Cover Page for Protocol and Statistical Analysis Plan

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Official title of study:	Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A
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16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN7008-3809

guardian™4

Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase:

3

Author:

Name: [redacted]
Department:Haemostasis, Clinical Operations FVIII

Table of Contents

Page

Table of Figures

Page

Table of Tables

Page

List of Abbreviations

AE	adverse event
BP	blood pressure
BU	Bethesda units
BW	body weight
CD4+	T-lymphocyte subtype
CI	confidence interval
CRF	case report form
CRO	contract research organisation
CTR	clinical trial report
CV	curriculum vitae
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
ED	exposure days
EDC	electronic data capture
EMA	European Medicines Agency
EoT	end of trial
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPFV	first patient first visit
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C
HE	health economics
Hemo-Sat P	haemophilia satisfaction questionnaire for parents
HIV	human immunodeficiency virus
IB	Investigator´s brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	international units
IV/WRS	interactive voice/web response system
IVIG	intravenous immunoglobulin
LAR	legally authorised representative
LOD	limit of detection
LPFV	last patient first visit
LPLV	last patient last visit
MESI	medical events of special interest
N8	Novo Nordisk's recombinant FVIII product
NOAEL	no observed adverse effect level
PK	pharmacokinetic
PRO	patient reported outcomes
PTP	previously treated patients
PUP	previously untreated patients
rFVIII	recombinant Factor Eight product
SAE	serious adverse event

T1/2	Pharmacokinetic half life
TMM	trial materials manual
TVP	trial validation plan
NNC 0155-000-004	Novo Nordisk code for N8 (investigational medicinal product)

1 Summary

Objectives and Endpoints

Primary Objective:

- To evaluate safety of NNC 0155-0000-0004 in paediatric previously untreated patients (PUP) [1] with haemophilia A

Key Secondary Objectives:

- To evaluate efficacy of NNC 0155-0000-0004 in treatment of bleeds in paediatric PUP with haemophilia A
- To evaluate preventive effect of NNC 0155-0000-0004 on bleeds in paediatric PUP with haemophilia A

Primary Endpoint:

- Incidence rate of FVIII inhibitors (≥0.6 BU/mL) will be evaluated from Visit 1 to End of Trial Visit/Visit 7

Key Secondary Endpoints:

- Haemostatic effect of NNC 0155-0000-0004 on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None will be evaluated from Visit 2 to End of Trial Visit/Visit 7
- Annualized bleeding rate will be evaluated from Visit 2 to End of Trial Visit/Visit 7

Trial Design

A multi-centre, multi-national, non-randomised, open-label, safety and efficacy trial in PUP with haemophilia A.

The patients will receive preventive treatment with NNC 0155-0000-0004 until they reach a minimum of 100 exposure days[2] (ED). The patients will stay in the trial for approximately 9-24 months, and the estimated total duration of the trial is approximately 55 months.

[1] Previously untreated patients refers to those patients who have never been treated with clotting factor products (except previous exposure to blood components)

[2] Exposure day (ED) is any day that the patient has been exposed to trial product. This will be used for reporting purposes.

The trial is designed in accordance with European Medicines Agency (EMA) draft guideline from July 2009 on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products.[1]

Trial Population

Approximately 120 PUP with severe (baseline level FVIII ≤1%) haemophilia A without inhibitors below 6 years of age in a non-bleeding state will be enroled to allow for at least 100 patients to complete the trial.

Key Inclusion Criteria:

- Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
- Male patients with congenital severe haemophilia A (baseline level FVIII ≤1%)
- Age < 6 years
- No prior use of purified clotting factor products (previous exposure to blood components is acceptable)

Key Exclusion Criteria:

- Known or suspected allergy to hamster protein or intolerance to trial product(s) or related products
- Previous participation in this trial defined as withdrawal after administration of trial product
- Congenital or acquired coagulation disorders other than haemophilia A
- FVIII inhibitor (≥ 0.6 BU/mL) at screening
- Ongoing treatment or planned treatment during the trial with immunomodulatory agents (e.g. intravenous immunoglobulin (IVIG)), routine systemic corticosteroids)
- Platelet count <50,000 platelets/µL

Main Assessments:

- Presence of FVIII inhibitors will be tested throughout the trial
- Evaluation of haemostasis, following NNC 0155-0000-0004 administration, as Excellent, Good, Moderate or None
- Consumption of NNC 0155-0000-0004 IU/kg body weight (BW) will be monitored throughout the trial.

