Updated Protocol no. 4

Including Global Substantial Amendment 1 dated 11 January 2013, Global Protocol Amendment 2 dated 22 January 2014, Global Protocol Amendment 4 dated 11 August 2014 and Global Protocol Amendment 5 dated 02 February 2016

Study ID: NN1841-3868

EU PAS Register No: ENCEPP/SDPP/3687

Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional study

Protocol originator:
[redacted], [redacted]
Haem, ClinOps 4

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ANNEX 1. List of Stand-alone Documents

ANNEX 2. ENCePP Checklist for Study Protocols

1 List of abbreviations

Anti-FXIII antibody	FXIII antibody
CRF	case report form
CRO	Contract Research Organisation
EMA	European Medicines Agency
EU SmPC	European Summary of Product Characteristics
FDAAA	Food and Drug Administration Amendments Act
FPFV	first patient first visit
FXIII	Factor XIII
FXIII CD	Congenital FXIII deficiency
GPP	Good Pharmacoepidemiology Practices
ICMJE	International Committee of Medical Journal Editors
LAR	legally acceptable representative
LPFV	last patient first visit
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
ND	Not Done
PASS	Post-authorisation safety study
PRO-RBDD	Prospective Rare Bleeding Disorder Database
PSUR	Periodic Safety Update Report
rFXIII	recombinant factor XIII
US PI	United States Physician Information

2 PASS information

Title	Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study
Protocol version identifier	1.0
Date of last version of protocol	Updated protocol no 3, 11 August 2014
EU PAS Register number	ENCEPP/SDPP/3687
Active substance	Catridecacog. ATC code: ATC code: B02BD11
Medicinal product	NovoThirteen®, Tretten®, TRETTEN®
Product reference	EU/1/12/775/001 FDA BLA application number: 125398
Procedure number	EMEA/H/C/002284
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé DK -2880 Bagsværd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	This study is designed to further explore the safety profile and the effectiveness of rFXIII in clinical practice. <u>Primary objective:</u> • The aim of this non-interventional study is to investigate the incidence of specific adverse drug reactions associated with the use of recombinant factor XIII (rFXIII) in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect. <u>Secondary objectives:</u> • To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly, pregnant and lactating women, and patients with renal insufficiency). • To assess the use of rFXIII in patients with congenital FXIII A-subunit deficiency, also other than for prophylactic use. • To better understand the use of rFXIII and practice patterns in the usual care of patients.

Countries of study	Denmark, Canada, Hungary, Spain, Czech, Switzerland, Italy, UK (Scotland) and USA
Author	[redacted], [redacted] Haem ClinOps 4, Novo Nordisk A/S Vandtaarnsvej 108-110 2860 Soeborg Denmark

Marketing authorisation holder

Marketing authorisation holder (MAH)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	[redacted], [redacted] Novo Nordisk A/S Vandtaarnsvej 108-110 2860 Soeborg Denmark

3 Responsible parties

In this document Physician refers to the individual being overall responsible for the conduct of the non-interventional study at a study site, and the responsible for treating the patient with congenital FXIII A-subunit deficiency.

The Physician is accountable for the conduct of the study. If any tasks are delegated, the Physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

The medical care given to, and medical decisions made on behalf of, patients should always be the responsibility of a qualified Physician.

The Physician will follow the instructions from Novo Nordisk when processing data.

The Physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Physician will prevent any unauthorised access to data or any other processing of data against applicable law.

Upon request from Novo Nordisk, the Physician will provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

Blood samples for anti-FXIII antibodies will be analysed at central laboratories selected by Novo Nordisk or at Novo Nordisk.

During any period of unavailability, the Physician should delegate responsibility for medical care of patients to a specific qualified Physician who will be readily available to patients during that time.

If the Physician is no longer able to fulfil the role of Physician (e.g. if he/she retires), a new Physician will be appointed in consultation with Novo Nordisk. The Physician and site personnel must have sufficient English skills according to their assigned task(s).

Main author of protocol: [redacted], [redacted], Haem ClinOps 4, Novo Nordisk A/S, Vandtaarnsvej 108-110, DK-2860 Soeborg, Denmark.

Please refer to the Stand-alone documents (see Annex 1) for additional information about responsible parties. A list of all collaborating institutions and investigators will be made available to authorities upon request.

4 Abstract

4.1 Title

Use of rFXIII in treatment of congenital FXIII deficiency, a prospective multi-centre observational study (PASS), Version updated protocol no. 4.0, 02 February 2016.

EU PAS No: ENCEPP/SDPP/3687

Main author of protocol: [redacted], [redacted], Haem ClinOps 4, Novo Nordisk A/S, Vandtaarnsvej 108-110, DK-2860 Soeborg, Denmark.

4.2 Rationale and background

This protocol describes a post-marketing non-interventional study of recombinant human coagulation factor XIII (rFXIII).

The study is designed to observe the use of rFXIII in normal clinical practice and hereby further explore the safety profile and effectiveness of rFXIII. This study will expand our overall understanding of the safety profile of rFXIII. Emphasis will be placed on adverse drug reactions of special interest comprising; anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect. The overall safety of rFXIII in patients with congenital FXIII deficiency (FXIII CD) will also be explored under conditions of routine clinical care. The effectiveness of prophylactic treatment will be assessed by the evaluation of the annualised rate of bleeding (both non-treatment requiring bleeds and treatment requiring bleeds).

4.3 Research question and objectives

The research question behind the study is to collect long term safety data and to register treatment practices as they are actually performed – in a structured and documented way. This study will further explore the safety and effectiveness of rFXIII.

<u>Primary objective</u>
The aim of this non-interventional study is to investigate the incidence of specific adverse drug reactions associated with the use of rFXIII in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect.

<u>Secondary objectives</u>

- To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly, pregnant and lactating women, and patients with renal insufficiency).

- To assess the use of rFXIII in patients with congenital FXIII A subunit deficiency also other than for prophylactic use.
- To better understand the use of rFXIII and practice patterns in the usual care of patients.

Primary endpoint

Adverse drug reactions in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during study period up to 6 years.

Secondary endpoints

- All serious adverse events collected during study period up to 6 years[1]
- All medical events of special interest collected during study period up to 6 years[1]
- All medication errors and near medication errors collected during study period up to 6 years[1,2]
- Use of rFXIII in patients with congenital FXIII A-subunit deficiency also for other uses than for prophylactic treatment collected during study period up to 6 years.
- Annualised bleeding rate during the study period up to 6 years.

[1] The first three secondary endpoints will be presented by all patients as well as by special populations comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.
[2] Medication errors and near medication errors is a subset of the medical events of special interest.

4.4 Study design

This is a prospective, single-arm, multi-centre and multinational non-interventional post-authorisation safety study (PASS), of safety related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures are applied. The study assesses safety parameters in congenital FXIII A-subunit deficiency patients treated with rFXIII, who have been screened for inclusion and have provided signed informed consent for participation in this non-interventional study.

Study product

There will be no dispensing of any study medication as part of this study. The study medication used is the commercially available rFXIII. All direction for medication usage is solely at the discretion of the Physician in accordance with usual care and in accordance with the approved product label (EU SmPC, US PI or corresponding local prescribing information).

All patients enrolled in this non-interventional study will receive their medication through usual commercial channels.

4.5 Population

This non-interventional study will include patients with congenital FXIII A-subunit deficiency for whom the decision to treat with rFXIII has been made and who are willing to provide informed consent (or patient's legally acceptable representative (LAR) consent, if applicable). The study will aim at observing all patients exposed to rFXIII in the EU, and additional patients from selected non-EU countries. The study will run for 6 years, where after data will be reported and the study closed.

Inclusion criteria

- Informed consent obtained before any study-related activities. (Study-related activities are any procedure related to recording of data according to the protocol).
- Able and willing to provide signed informed consent (or patient's legally acceptable representative (LAR) consent, if applicable), as required by local ethics committee, governmental or regulatory authorities.
- Congenital FXIII A-subunit deficiency.
- Actual or planned exposure to the rFXIII.

Exclusion criteria

- Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

Withdrawal criteria

- The patient may withdraw at will at any time.
- The patient's parent or patient's LAR may withdraw the patient at any time.

4.6 Variables

The study is designed to observe the use of rFXIII in normal clinical practice and hereby further explore the safety profile and effectiveness of rFXIII.

The safety profile of rFXIII will be monitored via collection of data on adverse drug reactions comprising FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect. Also, all serious adverse events, all medical events of special interest and all medication errors and near medication errors will be collected.

The effectiveness of prophylactic treatment with rFXIII in patients with congenital FXIII A-subunit deficiency will be measured by collecting data on annualised bleeding rate. Also, data on treatment with rFXIII for other uses than prophylactic treatment in patients with congenital FXIII A-subunit deficiency will be collected.

4.7 Data sources

It is the intention of this non-interventional study to observe routine treatment of the individual patient. Data and results available in the patient's medical record, in the patient diary and from assessments and laboratory sampling performed according to clinical practice at the participating sites will be recorded in the paper Case Report Form (CRF). Information related to treatment and bleeding episodes will be captured in a patient diary by the patient or parent/caregiver. In case a patient is unable to enter a treatment or a bleeding episode in the diary, or is hospitalised, it should be reported in the patient record and subsequently in the paper CRF by the Physician. Further, contractual collaboration with the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) has been established.

4.8 Study size

No formal analysis of sample size has been conducted, but the adequacy of an expected number of patients has been considered.

Within Europe and the US, the study intends to recruit as many patients as possible among the FXIII CD patients treated with rFXIII. The total population in Europe of diagnosed patients with FXIII CD is between 300 and 400 patients, of which more than 10% are expected to receive rFXIII. Hence, in combination with the patients recruited outside Europe, a minimum of 30 patients are anticipated to be enrolled in the study.

Such an anticipated minimum number of patients are judged to facilitate a sufficient expansion to the safety experience of prophylactic treatment with rFXIII, taking into consideration the rarity of the disease.

4.9 Data analysis

This is a purely descriptive study and the statistical analyses and presentations do not include any testing of pre-specified hypotheses. All analyses and presentations will be based on the Full Analysis Set.

