Protocol

guardian™5

Study ID: NN7008-3553

EU PAS Register No.: ENCEPP/SDPP/5501

A Multi-centre Non-interventional Study of Safety and Efficacy of turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII ≤2%)

Non-interventional Study

Redacted protocol
Includes redaction of personal identifiable information only.

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Biopharm TrialOps4

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1 List of abbreviations

AESI	Adverse Event of Special Interest
AR	Adverse Reaction
BU	Bethesda Units
CD4+	T-lymphocyte Subtype
CRF	Case Report Form
CRO	Contract Research Organisation
ED	Exposure Day
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GPP	Good Pharmacoepidemiology Practice
ICMJE	The International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LPFV	Last patient First Visit
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder

PASS	Post-Authorisation Safety Study
pCRF	Paper Case Report Form
PI	Package Insert
PTP	Previously Treated Patients
rFVIII	Recombinant Factor Eight Product
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
UTN	Universal Trial Number
WHO	World Health Organisation

2 PASS information

Title	A Multi-centre Non-interventional Study of Safety and Efficacy of turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII ≤2%)
Protocol version identifier	Version 8.0, 01 March 2017
Date of last version of protocol	Version 6.0, 14 Jan 2016 (Version 7.0, never used)
EU PAS Register number	ENCEPP/SDPP/5501
Active substance	Turoctocog alfa. ATC code: B02BD02
Medicinal product	novoeight® / NovoEight®
Product reference	EU/1/13/888/001-006 FDA BLA application number: 125466
Procedure number	EMEA/H/C/002719
Marketing authorisation holder	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	The research question behind the study is to provide additional documentation of the immunogenicity, and obtain additional clinical data, of turoctocog alfa in the setting of normal clinical practise. <u>Primary objective:</u> To assess the incidence rate of FVIII inhibitors during long-term prevention and treatment of bleeds with turoctocog alfa in previously FVIII treated patients with severe and moderately severe haemophilia A (FVIII ≤2%) <u>Secondary objectives:</u> To further evaluate the general safety and obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery

Countries of study	Countries where product is marketed (2014-2020) will be considered for participation
Author	[redacted], [redacted] Biopharm TrialOps 4, Novo Nordisk A/S Vandtaarnsvej 108-110, 2860 Soeborg Denmark

Marketing Authorization 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 overall responsible for the conduct of the non-interventional study at a study site.

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 must 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 must prevent any unauthorised access to data or any other processing of data against applicable law.

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

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] Biopharm TrialOps 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

Title

A Multi-centre Non-interventional Study of Safety and Efficacy of turoctocog alfa (rFVIII) during Long-Term Treatment of Severe and Moderately Severe Haemophilia A (FVIII ≤2%)
Version 8.0, 01 March 2017, EU PAS No.: ENCEPP/SDPP/5501

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

Rationale and Background

In the recently revised "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products", the European Medicines Agency points to the importance of ensuring consistency between the outcome from pre-authorisation clinical studies and from long-term routine use, thus mandating a post-marketing investigation if the development program does not include enough exposure days[1]. This is also in view of the limited availability of patients suffering from haemophilia A.

According to the revised European Medicines Agency guideline the study population of the post-marketing investigation should reflect the population in the countries where the product is intended to be marketed, and should encompass 200 previously FVIII treated patients (>150 exposure days) who should be followed for 100 exposure days. The present guardian™5 study (NN7008-3553) is designed to provide additional documentation of the immunogenicity and clinical efficacy of turoctocog alfa in order to fulfil these requirements. However, in view of the extensive data already accumulated in completed and on-going guardian™ clinical trials (a total of >50,000 exposure days with turoctocog alfa in 214 patients), Novo Nordisk propose a study population of 50 previously FVIII treated patients who have not previously taken part in any guardian™ clinical trials. The U.S. Food and Drug Administration has approved Novo Nordisk A/S Biologics License Application for turoctocog alfa on the 16th October 2013. Additionally, on the 20th September 2013 the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion on turoctocog alfa.

Research question and objectives

The research question behind the study is to provide additional documentation of the immunogenicity, and obtain additional clinical data, of turoctocog alfa in the setting of normal clinical practise.

Primary objective:

To assess the incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) during long-term prevention and treatment of bleeds with turoctocog alfa in previously FVIII treated patients with severe and moderately severe haemophilia A (FVIII ≤2%)

Secondary objectives:

To further evaluate the general safety and obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery.

Primary endpoint:

Primary endpoint is the incidence rate of FVIII inhibitors (≥0.6 BUfor central laboratory analyses, or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors.

Key secondary endpoints are assessed by:

- Number of adverse reactions reported during the study period.
- Number of serious adverse reactions reported during the study period
- Haemostatic effect of turoctocog alfa in the treatment of bleeds as assessed by the patient or the Physician according to a predefined four point scale: Excellent, Good, Moderate, or None
- Haemostatic effect of turoctocog alfa during surgical procedures as assessed by an evaluation according to a predefined four point scale: Excellent, Good, Moderate, or None
- Annualised bleeding rate for patients using turoctocog alfa for preventive treatment
- Annualised bleeding rate for patients using turoctocog alfa for on-demand treatment

The endpoints will be analysed based on all available information until end of study i.e. within approximately 7 years.

The individual patient should stay in the study until a minimum of 100 exposure days with turoctocog alfa after inclusion in the study has been reached. The end of the study will occur when at least 50 patients have a minimum of 100 exposure days with turoctocog alfa after inclusion in the study.

Study design:

This is a prospective, multinational, non-randomised, single-arm, non-interventional post-authorisation safety study (PASS) in previously FVIII treated (>150 exposure days) patients with severe and moderately severe haemophilia A with FVIII ≤2%. Patient eligibility will be limited to patients for whom the decision to start treatment with commercially available turoctocog alfa is clearly separated from the decision to include the patient in this study. Total study duration is estimated to 7 years with a planned recruitment period of 70 months. For each patient, data will be collected in this study:

- until they reach a minimum of 100* exposure days with turoctocog alfa after inclusion in the study **or**
- until at least 50 patients have a minimum of 100* exposure days with turoctocog alfa after inclusion in the study

whichever comes first.

*the 100 EDs will count from the baseline visit (visit 1)

One exposure day (ED) is defined as each day a patient is administered turoctocog alfa and a‘day’ is implicit a ‘calendar day’.
E.g. a dosing with turoctocog alfa on 15 June 2015 at 22.30 and a new dose two hours later on 16-Jun-2015 at 00.30 counted as two exposure days.
Several doses with turoctocog alfa within the same calendar day should only be calculated as one exposure day.

Study product:

All patients enrolled in this study will receive their medication through usual commercial channels. Thus, the study product will not be sponsored or provided by Novo Nordisk. The study product used is the commercially available rFVIII, turoctocog alfa, which is a lyophilised powder in vials and the powder is to be reconstituted with solvent for injection in accordance with the Instruction For Use of the product. The study product will be administered as intravenous injections by the patient/parents/caregiver.

All direction for study product usage (prophylactic as well as on-demand) is solely at the discretion of the Physician in accordance with clinical daily practice and preferably in accordance with the approved product label (US Packet Insert (PI) European Summary of Product Characteristics (SmPC) or corresponding local prescribing information).

Likewise, patients undergoing surgical procedures will receive study product in accordance with the approved product label before, during and after surgery according to standard of practice of the participating clinic.

Population:

Approximately 80 previously FVIII treated (>150 exposure days) patients with severe and moderately severe haemophilia A (FVIII ≤2%) will be enrolled to allow for at least 50 patients to complete the study. Only patients for whom it has already been decided to start treatment with commercially available turoctocog alfa and who have not previously been enrolled in any clinical trials with turoctocog alfa will be eligible for the study.

Recruitment of patients will aim at a balanced age distribution with at least 20 % of patients being <12 years of age, to accommodate for the requirements in the present version of the European Medicines Agency guideline for factor VIII products[1].

Key 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.
- Previously FVIII treated (>150 exposure days at the time of first dosing with turoctocog alfa) male patients with the diagnosis of severe and moderately severe haemophilia A (FVIII ≤2%).
- The decision to initiate treatment with commercially available turoctocog alfa 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.
- A negative FVIII inhibitor test obtained not more than four weeks prior to first dosing with turoctocog alfa.

Key exclusion criteria:

- Contraindications for use according to the approved product information text (US Package insert (PI), European Summary of Product Characteristics (SmPC), or corresponding local prescribing information).
- Treatment with any investigational drug within 30 days prior to enrolment into the study.
- Previous participation in any clinical trial with turoctocog alfa.
- Treatment with other FVIII products after initiation of treatment with turoctocog alfa.

Variables

Key variables are incidence of inhibitor formation and efficacy in treatment and prevention of bleeds.

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 local clinical practice at the participating sites will be recorded in the paper Case Report Form. 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 Case Report Form by the Physician.

Study size

The sample size for the present study will be approximately 50 patients of which at least 10 patients (20%) should be <12 years old at time of enrolment.

Data analysis

No formal testing of statistical hypotheses will be performed. Evaluation of data will be based upon descriptive statistics, i.e. summary tables, listings, and figures. Categorical data will be summarised by frequency tables while continuous data will be summarised by mean, standard deviation, minimum and maximum value.

