur. It can also be given when a bleed occurs with the aim to stop the bleed and/or to stop it from becoming more severe, i.e., on demand treatment. The type of replacement treatment may depend on the severity of the disease [2].

At the Malmö Hemophilia Center (MHC) in Sweden patients diagnosed with bleeding disorders have been treated prophylactically since 1958. The treatment has intensified over time and today patients at the MHC, as well as Swedish patients in general, are treated from

the age of 1-3 years [2]. Injections with replacement treatment for hemophilia A is generally given three to four times a week and for hemophilia B twice a week, when the disease is severe. The patients that belong to the MHC are well monitored - their treatments and outcomes have been registered in the Malmö Hemophilia Register (MHR) since 1977. The MHR therefore represents the best available source of information on treatments and outcomes of hemophilia in Sweden.

The first type of treatment available for Hemophilia A and B had a low percentage of coagulation factors and blood borne viruses such as Hepatitis C and HIV could be transferred to the patient. In the 1990's products that were produced using gene technology, recombinant products, with no risk of blood borne viruses, came to the market. Today several such products, among them ReFacto that was introduced in 1999 (ReFacto AF in 2009), exist for treatment of hemophilia A and most patients are treated with recombinant products [2, 3]. For treatment of hemophilia B four different replacement treatments exist and one of them (BeneFIX) is produced using gene technology [4]. In the US products with extended half-life, that make less frequent dosing possible, are available. These products are expected to be available in the European market in the end of 2015/early 2016.

The aim of this study is to analyze the real world use of BeneFIX and ReFacto/ReFacto AF in hemophilia patients in Sweden. Sweden has a long tradition of population-based research within many therapeutic areas. Information in different registers can be record-linked by using the Swedish Personal Identification Number (PIN) that is unique to each Swedish citizen. The information available in the MHR linked together with information on treatments prescribed and picked up at the pharmacy, available in the Swedish prescription register, (held by the National Board of Health and Welfare, NBHW) provide a unique opportunity to provide in depth knowledge on actual treatment patterns and outcomes for patients diagnosed with hemophilia.

To our knowledge, no study to date has addressed in detail treatment outcomes, prescription patterns, actual treatment patterns, and the associated costs in a cohort of patients with coagulation disorders that are treated with BeneFIX or ReFacto/ReFacto AF. Previous

research that has looked at treatment of hemophilia has e.g. focused on differences between the treatment regimens and the associated outcomes, see e.g. Berntorp et al (2012) for a review of such articles [5]. Recent research based on Swedish data investigates the long-term outcomes in hemophilia patients [6]. Previous research has also focused on real world treatment and outcomes in patients with inhibitors (see e.g. Osooli M et al (2015) for a systematic review of reasons for inhibitors and on what registries around the world have contributed to the learnings about inhibitors) [7-9]. Previous research has also focused on the HRQoL of hemophilia patients) [10].

## 6. RESEARCH QUESTION AND OBJECTIVES

This study is explorative, i.e., not hypothesis driven. The overall aim of the study is to describe demographic and clinical characteristics, treatment patterns and outcomes, as well as the related direct treatment costs in the populations of hemophilia patients treated with BeneFIX and ReFacto/ReFacto AF, and in subgroups (e.g. level of severity) at the MHC in Sweden.

In more detail the primary objectives are:

- To describe basic demographic and clinical characteristics
- To describe prescription patterns, actual treatment patterns, and the relative dose intensity
- To describe treatment outcomes such as bleed and joint damage
- To study the relationship between bleed and actual treatment patterns
- To describe the use of replacement treatment administered in hospital in connection with invasive procedures

The secondary objectives are:

- To describe the costs associated with the prescription and actual treatment patterns

- To describe the costs associated with replacement treatment administered in hospitals

Patients that develop inhibitory antibodies will be included but analyzed separately.

## 7. RESEARCH METHODS

Methodology for the statistical analyses will be detailed in a statistical analysis plan (SAP).