4.10 Milestones

Planned date for FPFV:	17 May 2013
Planned date for last patient first visit (LPFV):	17 May 2017
Planned completion of the last patient (LPLV):	29 Jun 2019
Planned completion of non-interventional study report:	28 Dec 2019

5 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	11-Jan- 2013	Section 2	For analysis of human EDTA plasma requires approximately 2 ml whole blood (0.5 1 ml EDTA plasma).	Change of collected volume of blood (optional blood sample) taken at the Visit 1 for FXIII activity samples from1 ml tube for the blood collection to 2 ml blood will need to be collected for the FXIII activity analysis
2	22-Jan-2014	Section 2.4 (section 8.1/visit procedures, 8.3/Assessments for safety and 15.2.3/Baseline characteristics) and accordingly in the flow chart section 2.2 (section 2	To collect blood samples for testing of anti-FXIII antibodies at visit 1 and at a visit to be conducted 1 year after entry of the patient into the study	FDA Post approval commitment to ensure data on FXIII antibody development from as many patients as possible
3	04-Feb-2014	Throughout the whole protocol	Withdrawn internally by Novo Nordisk. Main rationale for preparing this amendment was clarifications with regards to wording in the Updated Protocol, no. 2, dated 22 Jan 2014.	The changes from Amendment 3 have been implemented in Amendment 4.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
4	11-Aug-2014	Throughout the whole protocol	The main rationale for amending the protocol is due to EMA has published new requirements for non-interventional PASS (EMA/623947/2012) studies regarding protocol format and content. General updates since last protocol update 2 have been implemented in the updated protocol 3.	The update of the protocol to the EMA/PRAC (Pharmacovigilance Risk Assessment Committee) required protocol template is not a strict regulatory requirement, but is encouraged for PASS protocols submitted before 10 Jan 2013 (the original mentor™6 protocol was submitted to EMA for assessment in June 2012). Please refer to page 3: Rationale for the Amendment
5	02 February 2016	Section 2 PASS information, Section 3 Responsible parties, Section 4.1 Title, Section 4.3 Primary endpoint, Secondary endpoints,	Recruitment period extended with 1 year to 17-May-2017. Definition of concomitant illness updated. Minor administrative changes implemented.	With the current recruitment rate it will not be possible to reach the anticipated number of 30 patients within the current recruitment period .

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
		Section 4.5 Population, Section 4.8 Study size, Section 4.10 Milestones, Section 6 Milestones, Section 8.2.1 Primary endpoint, Section 8.2.2 Secondary endpoints, Section 9.1.1 Type of study, Section 9.1.2 Rationale for study design, Section 9.1.3 Treatment of patients, Section 9.3.2.7 Concomitant illnesses, Section 9.5 Study size, Section 9.7.2.2 Secondary endpoints.		Definition of concomitant illness aligned with other trials/studies in the project.

6 Milestones[1]

Milestone	Planned date
Start of data collection Defined as first entry of patient data	17 May 2013
Interim report 1	17 May 2015
Interim report 2	17 May 2017
End (or completion) of study Defined as the Last Patient Last Visit (LPLV)	29 Jun 2019
End of data collection Defined as the date from which the analytical dataset is completely available	17 Aug 2019
Registration in the EU PAS Register	28 May 2013
Final report of study results Planned completion of non-interventional study report	28 Dec 2019

Planned duration of recruitment period is 4 years after first patient first visit (FPFV) in the study.

All study visits should be performed according to normal local clinical practice. No additional visits should be conducted due to the participation in this study. It is recommended that assessment visits occur every one to six months depending on usual practice. The study will be terminated after 6 years; hereafter no more assessment visits will be performed.

The patient's next visit to the clinic will be defined as their end of study visit (visit 3), and should be performed within 3 months of study termination. The end of study assessments should be performed (for more details see section 9.3.1.3).

This study is subject to registration no longer than 21 days after enrolment of the first study participant according to Novo Nordisk requirement on non-interventional study disclosure. For countries outside the US, only the main study site per country will be disclosed via facility name, city and country on the study registration. In the US, all study sites will be registered.

For PASS studies in Europe, the study information should be available in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines

Agency and accessible through the European medicines web portal. The EU PAS Register is currently and temporarily hosted on the ENCePP website http://encepp.eu/.

Note: Study registration is regarded as the publication of an internationally agreed set of information (which can be found at the World Health Organisation (WHO) homepage) about the design, conduct and administration of clinical trials. These details are published on a publicly accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage), eg https://clinicaltrials.gov/.

Additionally contractual collaboration with the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) has been established.

7 Rationale and background

7.1 Background

This protocol describes a post-marketing non-interventional study of recombinant human coagulation factor XIII (rFXIII).

The study is designed to observe the use of rFXIII in normal clinical practice and hereby further explore the safety profile and effectiveness of rFXIII -in a structured and documented way. This study will expand our overall understanding of the longterm safety profile of rFXIII. Emphasis will be placed on adverse drug reactions of special interest comprising; anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect. The overall safety of rFXIII in patients with congenital FXIII deficiency (FXIII CD) will also be explored under conditions of routine clinical care. The effectiveness of prophylactic treatment will be assessed by the evaluation of the annualised bleeding rate (both non-treatment requiring bleeds and treatment requiring bleeds).

Participation in this study will benefit the patient by providing systematic assessments of safety, especially comprising anti-FXIII antibodies and lack of effect. Indirectly the patient will also benefit from improved knowledge of the clinical use of rFXIII that will be gathered in this study.

7.2 Rationale

Disease description
FXIII CD is a rare autosomal recessive bleeding disorder and a potentially life-threatening condition that occurs in approximately 1 in 2 million individuals. The disorder affects both genders and all ethnic groups equally[2]. The disorder is difficult to diagnose by usual laboratory screening tests[3] and is thus believed to be underdiagnosed, and the prevalence may be higher than estimated.

Coagulation factor XIII (FXIII), previously known as fibrin stabilising factor, is a plasma transglutaminase and is the late-stage enzyme in the blood coagulation cascade. In plasma, FXIII circulates as a heterotetramer [A_2B_2] composed of two FXIII-A subunits [A_2] and two FXIII-B subunits [B_2] held together by strong non-covalent bindings[4]. The FXIII B-subunits act as carrier molecules for the FXIII-A subunits in circulation[5,6], and is present in excess in plasma. Accordingly, there are two forms of FXIII CD, either affecting the A-subunit or the B-subunit of FXIII. However, more than 95% of all known inherited FXIII CD cases are due to mutations in the gene encoding the catalytic A-subunit, located on chromosome 6[7].

Clinical manifestations
The majority of homozygous patients not receiving prophylactic therapy with FXIII-containing products will experience recurrent spontaneous haemorrhages including subcutaneous haematomas, superficial ecchymoses, bleeding into muscles after strenuous exercise, epistaxis, gastrointestinal bleeding, central nervous system bleeds, especially in young children, and delayed bleeding from

sites of trauma. Patients may bleed around joints after trauma, but spontaneous haemarthrosis is considerably less common than in haemophilia patients. Delayed wound healing and heavy menses can also be signs of FXIII deficiency and there is a high rate of first trimester spontaneous abortions in pregnant women with FXIII CD.

Life-threatening bleeding may occur, including spontaneous intracranial haemorrhage, in 25–40% of patients[8]. This high risk of intracranial bleeding is unusual in inherited bleeding disorders and is the most common cause of death from bleeding in this population[3].

Treatment options
Treatment in relation to bleeds, surgery and bleeding prophylaxis is currently managed using plasma-derived FXIII freeze-dried products, cryoprecipitate, or fresh-frozen plasma. Desmopressin or antifibrinolytics do not have primary haemostatic effects in patients with homozygous FXIII deficiency[9].

The rFXIII product
The study medication, rFXIII, is manufactured as an intracellular, soluble protein in a yeast production strain (*Saccharomyces cerevisiae*). The purified protein is an rFXIII [A_2] homodimer and is freeze dried. Each vial contains 2500 IU and is supplied as a lyophilized powder. The product is to be reconstituted with sterile water and administered intravenously. Further details are available in the approved product information European Summary of Product Characteristics (EU SmPC), United States Physician Information (US PI) or corresponding local prescribing information.

8 Research question and objectives

8.1 Objectives

8.1.1 Primary objective

The aim of this non-interventional study is to investigate the incidence of specific adverse drug reactions associated with the use of recombinant factor XIII (rFXIII) in patients with congenital FXIII A-subunit deficiency, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect.

8.1.2 Secondary objectives

- To further explore the overall safety and effectiveness of rFXIII under conditions of routine clinical care in patients with congenital FXIII A-subunit deficiency, including special population (i.e., children, elderly, pregnant and lactating women, and patients with renal insufficiency).
- To assess the use of rFXIII in patients with congenital FXIII A-subunit deficiency, also other than for prophylactic use.
- To better understand the use of rFXIII and practice patterns in the usual care of patients.

8.2 Endpoints

8.2.1 Primary endpoint

Adverse drug reactions in patients with congenital FXIII A-subunit deficiency treated with rFXIII, comprising anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of effect, collected during study period up to 6 years.

8.2.2 Secondary endpoints

- All serious adverse events collected during study period up to 6 years[1]
- All medical events of special interest collected during study period up to 6 years[1]
- All medication errors and near medication errors collected during study period up to 6 years[1,2]
- Use of rFXIII in patients with congenital FXIII A-subunit deficiency also for other uses than for prophylactic treatment collected during study period up to 6 years.
- Annualised bleeding rate during the study period up to 6 years.

[1] The first three secondary endpoints will be presented by all patients as well as by special populations comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.
[2] Medication errors and near medication errors is a subset of the medical events of special interest.

9 Research methods

In this document Physician refers to the individual being overall responsible for the conduct of the non-interventional study at a study site, and the responsible for treating the patient with congenital FXIII A-subunit deficiency.

9.1 Study design

9.1.1 Type of study

This is a prospective, single-arm, multi-centre and multinational non-interventional PASS of safety related to treatment with rFXIII in patients with congenital FXIII A-subunit deficiency. No controls or blinding procedures are applied. There will be no dispensing of any study medication as part of this study. All direction for medication usage is solely at the discretion of the Physician in accordance with their usual care.

The non-interventional PASS will be accessible by all EU countries and other selected non-EU countries, where rFXIII is commercially available. The study duration is 6 years. During the conduct of the non-interventional study active follow-up with included sites will take place in order to ensure and maximise patient enrolment and retention and ensure that safety data are being collected and reported.

9.1.2 Rationale for study design

The rationale for choosing this study design is to assess safety related to treatment with rFXIII in a real-life setting in patients with congenital FXIII A-subunit deficiency. The multi-centre design chosen is to ensure sufficient screening pool of patients for the study. The multinational approach is selected to account for possible variations related to ethnic groups.

Observing patients exposed to rFXIII for up to 6 years is considered an appropriate and reasonable time allowing for further expansion of the known safety of rFXIII for the treatment of FXIII CD. Due to the rarity of the disease and very limited available data with regards to rare adverse events, a systematic sample size calculation is not feasible. It is acknowledged that the small target population limits the potential for enrolment and not all of the diagnosed patients have a current need for treatment of their FXIII CD. The availability of patients for enrolment in the study will also be determined by market uptake of rFXIII for prophylactic treatment of patients with FXIII CD.

Based on the World Federation of Haemophilia (WFH) 68 annual report of 2008[10] the number of diagnosed FXIII CD patients in North America is 136 and in Europe it is 213 resulting in a total of 349 patients in countries in which rFXIII will be marketed. Not all of these patients have a current need for treatment of their FXIII CD disease. The market penetration of rFXIII for the treatment of FXIII CD will determine the number of patients eligible for inclusion in this study.

9.1.3 Treatment of patients

The treatment regimens will be in accordance with the approved product labelling in the country of residence of the patient, if rFXIII is used for other indications in patients with FXIII CD this information will also be collected. It is recommended that data collection happens in conjunction with otherwise scheduled visits to the clinic. Patients are expected to remain in the study for up to 6 years depending on time of enrolment.