Milestones

Planned date for First Patient First Visit:	01-Jun-2014
Planned completion of the last patient:	Q2/-2021
Planned completion of non-interventional study report:	Q4/-2021

5 Amendments and updates

Amendment number	Version date	Rationale for change	Protocol sections changed
2.0	22-Sep-2015	The present guardian™5 recruitment status is significantly below planned target. The main reason for the low recruitment is the protocol inclusion criteria requiring that patients should be turoctocog alfa naïve i.e. "No previous exposure to turoctocog alfa". Therefore patients have to consent to the study BEFORE receiving their first dosage. Most sites are reluctant to commit to study participation until they have started to prescribe turoctocog alfa. As the switch to turoctocog alfa for the majority of patients usually occur within the initial period (first three months) after launch of turoctocog alfa in each country, the availability of eligible patients has already dropped significantly by the time sites have agreed to participate. The 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' requires study patients to be free from inhibitors at inclusion, but do not require patients to be naïve. Requiring no previous participation in turoctocog alfa studies is therefore sufficient to ensure that only patients who are new to turoctocog alfa will join this non-interventional study. To minimise the chance of deselection of patients who have developed inhibitors in the period between switching to turoctocog alfa and study inclusion, patients with clinical suspicion of inhibitors will be eligible, but only if they do not have a history of inhibitors on previous FVIII products and if a negative inhibitor test has been obtained prior to first	1, 2, 3, 4, 5, 6, 7, 9 & 11

Amendment number	Version date	Rationale for change	Protocol sections changed
		dosing (sampled within four weeks prior to first dosing) with turoctocog alfa. In this way selection bias with regards to patients that may have developed inhibitors to turoctocog alfa prior to study inclusion will be avoided. Patients receiving other FVIII products after the first dosing with turoctocog alfa should also be excluded to ensure that development of an inhibitor can be directly linked to turoctocog alfa.	
3.0	06 Jan 2016	According to the European Medicines Agency *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products* (dated 21 July 2011) a separate progress study report should be provided to the relevant Competent Authority(ies) 2 years after the start of the post-marketing investigation. Study protocol version 5.0 dated 22 September 2015 section 6 Milestones list that an interim report is planned at 2 years after study start. Additionally protocol section 6 *Milestones* and protocol section 12.3 *Progress reports and final report* does not mention that a progress report will be provided to the relevant competent authorities 2 years after the start of the study. Accordingly, the rationale for this amendment is to state that a separate progress report is to be provided to the relevant competent authorities 2 years after the study start and to amend the planned timelines for the interim study report.	2, 6, 9.7.2 & 12.3
4.0	13 Jan 2017	The present guardian™5 recruitment status is significantly below planned target. The timelines have been changed according to the current enrolment rate within the study.	1, 2, 4, 5, 6, 9.1.1, 9.2.4, Table 9.1, 9.3.1.1, 9.3.1.2, 9.3.1.3, 9.3.3.4,

Amendment number	Version date	Rationale for change	Protocol sections changed
		The aim of this study is to collect real life data for NovoEight® treatment. To be able to fulfil this aim, withdrawal criteria No. 1, No. 2 and No. 3 have been deleted, in order to avoid bias within the collected data. A new withdrawal criterion 4 has been created. The changes in the withdrawal criteria results also in a change in the concomitant medication section (9.3.4.6), where allowed and prohibited medications have been deleted. Changes are required to the End of Study procedure to get as much data in after 50 patients have reached a minimum of 100 EDs. Specific laboratory analyses in data collected for haematology, biochemistry and viral antibody information are not done within this study. Therefore it was decided to delete collection for haematology, biochemistry and viral antibody information for all visits from the protocol. Only HIV status and T cell subset CD4+ data will be collected at visit1 to verify inclusion criteria no. 7 for HIV positive patients. For all further visits also T cell subset: CD4+ will be deleted. This amendment includes also minor changes to the layout and wording within the flow chart. The name of the main author and the MAH (Marketing Authorisation Holder) were adapted within the whole protocol. The separated sections of change will not be listed in the amendment. The term MESI (Medical Event of Special Interest) has been updated to AESI (Adverse Event of Special Interest) within the whole	9.3.3.5, previous 9.3.3.8, previous 9.3.3.9, 9.3.4.6, 9.3.4.9, 9.7.2, 9.7.3, 9.7.4, 9.7.5, 10.1

Amendment number	Version date	Rationale for change	Protocol sections changed
		protocol to follow the term according to our current SOP (Standard Operation Procedure). The separated sections of change will not be listed in the amendment.	

6 Milestones

Planned duration of enrolment period is 70 months.

Milestone	**Planned date**
Start of data collection *Defined as first entry of patient data*	01-Jun-2014
Progress report	01-Jun-2016
Interim report	01-Nov-2016 Q4/2018
End of study *Defined as Last Patient Last Visit (LPLV)*	Q2/2021
End of data collection	Q2/2021
Final report of study results	Q4/2021

The planned duration of this study is 7 years. The study will be concluded when at least 50 patients in the study have reached a minimum 100 exposure days (EDs) after inclusion in the study.

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.

The study information is made available in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines Agency (EMA) 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), e.g. www.ClinicalTrials.gov.

7 Rationale and background

7.1 Background

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutation in the coagulation factor eight (FVIII) gene on the long arm of the X-chromosome. Approximately 1 in 5,000 male births give rise to haemophilia A. Classification of the severity of haemophilia A is based on plasma levels of FVIII, with patients <1% factor defined as severe; 1–5% as moderately severe; and 5-40% as mild[2]. Patients with haemophilia A lack or have a reduced production of FVIII, or they produce biochemically defective FVIII molecules. With a deficiency or absence of this factor, the activation of coagulation factor X becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug formed in these patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis and prolonged bleeds[3].

Recurrent bleeds in the same location, most commonly a weight-bearing joint, lead to chronic arthropathy, muscular atrophy, and deformities. Treatment of bleeds as they manifest may delay this process, but does not prevent it[4]. For this reason, primary prophylaxis with regular FVIII injections in the non-bleeding state is standard practice from early childhood to at least 18 years of age. The primary goals of haemophilia therapy for patients are the prevention of bleeds, the rapid and definitive treatment of bleeds that do occur, and the provision of adequate haemostasis during surgery and other major challenges to haemostasis. A very serious complication to haemophilia treatment is inhibitor development. Inhibitors are antibodies formed as an immune response to allogeneic FVIII and which reduce or eliminate the activity of FVIII proteins.

Turoctocog alfa is a new recombinant FVIII product intended for FVIII substitution therapy, which is the standard of care for haemophilia A patients.

7.2 Rationale

This protocol describes a non-interventional post authorisation safety study (PASS) of recombinant human coagulation factor VIII (rFVIII).

The major concern in the treatment of haemophilia A is the development of inhibitors against FVIII[5]. The presence of inhibitors neutralizes the effect of FVIII replacement therapy, resulting in increased risk of severe bleeding and development of debilitating haemophilic arthropathy and muscular atrophies, with severe consequences on quality-of-life for the patient.

The risk of developing inhibitors against FVIII is related to the mutation type in the FVIII gene[6,7], and possibly to other both genetic and non-genetic factors such as immunoregulatory genes, HLA-type, intensity of treatment, vaccinations or other challenges to the immune system[8,9]. Inhibitor development in haemophilia A in most cases occurs during the early phases of replacement therapy, usually during the first 50 EDs[10]. The risk of developing inhibitors against FVIII in previously

untreated patients is related to the mutation type in the FVIII gene[6,7], and possibly to other both genetic and non-genetic factors such as immunoregulatory genes, HLAtype, intensity of treatment, vaccinations or other challenges to the immune system[8,9]. In previously treated patients, inhibitors develop rarely, with an incidence of an approximate rate of 3 per 1000 patient years[11]. Switching to another FVIII product has not been shown to be associated with increased incidence of inhibitor development[12,13]. When inhibitors have been detected following switching, time and number of EDs between switching and detection varied considerably, providing no clear indication that inhibitors are more likely to develop in the initial period after switching[12].

Novo Nordisk has developed turoctocog alfa, a B-domain truncated human recombinant FVIII for use in patients with haemophilia A[14,15]. The First Human Dose and PK trial (NN7008-3522) comparing turoctocog alfa and Advate® has been completed[16]. The data from the 23 patients showed mean PK profiles of turoctocog alfa comparable to Advate® within the defined limits of comparability.

Clinical experience included in the marketing application comprises phase 3 results from the pivotal (guardian™1 - NN7008-3543) and paediatric trials (guardian™3 - NN7008-3545) in patients with severe haemophilia A (FVIII<1 %). In the guardian™1 (NN7008-3543) trial, 146 adult and adolescent patients (>12 years of age) were followed during 75 EDs of preventive dosing with turoctocog alfa either 3 times weekly or every second day. Efficacy in bleeding prevention was demonstrated by a bleeding frequency clearly within the range expected during prophylaxis treatment in haemophilia A (mean annualised bleeding rate of 6.5 bleeds/year). Spontaneous and traumatic bleeds during the trial were treated with a mean dose of 30.4 IU/kg BW (mean total dose used was 45.6 IU/kg BW until stop of bleed), and using a predefined four-point scale (Excellent, Good, Moderate or None) the haemostatic effect of turoctocog alfa was rated as excellent or good in 81 % of all bleeds.

In the paediatric guardian™3 (NN7008-3545) trial, 63 previously treated patients <12 years of age (<6 years n=31; n=32 6-11 years of age) were dosed with turoctocog alfa and 60 patients completed 50 preventive EDs using a regimen similar to that in the adult/adolescent trial. The bleeding frequency was low with a mean annualised bleeding rate of 5.3 bleeds/year using a mean preventive dose of 36.8 IU/kg BW. Emergent bleeds in the trial were treated with a mean dose of 40.4 IU/kg BW (mean total dose of 50.2 IU/kg BW per bleed) and the haemostatic efficacy was rated as excellent or good in 92.1 % of all bleeds. The number of infusions required to control a bleed was 1-2 in >95 % of bleeds.