Furthermore, physical examination, vital signs, laboratory tests, and recording of AEs and SAEs will be performed for safety assessments.

Patients with development of inhibitors

In case of inhibitor development, the clinical evaluation will take into account the inhibitor titre, and different patient and treatment characteristics.

Patients with inhibitor formation will be offered continued treatment with NNC 0155-0000-0004.

Surgery

Patients undergoing surgical procedures will receive NNC 0155-0000-0004 bleeding preventive treatment before, during and after surgery according to standard of practice of the participating site.

Trial Product

Each patient will receive bleeding preventive treatment with a dose of NNC 0155-0000-0004 (hereafter named N8) of 15-60 IU/kg BW. The exact dose of N8 is decided by the Investigator based on the patient's clinical profile. It is recommended to have at least one day between each N8 preventive dose.

The initial infusions will be administered at the investigational site, but after adequate instruction and practice the goal is to implement home treatment with intravenous (i.v.) injections given by the parent or a support person. N8 will be supplied as freeze dried powder to be reconstituted with a sterile sodium chloride solution for injection.

The dose for treatment of bleeds is decided by the Investigator but should be approximately 25-50 IU/kg in accordance with Guidelines for the Management of Haemophilia[2]. The maximum total daily dose of N8 for the treatment of bleeds is 200 IU/kg with a maximum dose per infusion of 100 IU/kg. This maximum limit does not apply during inhibitor treatment for patients with inhibitors.

2 Flow Chart

Table 2–1 Visit Flow Chart

Visit number	Screen. Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Unscheduled Visit
Visit window	NA	14 ± 7 d post V1	10^{th} -15^{th} ED	20^{th} -25^{th} ED	50^{th} -55^{th} ED	75^{th} -80^{th} ED	100^{th} -110^{th} ED	
PATIENT RELATED INFO / ASSESSMENTS								
Informed consent	●							
Inclusion/Exclusion Criteria	●	●						
Consent for FVIII genotype test	●							
Withdrawal Criteria		●	●	●	●	●	●	●b
Haemophilia treatment history	●							
Concomitant illnesses / Medical history	●							
Concomitant medication	●	●	●	●	●	●	●	●b
Demography	●							
Body measurements	●	●d	●d	●d	●d	●d	●	●b, d
FVIII genotype test		●f						
Details of haemophilia	●							
EFFICACY								
Bleed(s)		●	●	●	●	●	●	●b
SAFETY								
Adverse events	●	●	●	●	●	●	●	●b
Physical examination	●	●	●	●	●	●	●	●b
Vital signs	●						●	
FVIII activity	●a							
FVIII inhibitors	●a		●a	●a	●a	●a	●a	●a, b
FVIII trough level			●b	●b	●b	●b		●b
FVIII recovery								●b, c
FVIII (N8) half life (T1/2)								●b
Biochemistry	●						●	
Haematology	●						●	
OTHER ASSESSMENTS								

Visit number	Screen. Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Unscheduled Visit
PRO questionnaire	●		●				●	
HE assessment		●	●	●	●	●	●	●
Viral antibody test (if HIV, HBsAg and/or HCV status unknown)	●b							
T cells subset: CD4+	●h							
TRIAL MATERIAL								
N8 administration		●b	●	●	●	●		●b
Home treatment training		●						
Diary and Trial card dispensing and/or collection	●e	●e	●e	●e	●e	●e	●	●b
Review of patient diary and entry of data in eCRF			●	●	●	●	●	●b
Enrolment session in IV/WRS	●							
Completion session in IV/WRS							●	
Drug dispensing and accountability		●g	●	●	●	●	●g	●b
End of trial form							●	

a – minimum 48 hours washout period of N8 (or blood component products at Visit 1)

b – if applicable

c – mandatory to confirm clinical relevant inhibitors and inhibitor treatment success