The study medication used is the commercially available rFXIII (Coagulation Factor XIII A-subunit (recombinant)/INN name: catridecacog, 2500 IU (15 mg)). Administration will be according to the approved package insert (for further information see US PI, EU SmPC, or corresponding local prescribing information). The medication will not be supplied by Novo Nordisk. All direction for medication usage is solely at the discretion of the Physicians in accordance with their usual care guided by the provided product information (US PI and EU SmPC, or corresponding local prescribing information).

There will be no dispensing of any study medication as part of this study. No auxiliary dispensing materials or devices apart from those provided with the commercially available rFXIII product are expected to be used.

The decision to initiate treatment with commercially available catridecacog has been made by the patient/parent and the patient's treating physician before and independently from the decision to include the patient in this study.

For the collection of blood samples, tubes will be provided.

9.1.4 Rationale for treatment

Patients with FXIII CD are lacking the coagulation factor XIII and are therefore predisposed to bleeding from multiple locations; the most serious being intracerebral bleeds (see section 7.2). This is the most common cause of death in this patient group. Treatment with FXIII containing products are therefore used for three purposes: Treatment of an on-going bleed, prevention of bleed in relation to a surgical procedure or general prophylaxis. Due to the long half-life of rFXIII once monthly injection will provide prophylaxis in this patient group (for further information see US PI and EU SmPC, or corresponding local prescribing information).

9.1.5 Study Supplies

9.1.5.1 Study product

The study medication is the commercially available rFXIII (Coagulation Factor XIII A-subunit (recombinant)/INN name: catridecacog, 2500 IU (15mg)) supplied as a lyophilized powder in vials. The powder is to be reconstituted with solvent for injection. After reconstitution the solution is 833

IU/ml corresponding to 5mg/ml. Study medication is to be administrated according to approved product information (EU SmPC, US PI or corresponding local prescription information).

Final approved EU SmPC, US PI or corresponding local prescription is attached to the protocol as country specific product information.

The study medication will not be supplied by Novo Nordisk. All patients enrolled in this non-interventional study will receive their medication through usual commercial channels.

9.1.5.2 Packaging and labelling of study product

These will be as available in the market by prescription and purchase/supply as in routine practice and according to local regulations.

9.1.5.3 Auxiliary supply

No other items or special equipment are required.

9.2 Setting

9.2.1 Number of patients to be studied

Countries planned to participate: All countries in EU where rFXIII is marketed and commercially available will be included. Additional countries where rFXIII is marketed and commercially available may be added to the study (preliminary planned to be Canada, Israel, Switzerland and US).

Anticipated number of study sites: approximately 25-45 (all sites in EU countries and selected non-EU sites where rFXIII is marketed and commercially available and patient(s) are planned to be dosed with rFXIII is to be offered participation in the study if sites have the needed qualifications to perform an non-interventional PASS).

Anticipated number of patients to be included at each study site: 1-10.

9.2.2 Inclusion criteria

1. Informed consent obtained before any study-related activities. (Study-related activities are any procedure related to recording of data according to the protocol).
2. Able and willing to provide signed informed consent (or patient's legally acceptable representative (LAR) consent, if applicable), as required by local ethics committee, governmental or regulatory authorities.
3. Congenital FXIII A-subunit deficiency.
4. Actual or planned exposure to the rFXIII.

9.2.3 Exclusion criteria

1. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

9.2.4 Withdrawal criteria

1. The patient may withdraw at will at any time.
2. The patient's parent or patient's LAR may withdraw the patient at any time.

If antibodies to rFXIII product are detected, the treatment with rFXIII may be continued, interrupted or discontinued at the discretion of the Physician. It is strongly encouraged that the patients remain in the study and have regular follow-up visits for monitoring of antibodies until the level has diminished to below clinical significance or detection limit.

Interruption of treatment with rFXIII or termination of treatment with rFXIII is not a criterion for withdrawal from this study.

9.2.5 Rationale for selection criteria

The study population are the patients who based on the indication will benefit from rFXIII treatment. The results of this study can be applied to patients with congenital FXIII A-subunit deficiency. The very few inclusion and exclusion criteria will reduce selection bias. As a multi-centre, multinational population has been selected the generalizability of the study is evaluated as high.

9.2.6 Flow chart

Table 9–1 Flow chart

Study periods	Visit 1	Assessment visits (visit 2.1, 2.2, 2.3 …)	End of study visit (visit 3)
Visit type	Visit 1	In conjunction with regular visit to clinic	
Visit window/days	Day 0	Visits with recommended 1-6 months interval.	
PATIENT RELATED ASSESSMENTS			
Informed consent	X		
In/exclusion criteria	X		
Withdrawal criteria		X	
Demography	X		
Bleeding treatment history/history of bleeding episodes	X		
Pre-defined complications	X		
Medical history/concomitant illness	X		
Details of diagnosis of FXIII deficiency (FXIII activity and anti-FXIII antibodies)	X		
Concomitant medication	X	X	X
Concomitant illness		X	X
Body measurements	X	X[2]	X[2]
Vital signs	X		X
Participation in registries	X	X	X
SAFETY ASSESSMENTS			
Adverse drug reaction assessment		X	X
Specific adverse drug reaction assessment			
Blood samples for anti-FXIII antibodies[1]	X[4]	X[4]	X[3]
Embolic and thrombotic events		X	X
Lack of therapeutic effect		X	X
Allergic reactions		X	X
Optional blood samples for FXIII activity[1]	X[3]	X[3]	X[3]
Serious adverse event		X	X
Medical event of special interest		X	X
Medication errors and near medication errors		X	X

BLEEDING ASSESSMENTS			
Bleeding episode description		X	X
Bleeding episodes since last visit		X	X
OTHER ASSESSMENTS			
Diary (instruction/evaluation) o Prophylactic treatment regimes o Bleeding episode description o Prophylactic treatment related to surgery	X	X	X
Documentation of pregnancy		X	X

Footer	Description
[1]	Blood samples to be drawn prior to any planned rFXIII injection
[2]	Body weight only
[3]	Performed as part of routine clinical care established by the Physician, or in case of lack of therapeutic effect and tested simultaneously when a blood sample for anti-FXIII antibodies is collected at a visit after Visit 1for patients consenting to testing.
[4]	At Visit 1 and at a visit to be conducted 1 year after entry of the patient into the study for patients consenting to testing. Performed where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study. May also be collected at any visit as part of routine clinical care established by the Physician, or in case of lack of therapeutic effect.

9.3 Variables

It is the intention of this study to observe routine treatment of the individual patients. Therefore, the assessments are limited to examinations and collection of information needed to characterise the patient population at initiation and at the end of the study. All study visits should be performed according to normal local clinical practice. No additional visits should be conducted due to the participation in this study. The Physician is encouraged to collect blood samples for FXIII activity and anti-FXIII antibody assessment at the visits mentioned below, see section 9.3.1.1, 9.3.1.2 and 9.3.1.3).

Additionally, due to a regulatory request from the FDA, collection of blood samples for anti-FXIII antibody assessment at Visit 1 and at a visit to be conducted 1 year after the patient entry into the study-for patients consenting to testing. These 2 blood samples should be taken in countries where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study (see section 9.3.3.2).

What information to be reported?

The following information, collected as part of normal clinical practise should be reported:

1. Safety information including (see section 11)
    a. adverse drug reactions
    b. serious adverse events
    c. medical events of special interest including all medication or near medication errors

d. Pregnancy in female patients or in the partners of male patients.

2. Bleeding episodes (haemostatic treatment used, treatment-requiring bleeding episodes and non-treatment requiring bleeding episodes)
3. Effect of prophylaxis
4. Surgical interventions

This information will be collected as part of the treatment schedule established by the Physician. A patient diary will be provided if it's part of routine practice at the clinic/department to assist data collection for patients on home treatment.

When should the information be reported?
1. When clinical suspicion of decreased therapeutic effect emerges
2. At occurrence of adverse drug reaction, serious adverse event or medical event of special interest
3. At routine visits with recommended one to six months intervals depending on usual practice
4. At occurrence of pregnancy
5. Follow up at end of study

The use of rFXIII will be in accordance with the approved product label,in addition, if rFXIII is used in patients with FXIII congenital A-subunit deficiency for other indications than prophylactic (e.g., treatment of bleed or surgery) this information should also be collected. Other haemostatic products and treatments used are to be collected in this study.

Details of the data collection process are described in the subsections below. The data collection should only be recorded in the patient's record and the CRF, if available or performed.

If clinical suspicion of lack of therapeutic effect emerges, the Physician is encouraged to draw blood for anti-FXIII antibody analysis and FXIII activity.

9.3.1 Visit procedures

Patients will obtain routine medical care at their respective clinic in accordance with local practices. All study visits should be performed according to normal local clinical practice. No additional visits should be conducted due to the participation in this study.

At each visit a care provider, in cooperation with the patient, should provide information as specified in the below sections, if available. For patients on home treatment the diary should serve as information base when relevant.
Safety information must be collected during each contact (visit or telephone) with the Physician or study site staff. This may be done by posing a simple question such as "have you experienced any problems since the last contact?"

The Physician must keep a patient enrolment log and a log of patients evaluated for but not included in the study throughout the enrolment period. As this is a non-randomised study, the allocation of patient identification is to be accomplished via a global unique number provided by an electronic system.

Patients enrolled in the study will be provided with contact address (es) and telephone number(s) of the Physician site and/or staff. During a patient's participation in the study, all relevant data should be entered in the CRF.

In case a patient is being prematurely withdrawn from the study the Physician will ensure that the procedures for the last visit are undertaken, if possible. The primary reason (adverse drug reaction or other) for discontinuation must be specified in the CRF.

9.3.1.1 Visit 1

Signed informed consent must be obtained before any data recording (including blood sampling) is performed for this non-interventional study.

At Visit 1 a blood sample for anti-FXIII antibodies, should be taken for patients consenting to testing in countries where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study.

The following will be recorded and observed, at the Visit1, after having obtained informed consent:

- Check the time, date and signature of informed consent.
- Check of inclusion and exclusion criteria (please refer to section (9.2.2 and 9.2.3).
- Demography (please refer to section 9.3.2.1).
- Bleeding treatment history (including prophylactic treatment) and History of Bleeding episodes (please refer to section 9.3.2.2).
- Prophylactic treatment regimen
- Pre-defined complications (please refer to section 9.3.2.3).
- Medical history/concomitant illnesses (please refer to section 9.3.2.4).
- Details on diagnosis of FXIII CD (please refer to section 9.3.2.5).
- Concomitant medication (please refer to section 9.3.2.6).
- Body measurements (please refer to section 9.3.2.8).
- Vital signs (please refer to section 9.3.2.9).
- Blood sample for anti-FXIII antibodies, if obtained (please refer to section 9.3.3.1 and 9.3.3.2).
- Optional blood sample for FXIII activity, if obtained (please refer to section 9.3.3.2).
- Diary (instruction) (please refer to section 9.3.5.1).
- Participation in registries (please refer to section 9.3.5.3).