After completion of the guardian™1 (NN7008-3543) and guardian™3 (NN7008-3545) trials, the vast majority of patients have continued treatment with turoctocog alfa within the extension trial guardian™2 (NN7008-3568). A 4th Interim analysis of the guardian™2 (NN7008-3568) trial with a cut-off date 25 March 2015 included 123 patients who have been on prophylaxis with turoctocg alfa for ≥36 months. In the entire guardian™ clinical trial programme, 242 previously treated patients

have been exposed to turoctocog alfa for >50 EDs, and the total exposure now exceeds 100,000 EDs. Despite regular testing and monitoring, no confirmed FVIII inhibitor or other safety concerns have yet been detected within the trials in previously treated patients.

In the recently revised guideline for FVIII products, European Medicines Agency (EMA) points to the importance of ensuring consistency between the outcome from pre-authorisation clinical studies and from long-term routine use, thus mandating a post-marketing investigation if the development program does not include enough EDs[1]. This is also in view of the limited availability of patients suffering from haemophilia A. The present guardian™5 study (NN7008-3553) is designed to provide additional documentation of the immunogenicity and clinical efficacy of turoctocog alfa.

The U.S. Food and Drug Administration (FDA) have approved Novo Nordisk A/S Biologics License Application (BLA) for turoctocog alfa on the 16th October 2013. Additionally, on the 20th September 2013 the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion on turoctocog alfa.

8 Research question and objectives

Please refer to section 7.2 for the rationale for the research question the study will address.

8.1 Objectives

8.1.1 Primary objective

- The primary objective is to assess the incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) during long-term prevention and treatment of bleeds with turoctocog alfa in previously FVIII treated (>150 EDs) patients with severe and moderately severe haemophilia A (FVIII ≤2%).

8.1.2 Secondary objective

- To further evaluate the general safety and obtain additional clinical experience of turoctocog alfa in prevention and treatment of bleeds and prevention of bleeds during and after surgery.

8.2 Endpoint(s)

8.2.1 Primary endpoint

- Incidence rate of FVIII inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors.

8.2.2 Secondary endpoints

Safety endpoints

- Number of adverse reactions (ARs) reported during the study period
- Number of serious adverse reactions (SARs) reported during the study period

Efficacy endpoints

- Haemostatic effect of turoctocog alfa in the treatment of bleeds as assessed by the patient or the Physician according to a predefined four point scale: Excellent, Good, Moderate, or None
- Haemostatic effect of turoctocog alfa during surgical procedures as assessed by evaluation according to a predefined four point scale: Excellent, Good, Moderate, or None
- Annualised bleeding rate for patients using turoctocog alfa for preventive treatment
- Annualised bleeding rate for patients using turoctocog alfa for on-demand treatment

- Total consumption of turoctocog alfa per patient (prevention, treatment of bleeds and surgery) per month
- Actual consumption of turoctocog alfa (IU/kg BW/months) for prevention
- Actual consumption of turoctocog alfa per bleed (IU/kg BW/bleeding episode)
- Actual consumption of turoctocog alfa (IU/kg BW) from the day of surgery until the day of return to preventive regimen

9 Research methods

- In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

9.1 Study design

9.1.1 Type of study

This is a prospective, multinational, non-randomised, non-interventional post-authorisation safety study (PASS) in previously FVIII treated (>150 EDs) patients with severe and moderately severe haemophilia A with FVIII ≤2%. Only patients for whom it has already been decided to start treatment or have already started treatment with commercially available turoctocog alfa and who has not previously participated in any guardian™ clinical trials will be eligible for the study.

Patients with FVIII between 1 and 2% are classified as moderately severe haemophilia A, but most often require treatment due to bleeding tendency. Inclusion of these patients in the present study is in accordance with the EMA guideline for a post marketing investigation for FVIII products [1], and this patient group is also part of the population intended for treatment with turoctocog alfa. This study will observe at least 50 patients for a minimum of 100 EDs to study product after inclusion in the study. The study duration is estimated to 7 years with a planned recruitment period of 70 months. For each patient, data will be collected in this study:

- until they reach a minimum of 100* EDs with turoctocog alfa after inclusion in the study **or**
- until at least 50 patients have a minimum of 100* EDs with turoctocog alfa after inclusion in the study

whichever comes first.

*the 100 EDs will count from the baseline visit (visit 1)

One exposure day (ED) is defined as each day a patient is administered turoctocog alfa and a‘day’ is implicit a ‘calendar day’.
E.g. a dosing with turoctocog alfa on 15 June 2015 at 22.30 and a new dose two hours later on 16-Jun-2015 at 00.30 counted as two exposure days.
Several doses with turoctocog alfa within the same calendar day should only be calculated as one exposure day.

Recruitment of patients will aim at a balanced age distribution with at least 20 % of patients being <12 years of age to accommodate for the requirements in the present version of the EMA guideline for factor VIII products[1], as described in section 9.5. This study will follow routine use of turoctocog alfa in a population with severe and moderately severe haemophilia A FVIII ≤2%. All relevant data recorded by the site during a patient’s participation in the study will be captured in the paper Case Report Form (pCRF).

No controls or blinding procedures are applied. There will be no dispensing of any study product as part of this study. All direction for study product usage (prophylactic as well as on-demand) is solely at the discretion of the Physician in accordance with clinical daily practice and preferably in accordance with the approved product label (US Package insert (PI), European Summary of Product Characteristics (SmPC) or corresponding local prescribing information).

The Physician is encouraged to perform clinical evaluation and blood testing for FVIII inhibitors in the presence of lack of therapeutic effect in accordance with the product labelling, and also as routine practice during visits to the clinic.

9.1.2 Rationale for study design

This study design will provide additional documentation of the safety and the clinical experience of turoctocog alfa in prevention and treatment of bleeds in PTP (>150 EDs) with severe and moderately severe haemophilia A (FVIII ≤2%). The study design is in accordance with EMA guideline from July 2011[1] for post-marketing investigations of rFVIII products.

An active comparator has not been chosen as extensive comparative data from recently registered rFVIII products are available in comparable global populations including patients from EU and US[17,18].

The rationale for choosing a multi-centre, multi-national design is to ensure a sufficient patient pool and relevant ethnic diversity of haemophilia A patients as turoctocog alfa is expected to be marketed globally.

9.1.3 Treatment of patients

Patients will be treated with commercially available turoctocog alfa as prescribed by the treating Physician in clinical daily practice and preferably according to the label for turoctocog alfa (US PI, European SmPC, or corresponding local prescribing information) in the respective countries. Thus, patients on prophylactic as well as on-demand treatment with turoctocog alfa can be included in the study. Patients undergoing surgical procedures during the study will receive turoctocog alfa bleeding preventive treatment before, during and after surgery according to the label for turoctocog alfa in the respective countries and standard of practice of the participating centre.

Patients who develop inhibitors can continue treatment with turoctocog alfa. If this is decided, the dosing and dosing frequency will be decided by the treating Physician based on the clinical evaluation, see Figure 9–1.

9.1.4 Rationale for treatment

Replacement therapy with recombinant or plasma-derived FVIII is the mainstay and standard in the management of patients with haemophilia A without inhibitors. Based on the accumulated clinical

and preclinical results for turoctocog alfa[14-16] it is expected that safety and efficacy of turoctocog alfa treatment will be similar to that of currently marketed recombinant FVIII products.

Please refer to the US PI, European SmPC and any updates thereof for further preclinical and clinical data.

9.2 Setting

9.2.1 Number of patients to be studied

The below listed numbers represent the sum of patients participating:

Planned number of patients to be included (baseline screening): Approx. 80

Planned number of patients to be included in the study: Approx. 70

Planned number of patients to complete the study: Approx. 50

Anticipated number of patients to be included in each country: Approx. 5-8

9.2.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered “yes”.

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. Previously FVIII treated (>150 EDs at the time of first dosing with turoctocog alfa) male patients with the diagnosis of congenital severe and moderately severe haemophilia A (FVIII ≤2%).
3. The decision to initiate treatment with commercially available turoctocog alfa 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.
4. Availability of a detailed and reliable patient documentation (patient records, diary, logbook etc.) covering either the last 50 EDs or the last 2 years per patient to confirm treatment modality (i.e. prophylaxis, on-demand or recent surgery) prior to enrolment.
5. A negative FVIII inhibitor test obtained not more than four weeks prior to first dosing with turoctocog alfa.
6. Patients with a history of FVIII inhibitors and who have been immune-tolerized to FVIII through Immune Tolerance Induction treatment must have FVIII plasma recovery level ≥66 % of expected level and a FVIII half- life (T½) of ≥6 h after a 72 h wash-out period (as demonstrated by available medical records).
7. No clinical suspicion of HIV-1 or, if HIV-1 seropositive, viral load <400.000 copies/mL and immunocompetent with CD4+ lymphocyte count ≥200/µL, as assessed during the last 6 months prior to the Baseline visit.

9.2.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Contraindications for use according to the approved product information text (US Package Insert (PI), European Summary of Product Characteristics (SmPC) or corresponding local prescribing information). This includes known or suspected allergy to turoctocog alfa or related products.
2. Previous participation and/or withdrawal from this study. Participation is defined as having given informed consent in this study.
3. Treatment with any investigational drug within 30 days prior to enrolment into the study
4. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Previous participation in any clinical trial with turoctocog alfa.
6. Treatment with other FVIII products after initiation of treatment with turoctocog alfa.