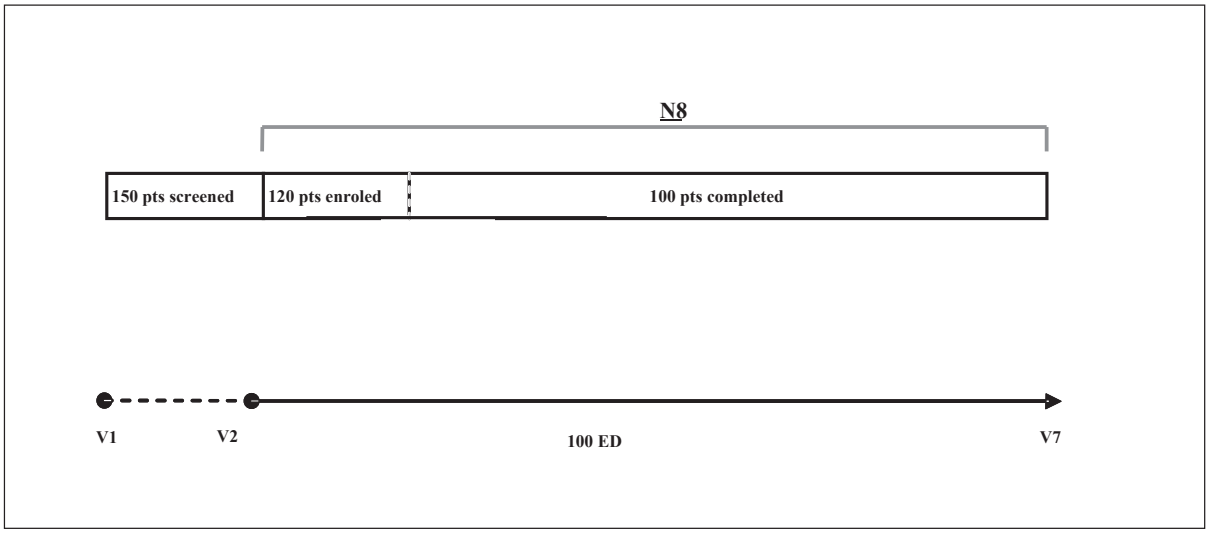
d – weight only

e – Visit 1 trial card only, Visit 2-6 diary card only

f – if not available, if allowed by law and after consent

g – Visit 2 dispensing only, Visit 7 accountability only

h – if HIV positive, last value of CD4+ T-cells (if available), or new cell count



150 patients are planned to be screened to get approximately 120 enroled, and 100 completers. Screening will be done at Visit 1, 14 ± 7 days prior to Visit 2. Preventive treatment with investigational product (N8) starts at Visit 2 (may start after the first two bleeds, see Section 5.3 and is completed at V7.

Figure 2–1 Trial Design

3 Introduction

In this document the Investigator refers to the individual overall responsible for the conduct of the clinical trial at a trial site.

3.1 Basic Information

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 hemophilia A is based on plasma level of FVIII, with patients <1% factor defined as severe; 1–5% as moderately severe; and 5-40% as mild.[3] 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 these factors, 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.[4]

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.[5] 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 most 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. This condition develops in about 30% of previously untreated patients (PUP) with severe haemophilia A following exposure to FVIII products.[6,7]

Substitution therapy with FVIII concentrates is the standard care of haemophilia A patients. N8 is a “third generation” recombinant FVIII similar to other marketed FVIII products of recombinant origin.[8]

The current document describes a clinical trial designed to demonstrate safety and efficacy of N8 used for both prevention (prophylaxis) and treatment of bleeds in PUP with haemophilia A.

3.1.1 Novo Nordisk' recombinant FVIII, N8

3.1.1.1 Pre-Clinical and Clinical Data

Novo Nordisk is developing a recombinant FVIII (rFVIII) product (N8) for treatment of haemophilia A. Please find current key pre-clinical and clinical data presented below.

For the full information on medicinal aspects, non-clinical data and quality of N8, please refer to the Investigator's Brochure (IB)[9].

N8 has been investigated in a single dose intravenously (i.v.) escalating dose trial and a 14 day daily i.v. toxicity and safety pharmacology trial including toxicokinetics in male cynomolgus monkeys. There were no adverse findings after a single dose of N8. Therefore the No Observed Adverse Effect Level (NOAEL) after the single dose is >5000 IU/kg, which was the highest dose tested.

In accordance with the EMA Guidelines[1,10], the clinical programme for N8 was initiated by a pharmacokinetic (PK) trial to document the essential PK characteristics of the product and to achieve initial safety information. The initial PK trial (NN7008-3522) has been designed as a comparative trial to the rFVIII product Advate® which is seen as the standard for recombinant FVIII treatments.