9.3.1.2 Assessment visits (visit 2.1, 2,2 etc.)

Patients will obtain routine medical care in their respective treatment centre in accordance with practices of the treatment site. Collection of data and assessment of rFXIII exposure may be performed at all clinical visits after the Visit 1. It is recommended that reporting visits occur with 1 to 6 months intervals according to usual practice. Data collection should happen in conjunction with the patient visits to the clinic.

If clinical suspicion of lack of therapeutic effect emerges or if part of scheduled treatment practice as established by the Physician, sampling for FXIII activity and anti-FXIII antibodies can be performed.

At an assessment visit 1 year after entry of the patient into the study a blood sample for anti-FXIII antibodies should be taken for patients consenting to testing, in countries where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study.

The following will be observed and recorded at the assessment visits:

- Assessment of treatment of bleeding episodes since last visit
    - Review of each bleeding episode since last visit (please refer to section 9.3.4.1).
    - Assessment of ineffective treatment episodes, if identified (please refer to section 9.3.3.2).
- Prophylactic treatment since last visit (please refer to section 9.3.5.1).
- Prophylactic treatment related to surgery since last visit (please refer to section 9.3.4.2).
- Adverse drug reaction assessment (please refer to section 9.3.3).
- Specific adverse drug reaction assessment (please refer to section 9.3.3.1).
    - Blood sample for anti-FXIII antibodies, if obtained (please refer to section 9.3.3.1 and 9.3.3.2).
    - Allergic reactions (please refer to section 9.3.3.1).
    - Embolic and thrombotic events (please refer to section 9.3.3.1).
    - Lack of therapeutic effect (please refer to section 9.3.3.1).
- Assessments of serious adverse events (please refer to section 9.3.3)
- Medical events of special interest (please refer to section 9.3.3)
- Assessment of medication error.
- Assessment of the use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic use.
- Blood sample for FXIII activity, if obtained (please refer to section 9.3.3.2).
- Concomitant medication assessment (please refer to section 9.3.2.6).
- Concomitant illness assessment (please refer to section 9.3.2.7).
- Body measurements (please refer to section 9.3.2.8).

- Diary (instruction/evaluation), (please refer to section 9.3.5.1).
- Assessments for withdrawal criteria (please refer to section 9.2.4).
- Participation in registries (please refer to section 9.3.5.3)
- Documentation of pregnancy (please refer to section 9.3.5.2).

9.3.1.3 End of study visit (visit 3)

The end of study visit will be performed 6 years after FPFV in the study. The patients' next visit to the clinic will be defined as their end of study visit, provided they have either a minimum of 2 years participation or 24 exposure days (whichever comes first, unless the patient has dropped out).

If the Physician finds it clinically relevant sampling for anti-FXIII antibodies and FXIII activity can be performed, as part of the treatment schedule established by the Physician and when clinical suspicion of lack of therapeutic effect emerges.

The following will be observed at the end of study visit:

- Assessment of treatment of bleeding episodes since last visit:
  - Review of each bleeding episode since last visit (please refer to section 9.3.4.1).
  - Assessment of ineffective treatment episodes, if identified (please refer to section 9.3.3.2).
- Prophylactic treatment regimen (please refer to section 9.3.5.1).
- Prophylactic treatment related to surgery (please refer to section 9.3.4.2).
- Adverse drug reaction assessment (please refer to section 9.3.3).
- Specific adverse drug reaction assessment (please refer to section 9.3.3.1).
- Optional blood sample for anti-FXIII antibodies, if obtained (please refer to 9.3.3.1 section and 9.3.3.2).
- Allergic reactions (please refer to section 9.3.3.1).
- Embolic and thrombotic (please refer to section 9.3.3.1).
- Lack of therapeutic effect (please refer to section 9.3.3.1).
- Assessments of serious adverse events (please refer to section 9.3.3).
- Medical events of special interest (please refer to section 9.3.3)
- Optional blood sample for FXIII activity, if obtained (please refer to section 9.3.3.2).
- Assessment of medication error.
- Assessment of the use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic use.
- Concomitant medication assessment (please refer to section 9.3.2.6).
- Concomitant illness assessment (please refer to section 9.3.2.7).
- Body weight measurement (please refer to section 9.3.2.8).
- Vital signs (please refer to section 9.3.2.9).
- Diary (evaluation), (please refer to section 9.3.5.1).

- Documentation of pregnancy (please refer to section 9.3.5.2).
- Participation in registries (please refer to section 9.3.5.3)
- Reason for early discontinuation; including date (please refer to section 9.2.4).

9.3.2 Patient related assessments

9.3.2.1 Demography

The following demographic parameters will be recorded at the Visit 1:

- Month and year of birth (in countries where this is not allowed only year of birth).
- Ethnic background (if allowed in the specific country, NA for France).
- Sex.

9.3.2.2 Bleeding treatment history and history of bleeding episodes

- Current prophylactic treatment and treatment for the last five years. If shorter, for the actual prophylactic period (name of product, dose, dose frequency and duration of prophylaxis (start/stop date)).
- Number of bleeds during prophylaxis treatment in the last 24 months (both treatment required and non-treatment requiring).
- On-demand treatment as reported by the patient.
- Number of treatment requiring bleeding episodes within the last 24 months.
- FXIII product used, and product used for the last five years. If shorter, for the actual on-demand period (name and yearly dose, if available).
- Surgeries within the last 12 months.
- Date of surgery.
- Type of surgery (minor/major and elective/emergency).
- Haemostatic product (name if available and dose).

9.3.2.3 Pre-defined complications

At the Visit 1 it will be recorded if the patient has been diagnosed with any of the following pre-defined complications:

- Coagulation disorders (other than congenital FXIII A-subunit deficiency).
- Allergic reactions to pharmaceutical drug.
- History of embolic or thrombotic events.
- Lack of therapeutic effect of FXIII containing products.

9.3.2.4 Medical history/concomitant illness

Details on medical history and concomitant illnesses will be recorded at the Visit 1 during a medical interview and review of relevant medical records.

All concomitant illnesses must be recorded at study entry, including any recent chronic infectious diseases (in the last 6 months). During the study period any change in concomitant illnesses will be recorded until end of study visit (see section 9.3.2.7).

9.3.2.5 Details on diagnosis of FXIII CD

Diagnosis of FXIII deficiency as evidenced in the patient's medical records

- Date of diagnosis.
- Underlying gene defect, if known (FXIII subunit A, FXIII subunit B, other).
    - Genotyping been performed.
    - Mutation been identified (mutation no.).
    - Type of mutation (substitution (missense, nonsense, splice site), deletion, insertion, duplication, inversion, translocation, other).
    - Description of the sequence variant (DNA level, Protein level).
- Type of disorder (FXIII heterozygous, homozygous, other).
- FXIII activity level at time of diagnosis.
- Current FXIII activity level, if available.
- History of anti-FXIII antibodies.

Nature of any antibodies detected in the past:

- Neutralising.
- Non-neutralising.

If any antibodies detected in the past:

- Most recent antibody value.
- Date of most recent antibody value.
- Date of first finding of antibodies.
- Historical maximum antibody value.

Family history (1st degree relatives, other relatives):

- History of antibodies toward FXIII
- Congenital haemostatic disorder (FXIII deficiency (heterozygous, homozygous) and other).
- Congenital pro-thrombotic disorders (FZ Leiden (G1691A), Prothrombin mutation (G20210A), Protein C deficiency, Protein S deficiency, Anti-thrombin deficiency, other.

9.3.2.6 Concomitant medication

Definition of concomitant medication: any medication other than rFXIII that is taken during the study, including reported at Visit 1

Details of all concomitant medication must be recorded at study entry (i.e., at the first visit, Visit 1), including any recent vaccinations (in the last 6 months). Any changes in medication must be recorded at each visit (assessment visits and end of study visit) in the CRF.

9.3.2.7 Concomitant illnesses

Definition of concomitant illness: any illness that is present at the start of the study (i.e. Visit 1).

Details of all concomitant illness must be recorded in the baseline CRF. The information collected for concomitant illness should include diagnosis, date of onset, date of resolution or continuation. A clinically significant worsening of a concomitant illness must be reported as an AE. If the change influences the patient's eligibility to continue in the study, the sponsor must be informed.

9.3.2.8 Body measurements

The following must be recorded in the patient´s record and the CRF, if available or performed:

- Height (cm or inches) without shoes will be measured at the Visit 1.
- Body weight (kg or lbs) will be recorded with standardised scale (patient in light clothing and without shoes) at the Visit 1, the assessment visits and end of study visit.

9.3.2.9 Vital signs

The following must be recorded in the patient´s record and the CRF, if available or performed:

Standard safety-related vital signs will be recorded at the Visit 1 and at the end of study visit:

- Pulse.
- Blood pressure (systolic and diastolic blood pressure).

Blood pressure and pulse rate should preferably be measured using an automatic device; after the patient has rested comfortably for 3 minutes. Measurements will be reported in the CRF.

9.3.3 Assessments for safety

Safety information must be collected during each contact (visit or telephone, excluding Visit 1 and safety visits, where the patient is not seeing the Physician or his staff e.g., visits to the laboratory) with the Physician or study site staff. This may be done by posing a simple question such as "have you experienced any problems since the last contact?" For definitions on safety information collected in this study see section 11.2.

After the first administration of rFXIII following enrolment in the study all adverse drug reactions, serious adverse events and medical events of special interest must be collected and reported according to section 11.3.

9.3.3.1 Specific adverse drug reactions events

In this study the incidence of specific adverse drug reactions and events are of special interest: anti-FXIII antibody, allergic reactions, embolic and thrombotic events, lack of effect. For definitions, see section 9.3.3.1.

Anti-FXIII antibodies

Detection of anti-FXIII antibodies (see section 9.3.3.2) in blood samples. Both FXIII non-neutralising and FXIII neutralising antibodies are considered to be medical events of special interest, and are to be reported as such (see section 11.2.4).

Allergic reaction

An allergic reaction is any acute or delayed type hypersensitivity reaction (clinical signs may include tightness of the chest, hypotension, anaphylaxis or various types of skin rashes), and is to be reported as a medical event of special interest (see section 11.2.4).

Embolic and thrombotic events

Any myocardial infarction, pulmonary embolism, cerebral thrombosis or infarction, and other significant embolic or thrombotic events, including visceral arterial embolus or thrombus, extremity arterial embolus or thrombus, portal venous thrombosis or deep venous thrombosis of extremity veins, are embolic and/or thrombotic events, and are to be reported as a medical event of special interest (see section 11.2.4). Superficial thrombophlebitis is not considered an embolic and thrombotic event.

Lack of therapeutic effect

In the case of suspected decrease or lack of therapeutic effect, including FXIII activities that fail to reach expected levels, analysis for antibodies should be performed (see section 9.3.3.2). Any suspicion of a lack of expected therapeutic effect is to be reported as a Medical event of special interest (see section 11.2.4).