### 7.1. Study design

The study will be carried out as a retrospective population-based register study. Detailed data for each patient diagnosed with hemophilia treated at the Skåne Univeristy Hospital (SUH) is collected in the MHR. The hemophilia patients treated at the SUH represent approximately 40 percent of the Swedish hemophilia population. The information in the MHR will be complemented with information from medical records. Information on drugs will be obtained from the Prescribed Drug Registry held by the NBHW. The information from the different sources will be record-linked at the MHC using the Swedish PINs that are unique to each Swedish citizen

The main strength of this study is that we are able to analyze the questions described in section 6. in a population-based setting.

### 7.2. Setting

The study population will consist of all patients diagnosed with hemophilia (D66.9 (hemophilia A) D67.9 (hemophilia B) in International Statistical Classification of Diseases and Related Health Problems (ICD-10) that have been registered in the MHR since 1977 and that have had at least one registered prescription of BeneFIX or ReFacto/ReFacto AF in the MHR since market authorization of the respective product (Benefix August 27 1997, ReFacto April 13 1999, ReFacto AF July 1 2009). Diseased individuals are included.

Information on drugs picked up at the pharmacy is available in the Prescribed Drug Register in from2005.

### 7.3. Exclusion criteria

There are no exclusion criteria for this study.

### 7.4. Variables

| **Background information** | | |
|---|---|---|
| **Variable** | **Data source(s)** | **Description** |
| Year of birth | Malmö Hemophilia Register | |
| Year of diagnosis | Malmö Hemophilia Register | |
| Year of death | Malmö Hemophilia Register | |
| Age at treatment start | Malmö Hemophilia Register | In months |
| Sex | Malmö Hemophilia Register | 1 = man, 2 = woman |
| Inhibitor status | Malmö Hemophilia Register | Current, ever, never |
| Disease severity | Malmö Hemophilia Register | Mild, moderate, severe |
| Type of bleeding disorder | Malmö Hemophilia Register | ICD-10 codes |
| Hepatitis C antibody infected | Malmö Hemophilia Register | 1 = yes, 2 = no |
| HIV positive | Malmö Hemophilia Register | 1 = yes, 2 = no |
| **Yearly information** | | |
| **Variable** | **Data source(s)** | **Description** |
| Prophylactic treatment | Malmö Hemophilia Register | 1 = yes, 2 = no |
| Body weight | Malmö Hemophilia Register | In kilogram at yearly evaluation |
| Traumatic Bleed joint | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |

| | | |
|---|---|---|
| Spontaneous bleed joint | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Traumatic bleed soft tissue | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Spontaneous bleed soft tissue | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Intracranial bleed | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Gastrointestinal bleed | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Urinary tract bleed | Malmö Hemophilia Register/Clinical records | Number of bleeds at yearly evaluation |
| Joint score Gilbert (World Federation of Hemophilia Physical Examination Score) | Malmö Hemophilia Register | Available until 2008/09 |
| Joint score HJHS | Malmö Hemophilia Register | Hemophilia Joint Health Score (HJHS)(0-143) (Available from 2008/09) |
| Surgery in joint for hemophilia related problems | Clinical records | For each surgery information on year of surgery and surgery type, treatment type and number of units |
| | Information on drug prescription | |
| Prescribed dose per infusion | Malmö Hemophilia Register | IU,U,µg |
| Prescribed dose per kilogram | Malmö Hemophilia Register | IU,U,µg |
| Prescribed frequency of infusion | Malmö Hemophilia Register | The weekly number of infusions, range from when needed to daily |
| Annual consumption of factor concentrate | Malmö Hemophilia Register | Patient reported consumption during calender year |
| **Information related to each drug expedition** | | |
| **Variable** | **Data source(s)** | **Description** |
| Product prescribed | The Prescribed Drug Register | ATC codes |
| Prescription date | The Prescribed Drug Register | Year month day |

| | | |
|---|---|---|
| Expedition date | The Prescribed Drug Register | Year month day |
| Dosage text | The Prescribed Drug Register | |
| Product identification number or package size (Number of IU) | The Prescribed Drug Register | |
| Number of expedited units | The Prescribed Drug Register | |
| Apris (AIP) | The Prescribed Drug Register | |
| Ppris (AUP) | The Prescribed Drug Register | |

### 7.5. Data sources

Individual data will be extracted from the MHR and supplemented with information on surgery and/or bleed episodes from medical records when deemed necessary. Information on drugs prescribed and picked up from the pharmacy come from the prescribed drug register at the NBHW. The information from the different sources will be record-linked at the MHC by using the Swedish PINs that are unique to each Swedish citizen.