9.2.4 Withdrawal criteria

The patient may withdraw at will at any time. The legally responsible person for the patient may withdraw the child from the study at will at any time.

The patient may be withdrawn from the study at the discretion of the Physician or the sponsor due to a safety concern.

A patient must be withdrawn if the following applies:

1. withdrawal criteria 1. deleted
2. withdrawal criteria 2. deleted
3. withdrawal criteria 3. deleted
4. Patients who started regular treatment with another FVIII products other than turoctocog alfa after initiation of study product treatment within this study.

9.2.5 Rationale for selection criteria

The study population are the patients who based on the indication will benefit from treatment with turoctocog alfa. As this is a non-interventional study the prospective patients should be identified amongst those patients for whom it has already been decided that they will switch to turoctocog alfa. As a multi-centre, multinational population has been selected the generalizability of the study is evaluated as high. The study is global and should include different ethnicities.

The study population characterised through the inclusion criteria:

- Criterion no. 1 is included in accordance with Good Pharmacoepidemiology Practice (GPP)[19]
- Criteria nos. 2, 4, 6 and 7 are derived from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived Factor VIII products[1]
- Criterion no. 3 is to ensure that patients are not prescribed turoctocog alfa because of study participation
- Criterion no. 5 is derived from the World Federation of Haemophilia guidelines for the management of haemophilia[20] and from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived Factor VIII products[1]

The study population characterised through the exclusion criteria:

Criterion no. 1 is a prerequisite for a non-interventional study
Criteria no. 2 is to ensure that a patient only counts once in the data analyses
Criterion no. 3 is selected to minimise any effect of other investigational compounds on the patient's coagulation and immune system
Criterion no. 4 serves to ensure adequate study understanding and cooperation

- Criterion no. 5 to avoid inclusion of patients that have been treated with turoctocog alfa for a long time (i.e. in the extension study)
- Criterion no. 6 derives from the World Federation of Haemophilia guidelines for the management of haemophilia[20] and from the EMA guidelines concerning post-marketing investigation of recombinant and human plasma-derived Factor VIII products[1]

The eligibility criteria are considered to allow inclusion of most patients with severe and moderately severe haemophilia A (FVIII ≤2%) and will thus not impose any significant limitation in the number of patients available for analysis.

Table 9–1 Flow chart

Visit number	**Baseline (Visit 1)**	**Assessment visits (Visit 2.1, 2.2, 2.3, ,)**	**End of study (Visit 3)**
Visit window[1]		0 - 99 EDs	≥100[2] EDs
PATIENT RELATED INFO / ASSESSMENTS[3]			
Informed consent	●		

Visit number	Baseline (Visit 1)	Assessment visits (Visit 2.1, 2.2, 2.3, ,)	End of study (Visit 3)
Visit window[1]		0 - 99 EDs	≥100[2] EDs
Consent to report FVIII genotype result	●		
Inclusion/Exclusion Criteria	●		
Withdrawal Criteria	●	●	●
Haemophilia treatment history	●		
Concomitant illnesses	●		
Medical history	●		
Concomitant medication	●	●	●
Demography	●		
Body measurements	●	●	●
FVIII genotype	●[4]	●[5]	●[5]
Details of haemophilia	●		
Family history of haemophilia	●		
EFFICACY[3]			
Bleed(s)		●	●
Surgery	●	●	●
SAFETY			
Adverse reactions	●	●	●

Visit number	**Baseline (Visit 1)**	**Assessment visits (Visit 2.1, 2.2, 2.3, ,)**	**End of study (Visit 3)**
Visit window[1]		0 - 99 EDs	≥100[2] EDs
Physical examination	●	●	●
Vital signs	●	●	●
FVIII recovery	●	●	●
FVIII trough level	●	●	●
FVIII inhibitors	●[6]	●[6]	●[6]
OTHER ASSESSMENTS			
HIV status	●[7]		
T cells subset: CD4+	●[8]		
STUDY MATERIAL			
Administration of turoctocog alfa	●	●	●
Diary dispensing and/or collection	●	●	●
Review of patient Diary data		●	●
End of Study form			●

[1]For patients with on-demand treatment, the time period between visits is recommended not to exceed 6 months

[2]100 EDs with turoctocog alfa after inclusion in the study

[3]In this non-interventional study, only results from assessments performed according to local clinical practice will be recorded. However, adverse reactions (ARs) should always be assessed and reported

[4]An available genotype result will be documented if consented to by the patient/LAR

[5]If a genotype test is performed during the study, the result will be documented, if consented to by the patient/LAR.

[6]A 48 hours washout period is recommended

[7]If assessment is performed. Can also be transferred from medical records, if available

[8]If HIV positive, last value of CD4+ T-cells dated no more than 6 months prior to study entry

9.3 Variables

It is the intention of this non-interventional study to observe routine treatment of the individual patient. Data and results from assessments and laboratory sampling performed according to clinical practice at the participating sites will be recorded upon availability.

The Physician is encouraged to perform assessments and blood sampling at all visits according to local clinical practice, if applicable, see section 9.3.2 through 9.3.4.9.

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 local clinical practice. No additional visits should be conducted due to the participation in this study.

At each visit the Physician should provide information as specified in the below sections, if available. 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. These logs can be combined in one document. Patient identification is to be accomplished via allocation of a six digit number which consists of a three digit site code and a three digit patient ID. Numbers will be provided by Novo Nordisk.

Signed informed consent must be obtained prior to any study related activities.

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

9.3.1.1 Baseline (Visit 1)

Visit 1 should preferably be performed at least 48 hours after last dose of current FVIII product if blood sampling of FVIII recovery and FVIII inhibitors is conducted during this visit.

Visit 1 will either be the first visit to the clinic after signing of the informed consent form or the clinic visit where the informed consent form is signed.

Data available in the patient's medical record at the time of the Baseline visit may be used as baseline data and should be entered in the pCRF. All relevant data necessary for evaluating whether or not a patient can be enrolled in the study e.g. inclusion/exclusion criteria must be available prior to enrolling a patient. A diary will be provided to patients to assist data collection during their participation in the study, see section 9.3.4.9.

In case a patient is evaluated as not eligible for study participation by the Physician during the baseline visit, please complete the Screening Failure form in the pCRF.

The following must be recorded in the pCRF after having obtained informed consent:

- Date of informed consent, see section 10.1
- Date of consent to FVIII genotype test result(s), see section 9.3.4.3
- Inclusion and exclusion criteria, see section 9.2.2 and 9.2.3
- Withdrawal criteria, see section 9.2.4

If available in the patient's medical record, the following must be recorded in the pCRF after having obtained informed consent:

- Demography, see section 9.3.4.1
- Haemophilia treatment history, see section 9.3.4.4
- Medical history, see section 9.3.4.5
- Concomitant illness, see section 9.3.4.5
- Concomitant medication, see section 9.3.4.6
- Haemophilia details, see section 9.3.4.7
- Family history of haemophilia, see section 9.3.4.8
- Adverse reactions, see section 11

If performed, the following must be recorded in the patients record and the pCRF after having obtained informed consent:

- Body measurement, see section 9.3.4.2
- Physical examination, see section 9.3.3.2
- Vital signs, see section 9.3.3.3
- Diary dispensing and training, see section 9.3.4.9
- Administration of study product, if applicable

The following laboratory results must be recorded in the pCRF, if available or performed:

- FVIII inhibitor, see section 9.3.3.5
- FVIII recovery, see section 9.3.3.6
- FVIII trough level, see section 9.3.3.7
- HIV status, see section 9.3.3.8
- T-cells sub-set: CD4+, see section 9.3.3.8

9.3.1.2 Assessment visits (Visits 2.1, 2.2, 2.3,.,)

The following must be performed and recorded:

- Withdrawal criteria see section 9.2.4

The most recent of the below specified data/blood results since the previous visit should be recorded in the pCRF.

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

- Physical examination
- Vital signs
- Body measurement
- Concomitant medication
- Bleeding episodes
- Adverse reactions
- Administration of study product
- Diary data review
- Dispensing of new diary

The following laboratory results must be recorded in the pCRF, if available or performed:

- FVIII inhibitor
- FVIII recovery
- FVIII trough level

Phone contacts

In case of a patient calls the site during the study all relevant study information should be entered in the patient medical record and subsequently in the pCRF.

Surgery

Patients undergoing surgery will be followed according to local clinical practice, and any visits should be documented in the pCRF.

For surgery, the following data should be recorded in the patient's record and the pCRF, if available:

- Type of surgery (planned or emergency)
- Surgery intervention:
  - Surgical procedure and indication
  - Clinical evaluation of haemostatic response during surgery (Excellent, Good, Moderate, or None)
- Date of surgery
- Study product doses in relation to peri-operative period (surgery day and post-surgical recovery period)
- FVIII inhibitor tests on the day of surgery and a second test in the interval 10 - 14 days post-surgery
- Clinical narrative of the procedure

Treatment and study assessments to be made in an emergency situation are at the discretion of the Physician. If a patient change his regular treatment to another FVIII products other than turoctocog alfa after initiation of study product treatment within this study the patient must be withdrawn from the study in accordance with withdrawal criteria no. 4, please see section 9.2.4.

For additional information, please see section 9.3.2.4.

9.3.1.3 End of study visit (Visit 3)

This visit will take place when the individual patient or at least 50 patients in the study have reached a minimum of 100 EDs after inclusion in the study whichever comes first. The visit*s* should be

scheduled according to local clinical practice and should if possible also be performed for withdrawals.