9.3.3.2 Blood sampling

Blood samples collected in this study are samples taken as part of routine treatment established by the Physician as follows:

- Anti-FXIII antibody (see section 9.3.3.2).
- FXIII activity (optional) (see section 9.3.3.2).
- Blood samples for anti-FXIII antibody assessment should be taken, at Visit 1 and at a visit to be conducted 1 year after the patient entry into the study for patients consenting to testing in countries where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study (see section 9.3.3.2).

The Physician is strongly encouraged to draw blood samples for FXIII activity and anti-FXIII antibodies if any indication of lack of therapeutic effect emerges.

Data collection should happen in conjunction with all otherwise scheduled visits to the clinic. Time and date of collection should be recorded in the CRF.

Blood samples for anti-FXIII antibodies (Central laboratory)
When judged necessary by the treating Physician, blood samples will be drawn for analysis of anti-FXIII antibodies prior to any planned rFXIII injection.

Sample for antibody analysis may be taken at any visit.

Additionally, samples for antibody analysis should be taken, at Visit 1 and at a visit to be conducted 1 year after entry of the patient into the study, for patients consenting to testing, in countries where the collection of blood samples for anti-FXIII antibody assessment is possible within the confines of a non-interventional study.

When lack of therapeutic effect is indicated by bleeding or laboratory findings, the Physician is strongly encouraged to sample for anti-FXIII antibody detection as this is part of normal practice.

The antibody assessment is a stepwise tiered process involving detection of anti-rXIII binding antibodies (antibody specificity, titer, isotyping) and evaluation of neutralising antibody capacity. Analytical protocols (both ELISA protocol and activity based assay) have been validated. Simultaneously and as supplement to the antibody assessment, one sample will be subjected to activity analysis (see below). If specific rFXIII antibodies (anti-FXIII) are detected at any time it is highly recommended that a confirmatory sample is drawn and analysed, and if confirmed, that monitoring is continued according to clinical practice.

All positive anti-FXIII antibodies should be reported as a medical event of special interest (see section 11.2.4).

The results of anti-FXIII antibodies will be reported according to section 9.6.2.2.

Central laboratory assessments
Laboratory analysis and reporting will be performed by a central laboratory designated by Novo Nordisk. Laboratory data from the central laboratories will be reported to the site and Novo Nordisk. Laboratory data will be reported to Novo Nordisk with an identifier in a manner that anonymity of patients will be maintained. All central laboratory analyses will be paid for by the sponsor.

The quality control of the central laboratory test results will be performed according to the regulations and specifications set by the authorities at the location of the central laboratory used for this study.

Laboratory kits with tubes will be provided to the sites for the collection of blood samples.

Volume of blood for FXIII antibody
Evaluation of anti-FXIII antibodies requires approximately 2 mL blood.

Blood samples for FXIII activity (Central laboratory)
When judged necessary by the treating Physician, blood sampling will be drawn for analysis of FXIII activity prior to any planned rFXIII injection.

FXIII activity test at Visit 1 is made to characterise the patient population at initiation. Samples for FXIII activity may be taken at Visit 1 and any assessments visit (with recommended one to six months interval depending on usual practice, unscheduled visit and end of study visit).

As routine practice or when lack of therapeutic effect is indicated by bleeding or laboratory findings, including FXIII activities that fail to reach expected levels, the Physicians are strongly encouraged to sample for anti-FXIII antibody assessment as this is part of normal practice.

An optional analysis for FXIII activity at Visit 1 can be performed at the central laboratory. In case a blood sample at a further visit (after Visit 1) is taken for central laboratory analysis of anti-FXIII antibodies, a FXIII activity analysis is part of the antibody analysis (see section 9.3.3.2). The result of this FXIII activity analysis will be reported to the investigator together with the anti-FXIII antibody result.

If additional activity measurements are indicated these could be performed at local laboratories and reported in the CRF. Results from the central laboratory will overrule any local FXIII activity results obtained at local laboratories at the same time point.

The FXIII activity assay used at the central laboratory is the Berichrom ® assay. The assay is validated for analysis of human EDTA plasma and requires approximately 2 ml whole blood (1 ml EDTA plasma).

The results of FXIII activity in case of antibodies will be reported according to section 9.6.2.2.

Local laboratory assessment of FXIII activity
Since this is a non-interventional study; any procedures ordered by the Physician during this study will be the ones accepted as appropriate, to provide the best care for the patient at his/her discretion. If additional FXIII activity measurements are performed at local laboratories, the results should be reported in the CRF. This was requested by the Committee for Medicinal Products for Human Use

(CHMP) in their Day 180 List of Outstanding Issues for Clinical Aspects (dated 19 April 2012). Information on the used method will be captured in the CRF..

9.3.4 Assessments for bleedings

9.3.4.1 Bleeding episode description

All bleeding episodes (bleeding during prophylaxis, on-demand therapy and in relation to surgery) will be recorded in the CRF. If occurring during home treatment a diary will be used. The diary will be discussed with the patient and data transferred to the CRF at the assessment visits by the Physician.

Bleeding episodes requiring treatment with haemostatic agent

The following information will be collected for each bleeding episode requiring treatment with haemostatic agents (FXIII containing products or antifibrinolytics):

- Date and time of onset of bleeding.
- Cause of bleeding (spontaneous, traumatic or surgery).
    - If traumatic: case description.
- Severity of bleeding (see section 9.3.4.1).
- Site of bleeding (central nervous system bleeding (divided into intracranial haemorrhage or other), haemarthrosis, gastrointestinal bleeding, subcutaneous bleeding, muscular bleeding or other).
- Date and time of bleeding arrest (definition: it is not bleeding any more, evaluated by another person).
- Haemostatic drug used for treatment of bleeding episodes:
    - Drug name/product name/FXIII product (including rFXIII).
    - Date and time of treatment
    - Dose including information on whether the patient or the Physician decided regarding dose.
    - Treatment outcome (haemostatic response see 9.3.4.1).
    - Medication errors
- Other therapy used (e.g., compression, ice).
- Concomitant illness in relation to bleeding episodes.
- Concomitant medication in relation to bleeding episodes, e.g., antifibrinolytics.
- Adverse drug reactions, serious adverse events and medical events of special interest in connection with administration of the product.
- Allergic reactions (please refer to section 9.3.3.1).
- Embolic and thrombotic events (please refer to section 9.3.3.1).
- Lack of therapeutic effect (please refer to section 9.3.3.2).

Bleeding episodes not requiring treatment with haemostatic agent

The following will be recorded for the bleeding episodes not requiring treatment with a haemostatic agent:

- Date of bleeding.
- Cause of bleed (spontaneously or traumatic):
    - If traumatic: case description.
- Site of bleeding (central nervous system bleeding (divided into intracranial haemorrhage or other), haemarthrosis, gastrointestinal bleeding, subcutaneous bleeding, muscular bleeding or other).
- Date and time of bleeding arrest.

Definition of severity of bleeds

- **Mild/Moderate:** Minor uncomplicated bleeds.
- **Severe:** Major bleeds which require hospitalisation. All head, central nervous system and neck bleeds must be categorised as severe.

All mild or moderate bleeds which are active after 24 hours will change category to severe and the treatment responsibility should preferably be transferred to the Physician.

Definition of haemostatic response

- **Excellent:** abrupt pain relief and/or substantial improvement in signs of bleeding within approximately 8 hours after a single infusion.
- **Good/Effective:** some pain relief and/or improvement in signs of bleeding within approximately 8 hours after infusion of product, but not requiring more than one infusion for complete bleeding arrest.
- **Moderate/Partly effective:** slight beneficial effect on pain relief and/or minimal improvement in signs of bleeding within approximately 8 hours after the first product infusion, but not requiring more than one infusion for complete bleeding arrest.
- **None:** no improvement or worsening of symptoms or use of other FXIII products.

9.3.4.2 Surgery events

For all surgery events the following will be recorded, if available:

- Surgery description and indication (elective or emergency).
- Surgery type (minor or major surgery).
- Duration surgery hours (start and stop time of surgery).
- Haemostatic drug used in connection with surgery, beyond the monthly prophylactic rFXIII dose (covering other products and rFXIII, if used):
    - Drug name/product name.
    - Date and time of treatment.

- Dose and regimen.
- Haemostatic response during surgery (see section 9.3.4.2).
- Haemostatic response after surgery (see section 9.3.4.3).
- Blood products transfusion (yes/no):
  - Type (red blood cells, FFP platelets, or other).
- Adverse drug reactions, serious adverse events and medical events of special interest in connection with administration of the product.
- Allergic reactions (please refer to section 9.3.3.1).
- Embolic and thrombotic events (please refer to section 9.3.3.1).
- Lack of therapeutic effect (please refer to section 9.3.3.2), assessed as haemostatic response.

Definition of major surgery

Major surgery is any invasive operative procedure where any one or more of the following occur:

- A body cavity is entered.
- A mesenchymal barrier (e.g., pleura, peritoneum or dura) is crossed.
- A fascial plane is opened.
- An organ is removed.
- Normal anatomy is operatively altered.

These procedures may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation or with a combination of these modalities.

Definition of minor surgery

Minor surgery is any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated. Examples of minor surgery include vascular cut down for catheter placement, implanting pumps or ports in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire.

Dental surgery will be classified as minor or major based on above definitions.

Haemostatic response during surgery

Clinical evaluation of haemostatic response during surgery will be evaluated as follows:

- **Excellent:** blood loss less than expected.
- **Good:** blood loss as expected.
- **Moderate:** blood loss more than expected.
- **None:** uncontrolled bleeding.

9.3.4.3 Post-surgery events

For all post-surgery events (1-10 days after surgery), the following should be recorded, if available:

- Haemostatic response after surgery (see section 9.3.4.3).

- Presence of wound haematoma (yes/no).
- Allergic reactions (please refer to section 9.3.3.1).
- Embolic and thrombotic events (please refer to section 9.3.3.1).
- Lack of therapeutic effect (please refer to section 9.3.3.2), assessed as haemostatic response.
- Adverse drug reactions, serious adverse events and medical events of special interest.

Haemostatic response after surgery

Clinical evaluation of haemostatic response after surgery will be evaluated as follows:

- **Excellent:** better than expected in this type of patient and procedure.
- **Good:** as expected in this type of patient and procedure.
- **Moderate:** less than optimal for the type of procedure, maintained without change of treatment regimen.
- **None:** bleeding due to inadequate therapeutic effect with adequate dosing, change of regimen required.

9.3.5 Other assessments

9.3.5.1 Diary (instruction/evaluation)

A diary will be provided by Novo Nordisk if it's part of routine practice at the clinic/department. The patient will be instructed by the Physician on how to complete the diary. The following data on home treatment will be collected in the diary:

- Prophylactic treatment, on-demand treatment of bleed and prophylactic treatment related to surgery):
    - Product used (rFXIII or other).
    - Dose level.
    - Date and time of dose.
    - Information on whether the patient or the Physician decided regarding dose.
    - Cause.
- Body weight.
- Bleeding episodes (please refer to section 9.3.4.1):
    - Cause of bleed.
    - Onset of bleeding (date and time).
    - Arrest of bleeding (date and time).
    - Site of bleeding.
    - Severity.
    - Evaluation of achieved haemostasis.
- Allergic reaction.
- Embolic and thrombotic events.
- Lack of therapeutic effect.