The First Human Dose and PK trial (NN7008-3522) comparing N8 and Advate® has been completed. The trial included a comparison of PK profiles after a single dose administration of 50 IU/kg BW of Advate® and N8 (in this order of dosing) to patients with severe haemophilia A without FVIII inhibitors and in a non-bleeding state. The age of the trial population was 13–54 years. The data from the 23 patients showed mean PK profiles of N8 comparable to Advate® within the defined limits of comparability. These limits are the standard criteria for bioequivalence. No development of FVIII inhibitor activity was detected in these 23 patients and no Severe Adverse Events (SAEs) were reported. For further information on PK results and safety of N8 please refer to the IB[9].

Currently three clinical studies are ongoing in the Novo Nordisk development program, the pivotal phase 3 trial (guardian™ 1), the paediatric trial (guardian™ 3) and the extension trial (guardian™ 2), and the accumulated clinical experience with N8 is now approaching 10000 exposure days (ED).

3.1.1.2 Risks and Benefits

FVIII products are used in the standard care of patients with haemophilia A. Although not similar in structure, the effect of N8 is similar to other marketed FVIII products which are of either plasma derived or recombinant origin. N8 is a recombinant FVIII molecule with a truncated B-domain manufactured without additional human or animal plasma proteins.[8]

It is expected that the safety profile of N8 will be similar to that of other third generation recombinant products.

The potential benefits to patients of N8 are more treatment choices and a globally expanded access to safe and effective treatment of haemophilia A.

According to the EMA Guideline[1] it is stated that treatment with FVIII products in a clinical trial including PUP should start when:

- data are available from 20 previously treated patients (PTP) below 12 years of age with at least 50 ED of the investigational product
- a minimum of 10 of these PTP must be below 6 years of age
- PK data from 26 patients aged 0-12 years is available, including minimum 13 patients below 6 years of age.

After completing the present trial (guardian™ 4), patients will be offered to continue with N8 in an extension trial, see Section 5.4. This serves to minimise the patients' need of switching to other FVIII products.

For further information on risk and benefits and safety of N8 please refer to the IB[9].

3.2 Rationale for the Trial

Globally there is still a vast unmet medical need for treatment of haemophilia A. Through the development of new rFVIII products, the possibility for haemophilia A patients to choose between different FVIII products is increased. New products may also contribute to securing product supply, thereby increasing the opportunity for improved treatment in haemophilia A.

In order to achieve marketing authorisation for this product, EMA draft guidelines on clinical investigation of plasma derived and recombinant FVIII products and review of relevant Food and Drug Administration (FDA) approvals of recombinant FVIII and FIX products[1,11,12] are applied in the clinical development programme (see further details in the IB[9]). According to the draft EMA guideline on clinical Investigation of new FVIII products, the clinical programme must include a paediatric trial in PUP demonstrating safety and clinical efficacy in at least 100 patients.

The guardian™ 4 trial is a prospective clinical phase 3a trial intended at demonstrating safety and efficacy of N8 in PUP < 6 years of age with severe haemophilia A. The trial will continue until at least 100 patients have received at least 100 ED to N8.

3.2.1 Clinical Development Programme

The overall clinical development programme for N8 uses a stepwise approach, following the EMA draft guideline[1], by evaluating experience in older and previously treated patients (guardian™ 1)

before investigating in younger children (guardian™ 3) and finally in previously untreated patients, the study population of the present trial (guardian™ 4).

In addition, Novo Nordisk is conducting a phase 3b (guardian™ 2) extension trial and is planning further trials to collect ongoing longer term efficacy and safety data.

4 Objective(s) and Endpoint(s)

4.1 Objective(s)

Primary Objective

- To evaluate safety of N8 in paediatric previously untreated patients (PUP) with haemophilia A

Secondary Objectives

- To evaluate efficacy and safety of N8 in treatment of bleeds in paediatric PUP with haemophilia A
- To evaluate preventive effect of N8 on bleeds in paediatric PUP with haemophilia A
- To evaluate patient reported outcomes (PRO) impact of N8 treatment
- To evaluate the health economic (HE) impact of N8 treatment

4.2 Endpoint(s)

Primary Endpoint

- Incidence rate of FVIII inhibitors (≥0.6 BU/mL)

Secondary Endpoint(s)

Safety Endpoints:

- Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during the trial period
- Incidence rate of clinically relevant inhibitors defined as an inhibitor titre (≥0.6 BU/mL) combined with a decreased recovery (<66% of expected level)
- Incidence rate of high-titre inhibitors defined as inhibitor titre ≥ 5 BU/mL

Efficacy Endpoints:

- Haemostatic effect of N8 on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None
- Annualized bleeding rate
- Number of N8 infusions required per bleed
- Total consumption of N8 per patient (prevention, treatment of bleeds and during surgery) per month and annualised value
- Consumption of N8 (IU/kg/bleed) per bleed
- Consumption of N8 (IU/kg/ months) for bleed prevention

Patient Reported Outcomes (PRO) and Health Economics (HE) End points:

- Change in total scores for parent reported treatment satisfaction
- Health resource utlilisation and caregiver burden associated with bleeds

5 Trial Design

5.1 Type of Trial

This is a multi-centre, multi-national, non-randomised, open-label, safety and efficacy trial in a paediatric population of PUP with severe haemophilia A. There will only be one treatment arm and no comparator.

The trial comprises 7 planned visits. Patients will attend a screening visit (Visit 1) in order to assess their eligibility. At Visit 2 eligible patient will receive their first dose and will be scheduled to attend for 5 more visits, if applicable. Details on the trial design can be found in Figure 2–1 and details on the individual visits can be found in Table 2–1.

The patients will be scheduled to receive treatment with N8 for at least 100 ED, which for the individual patient translates into a duration of approximately 9-24 months depending on the dose regimens (and bleeding pattern). The total duration of the trial is estimated to be approximately 55 months.

Patients who develop inhibitors during the trial may continue treatment with N8 and will follow an alternative visit schedule, see Section 5.3.4

If needed, the patients can undergo minor or major surgical procedures during the trial, see Section 5.3.3. Upon completion of the surgery the patient can continue preventive treatment as before the surgery.

5.2 Rationale for Trial Design

This trial design (Figure 2–1) will provide documentation of the safety and efficacy of N8 in prevention and treatment of bleeds in paediatric PUP with severe haemophilia A. The trial design is in accordance with EMA draft guideline[1] from July 2009 for the development of rFVIII products.

The dose levels and preventive treatment regimens chosen in this trial have been based on accepted clinical practices for treatment of the PUP population and are standard practise in US and EU[2]. In addition, the doses are chosen to reflect potentially higher clearance in children and in line with the recommendations from the International Society for Thrombosis and Haemostasis[13].

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[14,15]. Furthermore, the completed PK trial NN7008-3522 confirmed similarity of PK profiles and bioequivalence of Advate® and N8, see Section 3.1.1.1. Finally, the pivotal phase 3 trial (guardian™ 1) including at least 110 PTP above 12 years of age for at least 75 ED is planned to be completed before the initiation of the present trial.

The rationale for choosing a multi-centre, multi-national design is to ensure a sufficient patient pool and relevant ethnic diversity of paediatric patients as N8 is expected to be marketed globally.

5.3 Treatment of Patients

Approximately 120 patients are expected to be enroled into the trial in order to have 100 patients completing the trial (estimated drop out rate is 20%). For replacement of withdrawn patients, please refer to Section 6.5.

Patients will enter a bleeding preventive regimen as described below, see Section 5.3.1. Preventive treatment can be postponed until a maximum of two bleeding episodes have occurred.
For prevention one single bolus dose of N8 is administered intravenously (i.v.) at each administration day. N8 should preferably be administered in the morning. The maximum duration of treatment of a patient from first to last N8 administration is approximately 24 month.

In most cases, treatment will be given at home with i.v. self-injection by the parent/caregiver/support person. However, on days when the patient is attending a trial visit, the dose will be administered at the clinic by a health care professional.

For an overview of the treatment regimens, please refer to Table 5–1.

Maximum dose

The maximum total daily dose of N8 for the treatment of bleeds is 200 IU/kg with a maximum dose per infusion of 100 IU/kg. This maximum limit does not apply during immune tolerance induction treatment for patients with inhibitors.

Prohibited medication

Treatment with FVIII products other than the investigational product, N8, is not allowed.

5.3.1 Preventive Treatment and Dose Adjustment

The preventive treatment regimens are meant to reflect the different dosing regimens applied globally for initial and continued treatment of PUP. The recommended dose is 15-50 IU/kg BW once weekly at the start of preventive treatment, but higher and more frequent doses may be necessary depending on the clinical situation. The regimen should then be gradually increased towards 20-50 IU/kg BW every second day or 20-60 IU/kg BW three times weekly.[16]

The decision to initiate preventive treatment will be made by the Investigator and the child's parent or legal representative with due consideration for the child's own wishes (if they are capable to express these wishes).