When Novo Nordisk has confirmed that a total number of 50 patients in the study have reached a minimum of 100 EDs, the sites must contact on-going patients and request that all patient diaries are returned to the site, and ask for any safety information since last visit. The contact can be performed during a regular site visit or a phone contact. To finalise the study documentation the data should be recorded in the pCRF not later than 8 weeks from the announcement that 50 patients have reached 100 EDs within the study.

The following must be reviewed and recorded:

- Withdrawal criteria

End of study form

The following must be recorded in the patients record and the pCRF, if available or performed:

- Physical examination
- Vital signs
- Body measurement
- Concomitant medication
- Bleeding episodes
- Adverse reactions
- Diary data review
- Administration of study product
- Surgery, for additional information please see section 9.3.1.2

The following laboratory results must be recorded in the pCRF, if available or performed:

- FVIII inhibitors
- FVIII recovery
- FVIII trough level

9.3.2 Assessments for efficacy

9.3.2.1 Bleeding episodes

During the entire study period all bleeds requiring treatment should be entered by the patient or parent/caregiver in the patient's diary. In case a patient is unable to enter a bleeding episode in the diary, or is hospitalised, it should be reported in the patient record and subsequently in the pCRF by the Physician at his/her earliest convenience. If a patient visits the site due to a bleed, treatment and

severity assessment data should be entered in the patient record and subsequently in the pCRF by the Physician.

Joint bleeds are either categorised as target joint or non-target joint bleeds. Target joints are defined as 3 or more bleeds in the same joint within 6 months. When there has been no bleed in this same joint for 12 months, such a joint is no longer considered a target joint.

For bleeds the following should be recorded in patient's diary and pCRF:

- Date and time of onset of bleeding episode
- Treatment of bleeding episode
- Location of the bleed (specify location e.g. joint, muscular etc.)
- Type of bleed (spontaneous, traumatic)
- Haemostatic drug used for treatment
- Dose level(s), strength(s) and time(s) of administration
- Other therapy used (compression, ice or other)
- Date and time of stop of bleeding episode
- Severity of the bleed (Mild/Moderate or Severe)
- Clinical evaluation of the haemostatic response (Excellent, Good, Moderate or None)

A need for haemostatic rescue therapy with another FVIII product will be assessed by the Physician via phone or during a site visit. Patients treated with FVIII products other than study product during the time of their participation in this study must be withdrawn from the study, see section 9.2.4.

9.3.2.2 Definition of severity of bleeding episodes

Mild/Moderate: Bleeding episodes that are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds. The details of mild/moderate bleedings should be recorded by the patient in the diary.

Severe: All intracranial, retroperitoneal and iliopsoas bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe. The details of severe bleeding episodes should be entered in the diary or if the patient is unable to fill in the diary or hospitalised, the Physician or study personnel should enter the data in the patient's medical record and subsequently in the pCRF. Bleeds at other locations than described above can always be considered severe at the Physician's discretion.

9.3.2.3 Definition of haemostatic response:

Excellent: abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion.

Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after one infusion, but possibly requiring more than one infusion for complete resolution.

Moderate: probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion.

None: no improvement, or worsening of symptoms within approximately 8 hours after the first infusion; usually requiring more than one infusion.

9.3.2.4 Definition of 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

9.3.2.5 Type of bleed

- Spontaneous
- Traumatic

9.3.3 Assessments for safety

9.3.3.1 Adverse reactions

All adverse reactions (ARs), either observed by the Physician or reported by the patient must be recorded and evaluated by the Physician. At each study related contact with the site, the patient should be asked about adverse reactions since the last contact. Please refer to section 11 for AR definitions, collection, recording, and reporting.

AR monitoring will be performed from a patient's first exposure to turoctocog alfa until a patient's last visit in the study.

9.3.3.2 Physical examination

The examination may include:

- Head, ears, eyes, nose, throat and neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Genito-urinary system
- Musculo-skeletal system
- Central and peripheral nervous system
- Skin

9.3.3.3 Vital signs

- Pulse
- Blood pressure

Blood pressure and pulse rate will be measured according to local practice; preferably after the patient has rested comfortably for 3 min.

9.3.3.4 Laboratory tests

Results of the following laboratory blood analyses will be recorded if available or performed during the duration of the study:

- FVIII inhibitor
- FVIII recovery
- FVIII trough level
- HIV status, only at visit 1 (includes HIV antibody and viral load, if HIV antibody positive)
- T-cells sub-set: CD4+, only at visit 1 for HIV positive patients

Any blood sampling ordered by the Physician during this study will be the ones regarded as appropriate to provide the best care for the patient at his/her discretion.

Local laboratory results should be reported in the pCRF. It is preferred that the FVIII trough level and the T cells subset: CD4+ values are reported in the listed units, see section 9.3.3.7 and 9.3.3.8, respectively. However, in the pCRF it will be possible to enter values in other units accepted by Novo Nordisk.

9.3.3.5 FVIII inhibitor testing

Blood sampling for inhibitor detection can be performed according to local clinical practice. As described in the EMA guideline[1], the Physician is encouraged to test for FVIII inhibitors according to Table 9–2, preferably at least 48 hours after last treatment If the patient is already being treated with turoctocog alfa at inclusion, the result of the inhibitor sample taken prior to initiated treatment

with turoctocog alfa must be available and negative. After inclusion in the study Novo Nordisk offer to provide analysis for FVIII inhibitors at a Central Laboratory selected by Novo Nordisk.

A positive inhibitor test is defined as ≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range. A patient has a confirmed inhibitor if the patient has been tested positive for inhibitors at two consecutive tests preferably within two weeks.

Table 9–2 Recommended laboratory scheme for FVIII inhibitors and recovery

	0 EDs	10-15 EDs	50-75 EDs	~100 EDs
FVIII inhibitors	X[1]	X[1]	X[1]	X[1]
FVIII recovery	X	X	X	X

[1]A 48 hours washout period is recommended

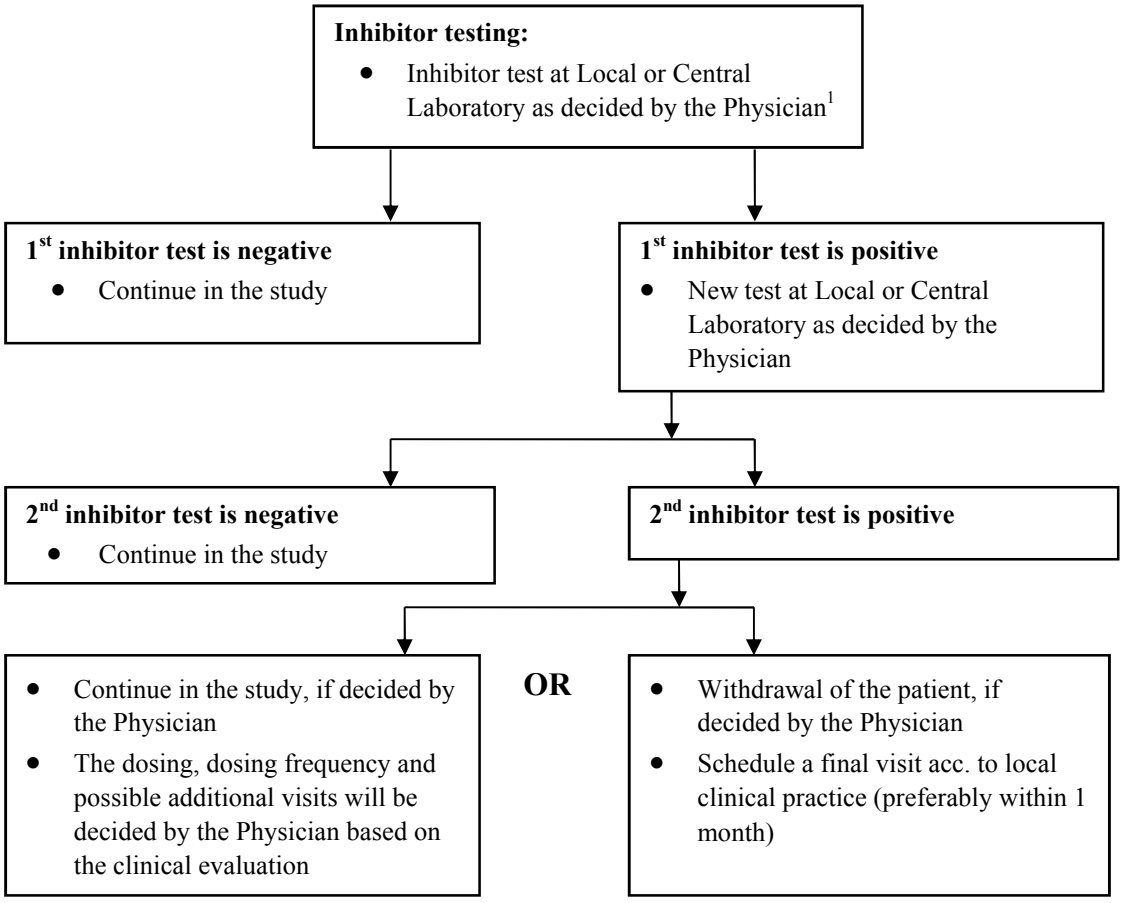
In the event that a patient has a positive inhibitor test obtained within 4 weeks prior to first dose of turoctocog alfa, the patient cannot be included in the study according to inclusion criteria no. 5, see section 9.2.2. In the event that a patient has a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa, the patient may proceed in the study but will not be included in the full analysis set. In the event that a patient has a positive inhibitor test (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) after inclusion and dosing in the study, the patient should visit the clinic again according to local practice (recommended to be performed as soon as possible - preferably within 2 weeks) to take a confirmatory inhibitor test on a separately drawn sample. The confirmatory sample should preferably be taken prior to any change of treatment. Even if the second inhibitor test is positive, the patient may continue in this study.