- Medication error.
- Other disease than FXIII CD (any change or new diseases).
- Diary completed by whom and completion date.

The diary has special sections covering surgery. The patient will be asked to bring the surgery section to the surgery where a professional care provider will fill out pages regarding the surgery performed.

The patient will be asked to bring the diary to the site at each visit. The Physician will together with the patient review the diary entries and enter relevant information into the CRF. Review date of the diary and the Physicians' conclusion should be entered in the CRF. Study medication administration performed at home will be entered into the diary, and study medication administration performed at the hospital by the site personnel will be entered into the CRF.

9.3.5.2 Documentation of pregnancy

Patients must be instructed to notify the Physician immediately if they become pregnant. Documentation of the pregnancy should be obtained. The Physician must report any pregnancy reported during the study to Novo Nordisk (for more details see section 11.5). The outcome of the pregnancy will be followed up at one month post the predicted gestation date. If a patient's partner becomes pregnant, this should be handled according to section 11.5).

9.3.5.3 Collaboration with registries

Cooperation with other existing local FXIII or rare bleeding disorders registries in EU, US and other countries have been sought in order to collect data on all patients with FXIII CD regardless of treatment. As a result of this, contractual collaboration with the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) has been established. Results from the non-interventional PASS (NN1841-3868) and PRO-RBDD will be included in the final study report. Patient participating in other registries e.g., PRO-RBDD will be identified in the CRF.

9.4 Data sources

It is the intention of this non-interventional study to observe routine treatment of the individual patient. Data and results available in the patient's medical record, in the patient diary and from assessments and laboratory sampling performed according to clinical practice at the participating sites will be recorded in the paper CRF. Information related to treatment and bleeding episodes will be captured in a patient diary by the patient or parent/caregiver. In case a patient is unable to enter a treatment or a bleeding episode in the diary, or is hospitalised, it should be reported in the patient record and subsequently in the paper CRF by the Physician. Further, contractual collaboration with the global Prospective Rare Bleeding Disorder Database (PRO-RBDD) has been established.

9.5 Study size

No formal analysis of sample size has been conducted, but the adequacy of an expected number of patients has been considered.

Within Europe and the US, the study intends to recruit as many patients as possible among the FXIII CD patients treated with rFXIII. The total population in Europe of diagnosed patients with FXIII CD is between 300 and 400 patients, of which more than 10% are expected to receive rFXIII. Hence, in combination with the patients recruited outside Europe, a minimum of 30 patients are anticipated to be enrolled in the study.

Such an anticipated minimum number of patients are judged to facilitate a sufficient expansion to the safety experience of prophylactic treatment with rFXIII, taking into consideration the rarity of the disease.

Assuming that the recruitment rate is approximately constant and that the last patient is recruited at the end of the 4-year recruitment period, the expected average study participation will be approximately 4.5 years.

9.6 Data management

9.6.1 Data management

Data management is the responsibility of Data Management, Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or Contract Research Organisation (CRO).

The patient and the biological material obtained from the patient will be identified by a patient number, study site, and study ID number. Appropriate measures such as encryption or deletion must be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements. Appropriate measures such as encryption of data files must be used to assure confidentiality of patient data when it is transmitted over open networks.

Laboratory data will be transferred electronically from the central laboratory performing clinical analyses. The electronic laboratory data will be considered source data. In cases where laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

9.6.2 CRFs and rules for completing

Novo Nordisk will provide the CRFs. Print legibly using a ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.

If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the respective answer field in the CRF. If the question is irrelevant (e.g., is not applicable) indicate this by writing "NA" (not applicable) in the respective answer field. Further guidance can be obtained from the instruction in the CRF.

By signing the affirmation statement, the Physician confirms that the information is complete and correct

9.6.2.1 Corrections to CRFs

Corrections to the data on the CRFs must only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that has been crossed out. Each correction must contain initials, date and explanation (if necessary) by the physician or the physician's authorised staff.

If corrections are made by the Physician's authorised staff after the date of the Physician's signature on the affirmation statement, the statement must be signed and dated again by the Physician.

Corrections necessary after the CRFs have been removed from the Physician's site must be documented on a data clarification form. Such corrections must be approved by the Physician or her/his authorised staff.

9.6.2.2 CRF flow

CRFs are produced on No Carbon Required (NCR) paper with one original and one copy. The top page (original page) of the CRFs is transferred by the monitor to the unit responsible for data entry as specified by Data Management, Novo Nordisk. One copy is to be archived with the Physicians study documentation.

Laboratory reports should preferably be signed and dated by the Physician on the day of the review of the analysis results and retained at the study site.

The results from the local laboratory should be entered in the CRF for each patient.

9.7 Data analysis

Novo Nordisk will be responsible for all statistical analyses.

9.7.1 Evaluability of patients for analysis

There will only be a Full Analysis Set in the study, comprising all patients who have entered into the study fulfilling the inclusion and exclusion criteria and having received at least one administration of rFXIII containing product in the study period. The Full Analysis Set will be identical to the Safety Analysis Set.

9.7.2 Statistical methods

This is a purely descriptive study and the statistical analyses and presentations do not include any testing of pre-specified hypotheses. All analyses and presentations will be based on the Full Analysis Set.

9.7.2.1 Primary endpoint

The primary endpoint comprises specific adverse drug reactions in terms of anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect occurring from first study related activity after signing the informed consent to the end of patient's participation in the study.

The referred specific adverse drug reactions of the primary endpoint (anti-FXIII antibodies, allergic reaction, embolic and thrombotic events and lack of therapeutic effect) will be summarised, displaying the number of reactions and the number and percent of patients experiencing the reaction relevant within system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Assessments of anti-FXIII antibodies will be provided by the central laboratory. The endpoint will be presented for all patients as well as by special populations, comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.

All the specific adverse drug reactions will further be listed with patient ID, site, age, preferred term, date of first dose, date of onset, date of arrest, severity, if it is serious or not, relationship to study drug, action, and outcome.

9.7.2.2 Secondary endpoints

The secondary endpoints cover the following five types of assessments:

1. All serious adverse events
2. All medical events of special interest
3. All medication errors and near medication errors
4. Use of rFXIII other than for prophylactic treatment.
5. Annualised bleeding rate

The first three secondary endpoints will be presented for all patients as well as by special populations, comprising children, elderly, pregnant and lactating women, and patients with renal insufficiency.

All the secondary endpoints will be collected from first study related activity after signing the informed consent to the end of patient's participation in the study, expected to last a maximum of 6 years.

Serious adverse events

Serious adverse events will be summarised, displaying the number of events and the number and percent of patients experiencing the reaction by MedDRA preferred term.

Serious adverse events will further be listed with patient ID, site, age, preferred term, date of first dose, date of onset, date of arrest, severity, if it is serious or not, relationship to study drug, action, and outcome.

Medical events of special interest

Medical events of special interest will be summarised, displaying the number of events and the number and percent of patients experiencing the reaction by MedDRA preferred term.

Medical events of special interest will further be listed with patient ID, site, age, preferred term, date of first dose, date of onset, date of arrest, severity, seriousness, relationship to study drug, action, and outcome.

Medication errors and near medication errors

Medication errors and near medication errors constitute a specific subset of medical events of special interest. They will be summarised, displaying the number of medication errors and the number and percent of patients experiencing the reaction by MedDRA preferred term.

Medication errors and near medication errors will further be listed with patient ID, site, age, preferred term, date of first dose, date of onset, date of arrest, severity, if it is serious or not, relationship to study drug, action, and outcome.

Use of rFXIII other than for prophylactic treatment

Use of rFXIII in patients with congenital FXIII A subunit deficiency, other than for prophylactic treatment will listed with patient ID, site, age and alternative purpose of the administration of rFXIII. A subsection for product doses should be added.

Annualised Bleeding rate

This secondary endpoint comprises the annualised rate of bleeding (covering both treatment requiring and non-treatment requiring), occurring from first study related activity after signing the informed consent to the end of patient's participation in the study.

Annualised bleeding rate will be summarised by cause (spontaneous, traumatic and surgery), therapeutic regimen (prophylactic therapy, on-demand therapy, surgery) severity, site of bleeding, haemostatic treatment administered (product name) and haemostatic response. The ratio between traumatic and spontaneous bleeding rates will further be summarised and listed and graphical displays of the bleeding rates and the referred ratio will be presented by patient, ordering the patients according to increasing values.

Bleeding episodes will further be listed, including information about cause, severity, location, date and time of onset, date and time of arrest, product name, dose, haemostatic response, related concomitant illness and related concomitant medication.

Presentation by previously untreated patients

To the extent that the study enrols patients, who receive their first administration of rFXIII within the scope of the present study, a separate presentation of both primary and secondary endpoints will be conducted for this group of patients.

9.7.3 Visit 1 characteristics

Visit 1 demographic information including body measurements will be summarised and listed. In addition, all Visit 1 details on adverse drug reactions, and adverse drug reactions of special interest (anti-FXIII antibodies, allergic reactions, embolic and thrombotic events and lack of therapeutic effect), result of blood sample for FXIII activity and anti-FXIII antibodies, diagnosis of FXIII deficiency, history of bleeding episodes, bleeding treatment, medical history, vital signs, pre-defined complication, concomitant medication and illness and history of FXIII antibodies will be summarised and listed.

9.7.4 Other assessments

9.7.4.1 Product dose

Assessment of doses of rFXIII will be summarized and listed.

9.7.4.2 FXIII activity

Assessments of FXIII activity will be summarised and listed.

9.7.4.3 Vital signs

Vital Signs will be summarised and listed.

9.7.4.4 Surgery events

Frequency of all surgery events will be summarised by magnitude (minor or major), indication and name of surgery.

Surgery events will be listed including also information of time period, total number of injections and dose as well as haemostatic response during and after surgery.

Haemostatic response during surgery and after surgery will further be summarised.

9.7.4.5 Concomitant illness and medication

Concomitant illness and medication will be summarised and listed.

9.7.4.6 Home treatment

Treatment administration recorded according to the patient diary will be summarised and listed.

9.7.4.7 Pregnancies

Pregnancies will be summarised and listed.

9.7.5 Interim analysis

An interim report is to be performed every two years after study start (FPFV). The interim report will include all the statistical descriptions listed in section 9.7.2.

9.7.6 Sequential safety analysis/safety monitoring

An annual status report will be developed for reporting to relevant Health Authorities; this is to be in connection with the Periodic Safety Update Report (PSUR) reporting to European Medicines Agency (EMA).

9.8 Quality control

9.8.1 Monitoring procedures

During the course of the study, the monitor should visit the study site at intervals. The purpose of these visits is to ensure that the CRFs are completed correctly, the protocol is adhered to, and to collect completed CRF pages. Data for at least 20% of the enrolled patients will be source data verified. The monitor will ensure that the CRFs are collected.