### 7.6. Study size

The register that will be used for this study contains information on all Swedish patients diagnosed with hemophilia that are treated at the MHC since 1977. The MHC is one of three hemophilia centers in Sweden and is responsible for treating about 40 percent of the Swedish hemophilia population. The approximate number of patients in the register that are relevant for this study amount to about 40 patients for BeneFIX and 20 patients for ReFacto/ReFacto AF .

### 7.7. Data management

Data from the MHR and from the NBHW will be record linked and all PIN will be replaced by patient study numbers, before they are sent to the vendor, the Swedish Institute for Health Economics (IHE). Data management at IHE will include quality and consistency checks. All corrections and editing will be tracked for transparency. All data storage and analyses will be carried out in statistical software Stata 13.0 or later versions.

### 7.8. Data analysis

All data will be displayed using standard statistical methods. Outcomes will be measured using a lifetime perspective while treatment patterns and associated costs will be analyzed using shorter time periods. Descriptive statistics will be carried out using frequency and percentage for categorical variables and mean, standard deviation, median, min and max for continuous variables.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

### 7.9. Quality control

The information in the MHR is of highest quality. The coverage in the register is 100 percent for the patients that are diagnosed with hemophilia and treated at the MHC. Quality control in the MHR is rigorous. Each data point is checked to ensure the high quality.

Information for the selected patients in the register will be complemented by information from medical records when deemed necessary. This is done by the MHC. Quality control in the process is rigorous. Each data entry is checked to ensure the high quality.

The information from the MHR will further be record-linked with information on relevant drugs prescribed and picked up at a Swedish pharmacy. Prescription records and information on what prescriptions that were actually picked up at the pharmacy are available in the prescribed drug register at the NBHW since 2005. The only exception is when a patient must be given emergency treatment at another hospital than SUS. The linking of data will be carried out at the MHC. Data will be treated with privacy and according to the Swedish Personal data act.

Data management carried out by the vendor will be tracked so that data editing and other data corrections in the preparation of the analysis data sets will be transparent.

### 7.10. Limitations of the research methods

The results from this population-based, retrospective cohort study will not necessarily be representative for other patient cohorts. Furthermore, the interpretation of results may be hampered by the small number of events available.

Some information in the register is self-reported e.g. bleeding, this may lead to underreporting. Information on prophylaxis that is given in the case of emergency at another hospital than SUS is not included in the data. This means that the total cost of prophylaxis is potentially underestimated. However, the risk of underestimation is judged to be very small.

### 7.11. Other aspects

Not applicable

## 8. PROTECTION OF HUMAN SUBJECTS

### 8.1. Patient Information and Consent

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

Data will be analyzed and presented at group level in reports and publications. Informed consent is not required due to the retrospective design of the study. The study will be advertised and patients included in the MHR will have an opt-out possibility carried out by the MHC. Data is anonymized in the file that will be used to carry out the analyses.

### 8.2. Patient withdrawal

Not applicable

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and opt-out option for the study participants 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.

This study will be sent for approval to the Research Ethics Committee in Lund, Sweden.

### 8.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in 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.

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

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 any Pfizer drug 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 any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form 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 a Pfizer product 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.

All research staff members will complete the Pfizer requirements regarding training on the following: *"Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

## 10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results in this study will be reported and discussed in a study report and a manuscript that will be sent to a scientific journal for review and publication.

## 11. 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

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## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

## ANNEX 2. ADDITIONAL INFORMATION

Not applicable