If this is decided, dosing, dosing frequency and more frequent visits for inhibitor sampling, if applicable, will be decided by the Physician based on the clinical evaluation. If a patient is to be withdrawn due to a confirmed inhibitor test, the Physician is encouraged to schedule an End of study visit (Visit 3) according to local clinical practice, and preferably within 1 month.

A positive inhibitor test should be reported as an AESI, see section 11.3. If the presence of inhibitors is confirmed by a second test this should be reported as a serious adverse reaction (SAR), see section 11.3. If the second inhibitor test is negative this should be reported as a follow-up to the reported AESI, see section 11.4. When lack of therapeutic effect is indicated by bleeding or laboratory findings, the Physician is encouraged to sample for FVIII inhibitor detection.

It is recommended that the Physician should upon a clinical suspicion of inhibitor development perform a FVIII inhibitor test.

The recommended process of inhibitor testing in case of a positive inhibitor test during the study is outlined in Figure 9–1.



[1]Recommended sampling times: 0 ED, 10-15 ED. 50-75 ED, ~100 ED- or in case of lack of therapeutic effect

Figure 9–1 Process flow for inhibitor testing

9.3.3.6 FVIII recovery

Blood samples collected for FVIII recovery in this study are samples taken as part of the routine treatment monitoring schedule established by the Physician.

In accordance with the EMA guideline[1], the Physician is encouraged to test for FVIII recovery at 0, 10-15, 50-75 and ~100 EDs as outlined in Table 9–2. Time and date of collection and result should be recorded in the pCRF. Novo Nordisk also offers to provide analysis of FVIII recovery samples i.e. 30 min post-dose, at a Central Laboratory selected by Novo Nordisk. No recovery samples are expected for patients on on-demand regimen.

9.3.3.7 FVIII trough level assessment – Local lab

Trough level (FVIII)

The Physician can at his/her discretion perform trough level assessments at any visit. The trough level is defined as the lowest level of FVIII measured immediately prior to dosing and reported as (IU/mL). The trough level will be determined at the local laboratory.

9.3.3.8 HIV status and T cell subset: CD4+– Local lab

- HIV status (includes HIV antibody and viral load, if HIV antibody positive)
- T cell subset: CD4+, if the patient is HIV positive the last value of CD4+ T cells (no more than 6 months prior to study entry) should be recorded

9.3.3.9 Central Laboratory tests

If the Physician is performing blood sampling for FVIII inhibitor and/or FVIII recovery test according to local clinical practice, the Physician is encouraged to send these samples to the Central Laboratory for analysis. Central Laboratory data will be reported to Novo Nordisk electronically in a manner that anonymity of patients will be maintained and, to the Physicians by fax or e-mail. Upon review of the laboratory results the Physician should sign and date the laboratory reports. The Central Laboratory is requested only to report analyses dictated by this protocol.

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 for blood sampling of analyses to be performed by the Central Laboratory will be provided to the sites.

Blood samples analysed by the Central Laboratory for measurement of inhibitors towards FVIII will be performed according to the Nijmegen modification of the Bethesda assay[21].

Blood samples for FVIII recovery will be analysed by the following two different assays:

One-stage clot activity assay

The one-stage bioassay (FVIII:C assay, clot assay) measures the activity of the compound in a specific process (clot formation). The FVIII:C assay is a modified one-stage clotting assay.

Chromogenic activity assay

A bioassay (FVIII:C chromogenic assay), which measures the activity of the compound with a two-stage method.

Recovery sampling should be performed in a non-bleeding state, and is assessed by the two methods specified above. If dose administered is known, incremental recovery is calculated as [IU/mL]/[IU/kg].

In case a patient receives treatment with his current FVIII product at Visit 1, and a recovery test is performed, the incremental recovery result is reported.

9.3.4 Other assessments

9.3.4.1 Demography

Collected as allowed by local law.

- Date of birth
- Ethnicity
- Race

9.3.4.2 Body measurement

- Body weight, wearing light clothing only and without shoes (kg/lbs)
- Height, without shoes (cm/inches)

9.3.4.3 FVIII genotype

All patients/parents/legally authorised representative (LAR) will be asked if available result(s) of previous FVIII genotype test(s) at Visit 1 may be documented in the study. If a genotype test is performed during the study, the result will be documented, if consented to, by the patients/parents/LAR. The Physician, patient or parent(s)/LAR have the right to refuse to provide such documentation. This will not stop the patient from participating or to continue in the study.

9.3.4.4 Haemophilia treatment history

- Prophylaxis/preventive regimen within the last 50 ED or the last two years
    - Number of months on prophylaxis
    - Current dose and frequency of dosing
    - Recombinant or plasma FVIII product
    - Number of doses with turoctocog alfa
    - Average number of bleeds per month
    - Documentation covering the last 50 ED/two years
- On-demand regimen within the last 50 ED or the last two years
    - Number of months with on-demand regimen
    - Recombinant or plasma FVIII product
    - Number of doses with turoctocog alfa
    - Average number of bleeds per month
    - Documentation covering the last 50 ED/two years

- History of switching FVIII products (type of products (from/to)), if available
- Surgeries within the last five years
    - Date of surgery
    - Indication
    - Recombinant or plasma FVIII product
    - Duration of surgical treatment
- Number of vaccinations in the last 12 months

9.3.4.5 Concomitant illness and Medical history

A concomitant illness is any illness that is present at the start of the study i.e. at the first visit. Details of all concomitant illnesses and medical history must be recorded at study entry i.e. at visit 1. The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution or continuation. A clinically significant worsening of a concomitant illness must be reported as an AR, see section 11.3 if the worsening is related to turoctocog alfa. If the change influences the patient's eligibility to continue in the study, the monitor must be informed.

Details on medical history will be recorded at the Baseline visit during a medical interview and review of relevant medical records. In the event that a diagnosis is unknown, the description of symptoms should be recorded.

9.3.4.6 Concomitant medication

A concomitant medication is any medication, other than the study product which is taken during the study. Details of any concomitant medication should be recorded at study entry i.e. at the first visit. Any changes in concomitant medication should be recorded at each visit as they occur. The recommended information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation. If a change is due to an AR then this should be recorded and reported according to section 11.3. If the change influences the patient's eligibility to continue in the study then the monitor should be informed.

9.3.4.7 Haemophilia details

- Diagnosis of haemophilia A (date)
- Classification of haemophilia A and FVIII level (%) from medical history
- Underlying gene defect (if known)
- Clinical suspicion of inhibitors, including transient inhibitors, from medical history
- Result of inhibitor tests and/or FVIII recovery values (including dose given and weight of the patient, for the last 5 years if available)

9.3.4.8 Family history of haemophilia

History of relatives with haemophilia A (as recalled by patient or parent/LAR or Physician)

9.3.4.9 Diary

Diaries will be used in this study. The patient should be asked to bring the diary(ies) to every visit to the site.

The following data should be captured by the patient and/or parent:

- Treatment
    - FVIII product used
    - Prophylaxis treatment
    - Every single dose level and strength
    - Date and time of dose administration
- Bleeds
    - Date and time of onset of bleeding episode
    - Treatment of bleeding episode
    - Location of the bleed (specify location e.g. joint, muscular etc.)
    - Type of bleed (spontaneous, traumatic)
    - Haemostatic drug used for treatment
    - Every single dose level(s), strength(s) and time(s) of administration
    - Other therapy used (compression, ice or other)
    - Date and time of stop of bleeding episode
    - Severity of the bleed (Mild/Moderate or Severe)
    - Clinical evaluation of the haemostatic response (Excellent, Good, Moderate or None)

The Physician should carefully instruct the patient in how to evaluate a bleed, the haemostatic response after treatment and how to complete the diary. The Physician is recommended to retrain the patient, if needed.

Entries made in the diary should preferably be reviewed by the Physician together with the patient/caregiver at each visit to the clinic; and should be entered in the pCRF by the site staff. The information in the patient's diary is regarded as source data. If information missing in the diary is available in the medical records, this information can be used.

In case study product administration is performed at the site, this should be entered in the medical record and subsequently in the pCRF for the respective assessment visit, by the Physician. The study product must not be reported in the diary when the administration is performed at the site.

9.3.5 Study product

The study product is the commercially available turoctocog alfa product manufactured by Novo Nordisk in vials containing lyophilised powder with rFVIII (human coagulation factor VIII

(recombinant)/INN name: turoctocog alfa)), and with solvent in a prefilled syringe. The powder is to be reconstituted with the solvent for injection in accordance with the Instruction For Use of the product.

Study product is to be administered according to approved product information (US PI, EU SmPC or corresponding local prescription information).

Commercially available turcotocog alfa used in this study should be stored according to the relevant Product Information for the products (US PI, European SmPC or corresponding local prescribing information).

The study product (i.e. the commercially available turoctocog alfa) will not be sponsored by Novo Nordisk.

9.3.5.1 Packaging and labelling of study product

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

9.3.5.2 Auxiliary supply

All items needed for reconstitution and administration of the study product will be supplied with the commercially available turoctocog alfa product.

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 patient's medical record from assessments and laboratory sampling performed according to clinical practice at the participating sites will be recorded in the pCRF as described in section 9.3. Treatment and information related to bleeding episodes will be captured in a patient diary by the patient or parent/caregiver as described in section 9.3.4.9. In case a patient is unable to enter a treatment or bleeding episode in the diary, or is hospitalised, it should be reported in the patients record and subsequently in the pCRF by the Physician.