9.8.2 Critical documents

Before the Physician starts the study (i.e., obtains informed consent from the first patient), the following documents must be available at Novo Nordisk:

- Regulatory approval and/or notification as required
- Curriculum Vitae (CV) of Physician (current, dated and signed and/or supported by an official regulatory document)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from IEC/IRB clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrollment procedures
- Copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement

9.8.3 Retention of study documentation

Patient notes must be kept for the maximum period permitted by the hospital, institution or private practice.

Novo Nordisk will comply with all the requirements of Good Pharmacoepidemiological Practice (GPP) and relevant national legislation related to archiving of study documentation. Records containing patient sensitive data must not be archived by Novo Nordisk, but must be kept with Physician and patient and according to local regulations pertaining to personal data protection.

The Physician must agree to archive the documentation pertaining to the study in an archive after completion or discontinuation of the study, if not otherwise notified. The Physician should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

9.8.4 Archiving of statistical programs

The final programs and outputs, and all relevant documentations used in the process of reporting the study will be archived.

9.9 Limitations of the research methods

As this is a non-interventional PASS there will be a number of potential confounding factors, which are controlled in randomised clinical trials. This involves selection bias of patients in relation to the willingness or ability to cooperate in a study like the non-interventional PASS with a diary. In addition the use of a patient diary introduces an increased risk of incorrectness of dose and bleeding evaluation; this will be minimised by review of the diary by the Physician before entering into the CRF. Concerning the issues of bleeding evaluation of home treatment the risk of misclassification is especially relevant. To minimise misclassification the patient and the Physician will evaluate the bleeding episodes together at the next visit, see section 9.3.5.1. Inconsistency checks and further medical checks by qualified medical persons to capture and resolve inconsistencies will be performed.

9.10 Other aspects

Not applicable section, as all aspects of the research method are covered by the previous sections.

10 Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practice (GPP[11]), applicable regulatory requirements~~,~~ and in accordance with the Declaration of Helsinki[12,13].

The burden added to the patient's life by participating in this study: is entering data into a diary. The diary for home treatment is recommended or required by most centers and will thus serve a disease management purpose apart from the purpose of reporting to the study. The potential benefits for the patient are the systematic assessments of safety, especially comprising anti-FXIII antibodies and lack of effect.

There are no risks associated with this activity. It is thus evaluated that the benefits outweigh the extra burden and risks associated with participating in this study.

When a patient's participation in the study ends, the patient will consult with the physician to decide on the best available treatment.

10.1 Informed consent form for study patients

Informed consent from all study participants is required before any data is entered into the CRF and/or any blood samples are sent to the Central Laboratory for analysis.

In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki[12,13].

Prior to any study-related activity, the physician must give the patient and/or the LAR oral and written information about the study in a form that the patient or the patient's LAR can read and understand. This includes the use of impartial witness where required.

A voluntary, signed and personally dated, informed consent form will be obtained from the patient and/or the patient's LAR prior to any study-related activity.

If the patient is under age, the physician and the parents/patient's legally acceptable representative will evaluate if the patient is at a level of maturity whereby the patient can sign the informed consent. National regulation on obtaining informed consent from patients under age must be observed. This signature does not substitute the signature of the parent(s) or the patient's LAR.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form.

If information becomes available that may be relevant to the patient's willingness to continue participating in the study, the physician must inform the patient and/or the patient's LAR in a timely manner and a revised written informed consent must be obtained.

10.2 Data handling

If the patient (or the patient's LAR) withdraws the previously given informed consent the patient's data will be handled as follows:

- Data collected will be used as part of the study population.
- Safety events will be reported to the department responsible for Global Safety, Novo Nordisk/regulatory authorities.

If data is used, it will always be in accordance with local law and IRB/IEC procedures.

10.3 Institutional Review Boards/Independent Ethics Committee

Before commencement of the study, the protocol, any amendments, patient information/informed consent form, any other written information to be provided to the patient, patient enrolment procedures, if any, package insert, the physician's current CV and/or other documentation evidencing qualifications, and other documents as required by the local institutional review board (IRB)/independent ethics committee (IEC) should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC or another relevant scientific body according to local legislation before commencement of the study.

During the study, the physician must promptly in accordance with local requirements report the following to the IRB/IEC: unexpected serious adverse drug reactions where a causal relationship cannot be ruled out, amendments to the protocol according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the study status and other documents as required by the local IRB/IEC.

Amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate immediate hazards to the patients.

The physician must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records should be filed in the physician's study file and copies must be sent to Novo Nordisk.

10.4 Regulatory authorities

Regulatory authorities will receive the non-interventional study application, amendments to the protocol, reports on serious adverse reaction, and the non-interventional study report according to national requirements.

10.5 Premature termination of the study

The sponsor, physician or a pertinent regulatory authority may decide to stop the study or part of the study at any time but agreement on procedures to be followed must be obtained.

If a study is prematurely terminated or suspended, the physician and/or sponsor should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the study the risk/benefit analysis has changed, the new evaluation should be provided to the IEC/IRB in case it will have an impact on the planned follow-up of the patients who have participated in the study. If so, the actions needed to protect the patients should be described.

10.6 Indemnity statement

Novo Nordisk carries product liability for its products and liability as assumed under the special laws, acts and/or guidelines for conducting non-interventional studies in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible.

Novo Nordisk accepts liability in accordance with local laws and guidelines.

11 Reporting of safety information

11.1 Safety information to be collected

In this study, the following safety information will be systematically collected:

- Adverse drug reactions (serious and non-serious)
- Serious adverse events
- Medical events of special interest including adverse events regardless of seriousness and causal relationship to the study medication
- Pregnancies in female patients and adverse events in the foetus or newborn infant
- Pregnancies in female partners of male patients and adverse reactions or serious adverse events in the foetus or newborn infant

If during this non-interventional study, a Novo Nordisk representative is informed of any other safety information related to a Novo Nordisk product, he/she should report this as solicited safety information **within 24 hours** to the local department responsible for drug safety.

Other safety information during the use of a Novo Nordisk product, ie safety information which is not collected as part the systematic collection, includes drug abuse or misuse and technical complaints.

Voluntary reporting of safety information by the physician should follow the same reporting process flow as for systematic collection, except for technical complaints where the spontaneous reporting process should be followed. The local department responsible for drug safety will handle the voluntary reports and may request follow-up information as per their statutory requirements.

11.2 Safety Definitions

11.2.1 Safety Information

All reports of Adverse Events occurring during the use of a Novo Nordisk product (this includes Occupational Exposure). In addition, any other information relevant to the safety of a Novo Nordisk product.

11.2.2 Adverse drug reaction

An adverse event for which a causal relationship between the product and the occurrence is suspected, i.e., judged possible or probable by the reporting or reviewing healthcare professional.

An adverse drug reaction can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, which is considered related to the medicinal product. A worsening of the Visit 1 condition if it is related to rFXIII is also considered an adverse drug reaction and should be reported in the CRF.

Note: This includes reactions from the first study related activity after the patient has signed the informed consent and until post registration follow-up period as defined in the protocol.

An adverse reaction is either a serious adverse reaction or a non-serious adverse reaction (for definitions, see below)

The following should not be recorded as adverse drug reactions;

- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first study related activity after the patient has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures. These should be recorded as medical history/concomitant illness.

An adverse drug reaction can also be a clinical laboratory abnormality regarded as clinically significant and with a causal relationship to the medicinal product i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity which requires active management (i.e., change of dose, discontinuation of study medication, more frequent follow-up or diagnostic investigation).

11.2.3 Adverse event

An adverse event is any untoward medical occurrence in a patient administered a product, which does not necessarily have a causal relationship with the study product. An adverse event is either a serious adverse event or a non-serious adverse event

Terms used to describe causal relationship to the study product:

- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an aetiology other than the study product

Seriousness criteria:
An adverse reaction or adverse event is a serious adverse reaction or serious adverse event, respectively, if the event or reaction results in any of the following seriousness criteria:

- Death
- A life-threatening* experience
- In-patient hospitalisation** or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity***
- A congenital anomaly/birth defect
- Important medical events**** that may not result in death, be life-threatening*, or require hospitalisation may be considered a serious adverse event or reaction when, based upon

appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition****.

* The term "life-threatening" in the definition of serious adverse drug reaction refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

** The term "hospitalisation" is used when a patient is: admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, study related and social purposes do not constitute adverse reactions or events and should therefore not be reported as adverse reactions or events including serious adverse reactions or events. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered adverse reactions or events including serious adverse events or reactions.

*** The term "disability/incapacity" means that following the reaction the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.

**** For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse

Non-serious adverse drug reaction or adverse event
An adverse drug reaction or adverse event that does not meet seriousness criteria is considered to be non-serious.

Severity assessment definitions:

- Mild – No or transient symptoms, no interference with the patient's daily activities.
- Moderate - Marked symptoms, moderate interference with the patient's daily activities.
- Severe - Considerable interference with the patient's daily activities, unacceptable.

Outcome categories and definitions:

- Recovered - Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient signed the informed consent.
- Recovering - The condition is improving and the patient is expected to recover from the event. This term should only be used when the patient has completed the study.
- Recovered with sequelae - As a result of the adverse drug reaction the patient suffered persistent and significant disability/incapacity (e.g., became blind, deaf, paralysed). If the

sequelae of an adverse drug reaction meet the seriousness criterion then the adverse drug reaction should be considered serious.

- Not recovered -The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- Fatal (only applicable if the patient died from a condition related to the reported adverse reaction or adverse event). Outcomes of other reported adverse reaction or adverse event in a patient before he/she died should be assessed as "recovered", "recovering" or "not recovered". An adverse reaction or adverse event with fatal outcome must be reported as a serious adverse reaction or serious adverse event).
- Unknown - This term should only be used in cases where the patient is lost to follow-up.

11.2.4 Medical events of special interest

A medical event of special interests is an event which, in the evaluation of safety, has a special focus or is collected to meet regulatory reporting requirements.

In this study all adverse events that are medical events of special interest must collected and reported regardless of seriousness and causal relationship to the study product. Medical events of special interest have the same reporting requirements and timelines as serious adverse events and reactions (see section 11.3).

The following are defined as medical events of special interest in this study:

- Medication errors and near medication errors including administration of wrong drug, wrong route of administration, administration of a high dose with the intention to cause harm or an accidental overdose. Any errors of reconstitution procedure or storage of the reconstituted product also are considered to be medication errors
- Suspected transmission of an infectious agent via the study product
- anti-FXIII antibodies (see section 9.3.3.1).
- Allergic reactions (see section 9.3.3.1).
- Embolic or thrombotic events (see section 9.3.3.1).
- Lack of therapeutic effect (see section 9.3.3.1).

11.3 Collection and reporting of safety information (adverse drug reactions, serious adverse events and medical events of special interest*)*

After the first administration of rFXIII following enrolment in the study all events meeting the definition of an adverse drug reaction, serious adverse event and/or medical event of special interest must be collected and reported. At each contact with the study site (visit or telephone, excluding Visit 1 and safety visits, where the patient is not seeing the physician or his staff e.g., visits to the laboratory), the patient must be asked about adverse drug reactions, serious adverse events and

medical events of special interest. This may be done by posing a simple question such as: "Have you experienced any problems since the last contact?

Serious adverse reactions, serious adverse events and medical events of special interest must be reported by the Physician on the applicable safety information forms to Novo Nordisk within the following timelines:

- Initial information must be reported on Adverse Events Form **within 24 hours of the Physician's knowledge of the event.**

- Further information must be reported on Safety Information Form **within 5 calendar days of the Physician's knowledge of the event.**

- If the initial reporting was made by any other means (e.g., phone call within 24 hours), initial and further safety information must be provided on the Adverse Event Form and the Safety Information Form **within 5 calendar days** of the Physician's knowledge of the event on the forms as described above

Non-serious adverse drug reactions, not fulfilling a medical event of special interest criterion, must be reported by the Physician to Novo Nordisk within the following timelines:

- Initial and further information must be reported on the applicable Adverse Event form **within 14 calendar days** of the Physician´s knowledge of the reactions.

Medical events of special interest must always be reported to the department responsible for Global Safety on the Adverse Event Form and the Safety Information Form or applicable forms, irrespective of seriousness within the same timelines as for serious adverse reactions/serious adverse events.

The Physician must complete and forward electronically, fax or courier copies of the Adverse Event Form and/or Safety Information Form as required for systematically collected events within the above specified timelines of obtaining knowledge about the event(s).

The Physician should record the diagnosis, if available. If no diagnosis is available the Physician should record each sign and symptom as individual adverse reactions or adverse events. When a diagnosis becomes available the diagnosis should be reported and the signs and symptoms covered by the diagnosis should be described.

If more than one sign or symptom is to be reported, use a separate adverse event form for each sign and symptom. However, if several symptoms or diagnosis occur as part of the same clinical picture only one safety information form can be used to describe all the serious adverse reactions or events.

Sponsor's assessment of expectedness is done according to the rFXIII company core data sheet.

In accordance with regulatory requirements, including Good Pharmacovigilance Practice, the sponsor will inform the regulatory authorities of study product related serious adverse reactions. In addition, the sponsor will inform the IECs/IRBs or another relevant scientific body of study product related serious adverse reactions, in accordance with the local requirements in force.

The sponsor will notify the physician of study medication related suspected unexpected serious adverse reactions (SUSARs) in accordance with the local requirements.

Any ongoing adverse drug reaction, serious adverse event or medical event of special interest starting before first administration of rFXIII in the study should be reported in the CRF as a concomitant illness and reported directly to Novo Nordisk or local health authority according to local laws and regulations.

11.4 Follow-up of safety information (adverse drug reactions, serious adverse events and medical events of special interest)

During and following a patient's participation in a non-interventional study, the physician/institution should ensure that adequate medical care is provided to the patient for any adverse drug reactions, including clinically significant laboratory values related to the study. The Physician/institution should inform the patient when medical care is needed for adverse drug reaction(s) of which the Physician becomes aware.

Follow-up information concerning previously reported serious adverse reactions, serious adverse events and medical events of special interest must be reported by the Physician **within 24 hours** of the Physician's knowledge of the follow-up information.

Follow-up information concerning previously reported non-serious adverse drug reactions, and non-serious adverse drug reactions fulfilling a medical event of special interest criteria must be reported by the Physician within **14 calendar days** of the Physician´s knowledge of the reaction.

All follow-up information requested by Novo Nordisk must be forwarded to Novo Nordisk within **14 calendar days** from the date specified on the request, unless otherwise specified in the follow-up information request.

The Physician must ensure that the worst case severity and seriousness is kept consistent through the series of forms used for safety reporting. The follow-up information should only include new

(updated and/or additional) information that reflects the situation at the time of the Physician's signature.

All serious adverse reactions and/, serious adverse events and/, medical events of special interest as well as non-serious adverse reactions and adverse events classified as severe or possibly/probably related to the study product must be followed until the outcome of the reaction or event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse reactions or serious adverse events on-going at the time of the death (i.e., the patient dies from another serious adverse event) can be closed with the outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the post-study follow-up period (as stated in this protocol) and is expected by the Physician to recover.

All other non-serious adverse reactions and non-serious adverse events must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of the post-treatment follow-up, whichever comes first, and until all queries related to these adverse reactions and adverse events have been resolved. Adverse reactions and adverse events on-going at time of death (i.e., patient dies from another adverse event) can be closed with an outcome of "recovering" or "not recovered".

11.5 Collection and reporting of pregnancies in female patients or male patients' female partners

In female patients, pregnancy must be reported within 14 calendar days of the Physician's first knowledge of the pregnancy. Follow-up information on the foetus or newborn infant from pregnancy in a patient must be collected at 1 month of age at the earliest. Information must be reported within 14 calendar days of the Physician's first knowledge of the pregnancy outcome. All Adverse events experienced by the foetus or newborn infant should be collected and reported regardless of causality assessment.

In male patients' pregnant partners, the pregnancy must be reported **within 14 calendar days of the Physician's first knowledge of the pregnancy or as soon as possible after receipt of informed consent.** However, no specific timeline applies for collecting follow-up information. Adverse reactions and any serious adverse events experienced by the foetus or newborn infant should be collected and reported.

Reporting of adverse reactions or adverse events in foetus, newborn infant or in connection with the pregnancy must be done on the same forms as described for reporting of adverse reactions and events. The reporting timelines are as described for other adverse events or reactions and other serious adverse events or reactions.

11.6 Precautions/Over-dosage

Please refer to the US PI, EU SmPC, and other product characteristics or corresponding local product labelling texts.

11.7 Safety committee(s)

11.7.1 Internal Novo Nordisk Safety Committeee

Novo Nordisk will constitute an internal Safety Committee to perform on-going safety surveillance of rFXIII.

The Safety Committee works according to a written guideline. The Safety Committee is responsible for reviewing any safety concern, signal or alert and determining actions to be taken according to the guidelines for the Safety Committee.

Reporting of pharmacovigilance data relevant to the risk-benefit balance of the product to competent authorities

During the conduct of this study, Novo Nordisk A/S will monitor the data generated and their implications for the risk-benefit balance of the product will be considered. Any new information that may affect the risk-benefit balance of the medicinal product will be communicated immediately in writing as an Emerging Safety Issue to the competent authorities of all the countries in which the product is authorised and EMA.

12 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of the study product. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk.

A Physician will be designated with the responsibility to review and sign the non-interventional Study Report (Signatory Physician).

The study report format and content will be based on Guideline for GPP issued by the International Society for Pharmacoepidemiology and the published STROBE statement.

12.1 Communication and publication

No permission to publish must be granted to any clinical research organisation (CRO) involved in the study described in this protocol.

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

Novo Nordisk reserves the right not to release data until specified milestones, e.g., a non-interventional study report is available. This includes the right not to release interim results from non-interventional studies, because such results may lead to conclusions that are later shown to be incorrect.

At the end of the study, one or more public disclosures for publication may be prepared collaboratively by physician(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication; for up to 60 days to protect intellectual property. The results of this study will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the Physician from each site will be named in the acknowledgement.

12.1.1 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria)[14]

12.1.2 Publications

The physician must ensure submission of the results of the study (either abstract or full study report) to IEC / IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In accordance with Novo Nordisk commitment to transparency on our clinical trial activities this study will be registered by Novo Nordisk at www.clinicaltrials.gov and www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct, which ensures compliance with requirements from International Committee of Medical Journal Editors (ICMJE)[15] and the Food and Drug Administration Amendments Act (FDAAA)[16].

Additionally, the study information will be made available in the EU PAS register web portal presently hosted at the ENCePP homepage http://encepp.eu/.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the Physicians' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk maintains the right to be informed of any Physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

In order to allow national competent authorities to review in advance the results and interpretations to be published Novo Nordisk will communicate to EMA and the relevant competent authorities of the EU Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication according to regulations.

12.1.3 Site-specific publication(s) by Physician(s)

For a multi-centre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk. It is Novo

Nordisk's policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the study.

Novo Nordisk reserves the right to prior review of such publication and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

12.2 Physician access to data and review of results

Individual Physician(s) will have their own research participants' data when the study is completed and the results have been reported.

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database. Generally, study databases are only made available to regulatory authorities.

12.3 Progress reports and final report

An interim analysis and a corresponding interim report is planned to be conducted and produced every second year from FPFV respectively. A final study report will be provided to relevant competent authorities within 12 months of study completion and will be disclosed via the EU PAS register web portal presently hosted at the ENCePP homepage http://encepp.eu/

13 References

1 EMA/330405/2012 Rev 1 1A2. GVP Module VIII: Post-authorization safety studies (together with EMA/395730/2012 Rev 1, 19 April 2013 - Annex: Member States' requirements for transmission of information on non-interventional post authorization safety studies). 2013.

2 Anwar R, Miloszewski KJ. Factor XIII deficiency. British journal of haematology 1999; 107(3):468-484.

3 Burrows RF, Ray JG, Burrows EA. Bleeding risk and reproductive capacity among patients with factor XIII deficiency: a case presentation and review of the literature. Obstet Gynecol Surv 2000; 55(2):103-108.

4 Meyer M. [Molecular biology of haemostasis: fibrinogen, factor XIII]. Hamostaseologie 2004; 24(2):108-115.

5 Lorand L, Gray AJ, Brown K, Credo RB, Curtis CG, Domanik RA et al. Dissociation of the subunit structure of fibrin stabilizing factor during activation of the zymogen. Biochem Biophys Res Commun 1974; 56(4):914-922.

6 Mary A, Achyuthan KE, Greenberg CS. b-chains prevent the proteolytic inactivation of the a-chains of plasma factor XIII. Biochim Biophys Acta 1988; 966(3):328-335.

7 Ivaskevicius V, Seitz R, Kohler HP, Schroeder V, Muszbek L, Ariens RA et al. International registry on factor XIII deficiency: a basis formed mostly on European data. Thromb Haemost 2007; 97(6):914-921.

8 Nugent DJ. Prophylaxis in rare coagulation disorders -- factor XIII deficiency. Thromb Res 2006; 118 Suppl 1:S23-S28.

9 Lee C, Berntorp E, Hoots K. Textbook of Hemophilia. 2 ed. Wiley-Blackwell, 2010.

10 World Federation of Haemophilia. Report on the annual global survey 2008. 2009.

11 ISPE (International Society for Pharmacoepidemiology). - Guidelines for Good Pharmacoepidemiology Practices (GPP). Revision 2, April, 2007. 2007.

12 World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington. 2002.

13 World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. 2013.

14 International Committee of Medical Journal Editors (ICMJE): Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication. Haematologica 2004; 89(3):264.

15 De AC, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. New Engl J Med 2004; 351(12):1250-1251.

16 Food and Drug Administration. Food and Drug Administration: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions. 2002.