For information on potential confounding variables please refer to section 9.9.

9.5 Study size

Sample size is based on regulatory (EMA) requirements[1]. According to the present version of the EMA guideline for factor VIII products[1] data from at least 200 patients with 100 EDs are required. At least 30% of these patients should be <12 years of age, corresponding to 60 patients.

Several of the patients in the guardian™2 (NN7008-3568) trial have already accomplished 100 EDs. As of 28-Aug-2012 167 patients in the guardian™2 (NN7008-3568) trial has more than 100 EDs. Of these 53 are children. Based on this, the sample size for the present study will be a total of

approximately 50 patients of which at least 10 patients (20%) should be <12 years old at time of enrolment.

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 to a 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 subjects in all presentations and publications as required by local/regional/national requirements. Appropriate measures such as encryption of data files will 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 Case Report Forms and rules for completing

Novo Nordisk will provide pCRFs for data capture in this study. 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 pCRF. 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 pCRFs 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 pCRFs have been removed from the Physician’s site must be documented on a Data Clarification Form (DCF). Such corrections must be approved by the physician or her/his authorised staff.

9.6.2.2 CRF flow

The Physician must ensure that data is recorded on the pCRFs as soon as possible after data is available (preferably within 3 days). pCRFs are produced on No Carbon Required paper with one original and one copy page. The top page (original page) is transferred by the monitor to the unit responsible for data entry as specified by Data Management, Novo Nordisk. The copy page is to be archived at site 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 be retained at the study site. The results from the local laboratory should be entered on the pCRF for each patient. Central Laboratory results will be transferred electronically to Novo Nordisk and loaded into the study database by Novo Nordisk. Laboratory reports from the Central Laboratory will be provided to the Physician.

When the final non-interventional study report is available the data will be archived by Novo Nordisk in Oracle Clinical version 4.6.4 or a later version.

9.7 Data analysis

Novo Nordisk will be responsible for the statistical analyses.

All summaries will show results for the full group of patients and for the subgroups of patients with endogenous FVIII level <1% and 1-2% at inclusion, as well as for the subgroups of patients below and above 12 years of age.

9.7.1 Statistical methods

No formal testing of statistical hypotheses will be performed. Evaluation of data will be based upon descriptive statistics, i.e. summary tables, listings, and figures. Categorical data will be summarised by frequency tables while continuous data will be summarised by mean, standard deviation, minimum and maximum value.

9.7.2 Interim analysis

An interim analysis covering all endpoints is planned to be performed with a data-cut 18 months and 35 months after the first patient data entry.

9.7.3 Primary endpoint

The incidence rate of inhibitors (≥0.6 BU for central laboratory analyses, or above the specific local laboratory reference range) represented as the percentage of patients developing inhibitors will be calculated and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the incidence rate the numerator will include all patients with inhibitors confirmed by laboratory except those patients who have received a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa. The denominator will include all patients in the trial exposed to turoctocog alfa,

except those patients who have received a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa, these patients will be listed separately.

In addition, the time to inhibitor development will be presented by Kaplan Meier plot. Furthermore, an annualised rate of inhibitors per patient year will be calculated using a Poisson model allowing for over-dispersion with a log-link function and the logarithm of the time spent in the trial as offset, if appropriate.

Analyses and presentations will be made for each treatment regimen (preventive treatment or on-demand treatment) and for all patients, and furthermore for each patient subgroup (Severity of Haemophilia A: severe, moderately severe or patients with surgery/invasive procedure).

9.7.4 Secondary endpoints

Safety endpoints

- Number of adverse reactions (ARs) reported during the study period
- Number of serious adverse reactions (SARs) reported during the study period

ARs and SARs reported during the study will be summarised by number of reactions and number of patients with any reaction. Since patients will have different durations in the study adverse reaction rates (reactions per 100 patient years of exposure) will also be calculated and presented. Similar summaries cross-classified by severity will also be made. The summary tables will be made by type of regimen.

Furthermore, listings will be provided displaying all ARs and SARs reported during the study including pertinent clinical information.

Efficacy endpoints

- Haemostatic effect of turoctocog alfa in the treatment of bleeds as assessed by the patient or the Physician according to a predefined four point scale: Excellent, Good, Moderate, or None

This endpoint will be summarised and listed. In addition treatment success will be summarised by counting Good or Excellent as success and None and Moderate as failure. Missing will be excluded since reporting the endpoint is optional.

- Haemostatic effect of turoctocog alfa during surgical procedures as assessed by evaluation according to a predefined four point scale: Excellent, Good, Moderate, or None

This endpoint will be summarised and listed. In addition treatment success will be summarised by counting Good or Excellent as success and None, Moderate as failure. Missing will be excluded since reporting the endpoint is optional.Annualised bleeding rate for patients using turoctocog alfa for preventive treatment

- Annualised bleeding rate for patients using turoctocog alfa for on-demand treatment

The annualised bleeding rate will be analysed by a negative binomial model and estimated annualised bleeding rate with confidence interval will be presented. As a sensitivity analysis, a Poisson model with over-dispersion will also be applied.

- Total consumption of turoctocog alfa per patient (prevention, treatment of bleeds and surgery) per month

This endpoint will be summarised and listed.

- Actual consumption of turoctocog alfa (IU/kg BW/months) for prevention

This endpoint will be summarised and listed.

- Actual consumption of turoctocog alfa per bleed (IU/kg BW/bleeding episode)

This endpoint will be summarised and listed.

- Actual consumption of turoctocog alfa (IU/kg BW) from the day of surgery until the day of return to preventive regimen

This endpoint will be summarised and listed.

9.7.5 Evaluability of patients for analysis

All main descriptions and analyses of safety and efficacy data will be based on the Full Analysis Set, as defined in ICH E9 Guidelines (Statistical Principles for Clinical Trials). The Full Analysis Set includes all dosed patients with data after dosing, except those patients who has had received a positive inhibitor test result after inclusion in the study for a test performed prior to first dose of turoctocog alfa, these patients will be listed separately.

No formal Per-Protocol analysis is planned. However, the sensibility of the results with respect to single patient's data may be investigated by performing additional analyses on subsets of data.

9.8 Quality control

9.8.1 Monitoring procedures

During the course of the study, the monitor should visit the study site at intervals specified in the monitoring guideline for the study. The purpose of these visits is to ensure that the protocol has been adhered to, that all issues and data have been recorded and to collect completed pCRF pages. The extent of source data verification and validation of endpoints will be described in the monitoring guideline for the study. The monitor must ensure that the pCRFs are completed and 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
- Curricula vitae 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 substantial amendment(s), if applicable
- Approval/favourable opinion from IRB/IEC or another relevant scientific body according to local legislation clearly identifying the documents reviewed: the protocol, any substantial amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IRB/IEC or another relevant scientific body according to local legislation approved patient information/informed consent form/any other written information/advertisement
- Non-interventional study agreement

9.8.3 Retention of study documentation

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

Novo Nordisk will comply with all the requirements of 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 the 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 for at least 5 years after final report/first publication of the study, whichever comes later. 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 procedures or in accordance with national regulations if they require a longer retention period.

9.8.4 Archiving of statistical programs

The programming plan is prepared with input from the Study Statistician using the Novo Nordisk's template. The programming plan is stored in the document sub-directory in the relevant study folder in the statistical computing environment. The final programs and outputs of a clinical study and all relevant documentations in form of specifications, data, programs, log files, output files, validation documentations and other documentation used in the process of reporting the study are saved in records. By saving all documentation used in the reporting process we are able to document when

and on which data, by which program(s) any given output is created. Furthermore, it will be possible at all times to regenerate all output, if necessary.

9.9 Limitations of the research methods

As this is a non-interventional study potential confounding factors can not be ruled out. Data collection will reflect routine clinical practise rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation. Concerning the issue of bleeding episode evaluation[22] of home treatment the risk of misclassification is relevant. Patients will receive and be asked to enter data (e.g. treatment and bleeds) in a diary. The Physician is encouraged to review the diary data together with the patient/caregiver during visits to the clinic.

9.10 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 or another relevant scientific body according to local legislation 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 or another relevant scientific body according to local legislation 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.

9.11 Indemnity statement

Novo Nordisk carries product liability for its products and liability assumed under the special laws, acts and/or guidelines for conducting clinical/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.

10 Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practice (GPP), reference[19].

The only burden added to the patient's life by participating in this study is entering of data into a diary. A diary for home treatment is recommended or required by most hospitals and will thus serve a disease management purpose apart from the purpose of reporting to the study. In this study, patients will be provided with a diary. The potential benefits for the patient are the systematic assessments of safety, especially comprising FVIII inhibitors and lack of effect.

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

10.1 Informed consent form for study patients

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

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

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[23].

If a patient is under age, then the patient´s assent must also be obtained according to local requirements.

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/parents and/or the patient's LAR in a timely manner and a revised written informed consent must be obtained.

Prior to any study-related activity, the Physician must give the patient and/or the patient's 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. In this study the notion of legal representative should be understood as either parents, or LAR, as defined in Member States' national laws, who consents on behalf of the child.

Children, incapable of giving consent, are included as patients in this study in accordance with Health Authority guidelines for development of FVIII products[1].

Consent: As a child is unable to provide legally binding consent, informed consent must be obtained from the parents/LAR on the child's behalf. The specific and written informed consent of the parents/LAR must be sought prior to enrolling a child in the study. Information should be given by an experienced Physician to each parent, or the LAR, on the purpose of the study and its nature.

Assent: When a patient deemed legally incompetent, such as a child, is able to give assent to decisions about participation in the study, the Physician must offer the possibility for the child to give assent in addition to the consent of the parents/LAR. An "Assent form" will be provided and can be used when appropriate and when the child is capable of forming an opinion and assessing.

The requirement for obtaining informed consent from a patient's LAR is that the patient is unable to provide informed consent, and the process has been approved by the relevant IRB/IEC.

An informed consent form for the male patient's female partner must be signed before any data is collected from the patient's female partners i.e. in case of pregnancy.

FVIII genotype

Patients/parents or LAR will be asked if available result(s) of previous FVIII genotype test(s) or result from a genotype test performed during the patient's participation in the study may be documented. If agreed to, this should be documented on a separate page in the Informed Consent form.

10.2 Data handling

If the patient/parents 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 must 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, the Physician's current CV and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC or another relevant scientific body according to local legislation 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 or another relevant scientific body according to local legislation: unexpected serious adverse reactions, 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 or another relevant scientific body according to local legislation.

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 or another relevant scientific body according to local legislation. 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, substantial/non-substantial amendments to the protocol, reports on SARs, and the non-interventional study report according to national requirements.

11 Reporting of safety information

11.1 Safety information to be collected

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

- Serious adverse reactions (SARs)
- Adverse reactions (ARs)
- Adverse events of special interest (AESI)
- Pregnancies in female partners of male patients and reactions in the foetus or new born infant

If during this non-interventional study, a Novo Nordisk representative is informed of any other safety information (i.e. safety information which is not collected as part the systematic collection, as described in this protocol) and 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 other safety information by the physician should follow the same reporting process flow as for systematic collection. 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

Safety Information

All reports of adverse reactions occurring during the use of a Novo Nordisk product should be reported. In addition, any other information relevant to the safety of a Novo Nordisk product should be reported.

Adverse reaction

An adverse reaction (AR) is an untoward medical occurrence in a patient administered a product for which a causal relationship between the product and the occurrence is suspected, i.e. judged possible or probable (for definitions, see below) by the reporter.

An AR can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, which is considered related to the product. An AR is either a serious adverse reaction (SAR) or a non-serious adverse reaction(for definitions, see below). ARs also includes a worsening of a concomitant illness if the

worsening is considered related to the product. Pre-existing conditions and procedures where the reason for the procedure is known should not be reported as adverse reactions.

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 AR is a SAR, if the 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 or incapacity
- A congenital anomaly or birth defect
- Important medical reactions that may not result in death, be life threatening or require hospitalisation may be considered a serious adverse reaction when - based on 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 formation of inhibitory antibodies must always be considered an SAR. Suspicion of transmission of infectious disease via trial product must always be considered an SAR.

a) The term “life threatening” refers to a reaction in which the patient was at risk of death at the time of the reaction. It does not refer to a reaction which hypothetically might have caused death if it was more severe.

b) 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 and should therefore not be reported as adverse reactions including serious adverse reactions. Likewise, hospital admissions for surgical procedures, planned prior to study inclusion, are not considered adverse reactions or serious adverse reactions.

c) A substantial disruption of a patient’s ability to conduct normal life functions e.g. following the reaction or clinical investigation the patient has significant, persistent or permanent change,

impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life.

d) 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 reaction

An adverse reaction that does not meet a seriousness criterion 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/resolved - The patient has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient has signed the informed consent.
- Recovering/resolving - The condition is improving and the patient is expected to recover from the condition.
- Recovered/resolved with sequelae - The patient has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If the sequela meets a seriousness criterion, the adverse reaction must be reported as a serious adverse reaction Not recovered/not resolved - 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. Outcomes of other reported adverse reaction in a patient before he/she died should be assessed as "recovered", "recovering" or "not recovered". An adverse reaction with fatal outcome must be reported as a serious adverse reaction.
- Unknown - This term should only be used in cases where the patient is lost to follow-up.

Adverse event of special interest

An adverse event of special interest (AESI) is an event which, in the evaluation of safety, has a special focus. An AESI should be reported following the same reporting requirements and timelines as for serious adverse reactions (see next section) irrespective of the AESI fulfils a serious criterion.

The following are defined as AESIs in this study:

1. Medication errors concerning study product:
   - Administration of wrong drug
   - Wrong route of administration, such as intramuscular instead of intravenous
   - Administration of a high dose with the intention to cause harm (e.g. suicide attempt)
   - Administration of an accidental overdose that is, a dose which may lead to significant health consequences, as judged by the Physician, irrespective of whether any serious adverse reaction criteria is fulfilled or not

2. Inhibitor formation against FVIII:
   - Blood samples for measurement of FVIII inhibitors are recommended to be sent to the Central Laboratory selected by Novo Nordisk. A positive result (≥0.6BU for central laboratory analyses, or above the specific local laboratory reference range) should be reported by the Physician as an AESI and a repeated second test should be performed, preferably within 2 weeks. Also a positive result reported by a local laboratory only, should be reported as an AESI by the Physician. If the presence of inhibitors is confirmed by a second test this should be reported as a SAR, see section 11.3. If the second inhibitor test is negative this should be reported as a follow-up to the reported AESI, see section 11.4

3. Allergic reactions:
   - Including anaphylactic reaction as defined by Sampson et al 2006[24]. Allergic reactions included, but are not limited to any acute immunoglobulin E (IgE) mediated reaction or delayed type hypersensitivity (clinical signs may include various types of skin rashes) that do not meet the definition of anaphylaxis as described by Sampson et al[24]. All hypersensitivity reactions reported as an AESI will be followed up with a hypersensitivity follow-up form

Disease-related bleeding

Disease-related bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia etc.) evaluated by the Physician as part of the underlying disease should only be reported as adverse reactions or serious adverse reactions if they are evaluated by the Physician as related to study product.

However, fatal or life-threatening bleeding episodes must be reported regardless of relatedness. All bleeding episodes from Baseline (Visit 1) until End of study (Visit 3) will be captured in the diary and pCRF.

11.3 Collection and reporting of safety information

At each study related contact with the site, the patient should be asked about possible experienced adverse reactions since the last contact.

The physician must report to Novo Nordisk within the following timelines:

For SARs and adverse events of special interest.

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

Non-serious ARs, not fulfilling an adverse 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.

The Physician must complete and forward electronically, fax or courier copies of the applicable paper forms for systematically collected reactions within the above specified timelines of obtaining knowledge about the reaction(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. 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 form for each sign and symptom. However, if several symptoms or diagnosis occur as part of the same clinical picture only one Adverse Event form or Safety Information form can be used to describe all the serious adverse reactions . AESIs must always be reported to the department responsible for Global Safety on the Adverse Event form and the Safety Information form, irrespective of seriousness within the same timelines as for serious adverse reactions as described above.

Sponsor's assessment of expectedness is done according to the turoctocog alfa (rFVIII) 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 product related suspected unexpected serious adverse reactions (SUSARs) in accordance with the local requirements.

11.4 Follow-up of safety information

Follow-up information concerning previously reported SARs and AESIs 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 ARs 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 SARs, AESIs as well as non-serious ARs must be followed until the outcome of the reaction is "recovered/resolved", "recovered/resolved with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse reactions 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/resolving" or "not recovered/not resolved".

Cases can be closed with an outcome of "recovering/resolving" when the patient has completed his participation in the study and is expected by the Physician to recover. All other non-serious ARs must be followed until the outcome of the reaction is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the End of study (Visit 3), whichever comes first, and until all queries related to these ARs have been resolved. ARs on-going at time of death (i.e. patient dies from another adverse event/reaction) can be closed with an outcome of "recovering/resolving" or "not recovered/not resolved".

11.5 Collection and reporting of pregnancies in male patient´s female partners

In male patient's pregnant partners, and if acceptable by the IEC/IRB or another relevant scientific body according to local legislation, an effort should be made to get medical information related to a pregnancy in a patients pregnant partner. In this case an ad-hoc informed consent from should be

presented to the pregnant partner to collect any adverse reactions and serious adverse events in the foetus or new-born infant, i.e. from birth to 1 month of age.

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 a signed informed consent from the pregnant partner**. However, no specific timeline applies for collecting follow-up information. Adverse reactions and any serious adverse events experienced by the foetus or new-born infant should be collected and reported. Pregnancy information concerning pregnancies in male patients pregnant partners must be reported by the Physician on the study specific Pregnancy form. Reporting of adverse reactions or adverse events in foetus, new-born infant or in connection with the pregnancy must be done on the same forms as described for reporting of adverse reactions. It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the partner, foetus of new-born infant. The reporting timelines are as described for other adverse reactions and other serious adverse reactions.

11.6 Precautions

Please refer to the US PI, European SmPC or corresponding local prescribing information.

11.7 Safety committee

Internal Novo Nordisk safety committee

Novo Nordisk has an internal safety committee that performs on-going safety surveillance of the study product.

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.

One of the participating Physician's will be assigned the responsibility to review and sign the non-interventional Study Report (Signatory Physician).

12.1 Communication and publication

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 manuscripts for publication will be prepared in collaboration between Physician(s) and Novo Nordisk. Novo Nordisk will not suppress or veto publications; however Novo Nordisk reserves the right to postpone publication and/or communication for a short time 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.

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)[25].

12.1.2 Publications

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 http://www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct.

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[26].

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

For a multi-centre 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

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.

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

12.3 Progress reports and final report

A progress report will be provided to relevant competent authorities 24 months after first patient data entry. Additionally, an interim analysis covering all endpoints is planned to be performed with a data-cut 18 months after the first patient data entry. A final study report will be provided to

relevant competent authorities within 6 months of study completion and will be disclosed via the EU PAS register web portal presently hosted at the ENCePP homepage http://encepp.eu/.

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