Changes of the preventive regimen should be documented and rationale for the change should be provided in the eCRF (e.g. insufficient dose, increased body weight, improved feasibility of home treatment, or 'other').

The Investigator can perform FVIII trough level [3] assessments, e.g. as a basis for adjustment of dose. If the trough level is below the assay limit of detection (LOD) of the clinic, the dose can be adjusted at the discretion of the Investigator.

5.3.2 Treatment of Bleeds and Dose Adjustment

During preventive treatment, break-through bleeds may occur and require extra doses of N8. Treatment should be started as soon as a bleed is identified. Mild/moderate bleeds can be treated at home, whereas severe bleeds (see Section 8.3.1.1) must always be evaluated by the Investigator, preferably at the clinic. However, even with severe bleeds treatment should be started immediately at home if possible. All bleeds must be reported to the clinic within 24 hours from onset of the bleed.

The dose for treatment of bleeds should aim at providing a post injection level of FVIII of at least 0.50 IU/mL. The bleeding pattern of the individual patient, as well as low trough levels described above, should be considered in adjustments of the preventive dose and at the Investigator's discretion.

Number and frequency of doses during bleeds is decided by the Investigator based on local guideline or standard of practice. This dosing may be prescribed at a scheduled or unscheduled visit at the clinic or by telephone contact to the clinic.

Blood sampling to assess post injection levels may be undertaken during the visit to the clinic at the discretion of the Investigator, and such blood sampling can be analysed by the local laboratory.

If a haemostatic response of bleeds cannot be achieved (i.e. the bleed does not stop) after after 48 hours using doses of N8 up to 200 IU/kg BW per day, another FVIII product may be selected at the discretion of the Investigator. The use of other FVIII products will result in withdrawal of the patient from the trial.

Each administered dose (IU given and time of day) as well as efficacy in treatment of bleeds will be registered in the diary and in the eCRF.

5.3.3 Treatment during Surgery

Patients undergoing surgical procedures will receive bleeding prophylaxis with N8 according to standard of practice at the participating site. The post injection level of FVIII for major surgery is

[3] The trough level is defined as the lowest level of FVIII measured immediately prior to the dosing and is reported as (IU/mL). The trough level will be determined at the local laboratory.

recommended to be at least 0.50 IU/mL. In the recovery period the patient should be dosed with N8 according to local standard of practice or general guidelines for treatment of patients with haemophilia A.

Treatment with N8 during surgery will be included in the overall count of ED.

5.3.4 Treatment of Patients with Inhibitors

Several genetic factors, such as FVIII gene mutation type, family history of inhibitors, ethnicity, have been associated with inhibitor development in patients with severe haemophilia.[15] Management of patients with inhibitors includes the treatment of bleeding episodes by the use of by-passing agents (rFVII or activated prothrombin complex concentrates) and the permanent eradication of the inhibitor through immune tolerance induction therapy.

Patients who develop inhibitors, within this trial, will be offered continued treatment with N8. The duration of the inhibitor treatment will be at least 12 months from the time of diagnosis of inhibitor. For patients who develop inhibitors during their first year in the trial (within 12 months) the inhibitor treatment may continue until a total trial duration of 24 months.
It may also be decided by the Investigator and/or parent/legal representative to withdraw the patient.

All patients, who are diagnosed with inhibitor and continue treatment with N8 will follow an alternative visit schedule, see Section 8.1.5.2.

The initiation, dose level and dosing frequency of inhibitor treatment will be decided by the Investigator based on clinical evaluation and local standards, and it should be documented in the eCRF. Within this trial, 'inhibitor treatment' includes Immune Tolerance Induction (ITI) as well as smaller dose adjustments with low responding and/or clinical insignificant inhibitors.

Transient inhibitors are defined in this trial as inhibitors which disappear within 3 months after two positive inhibitor tests.

Inhibitor treatment success is defined as (not applicable for patients with transient inhibitors):

- two consecutive blood samples showing inhibitor level <0.6 BU/mL
- FVIII plasma recovery ≥66 % of expected level
- N8 T1/2 of ≥6 h after a 72 h N8 washout period[17]

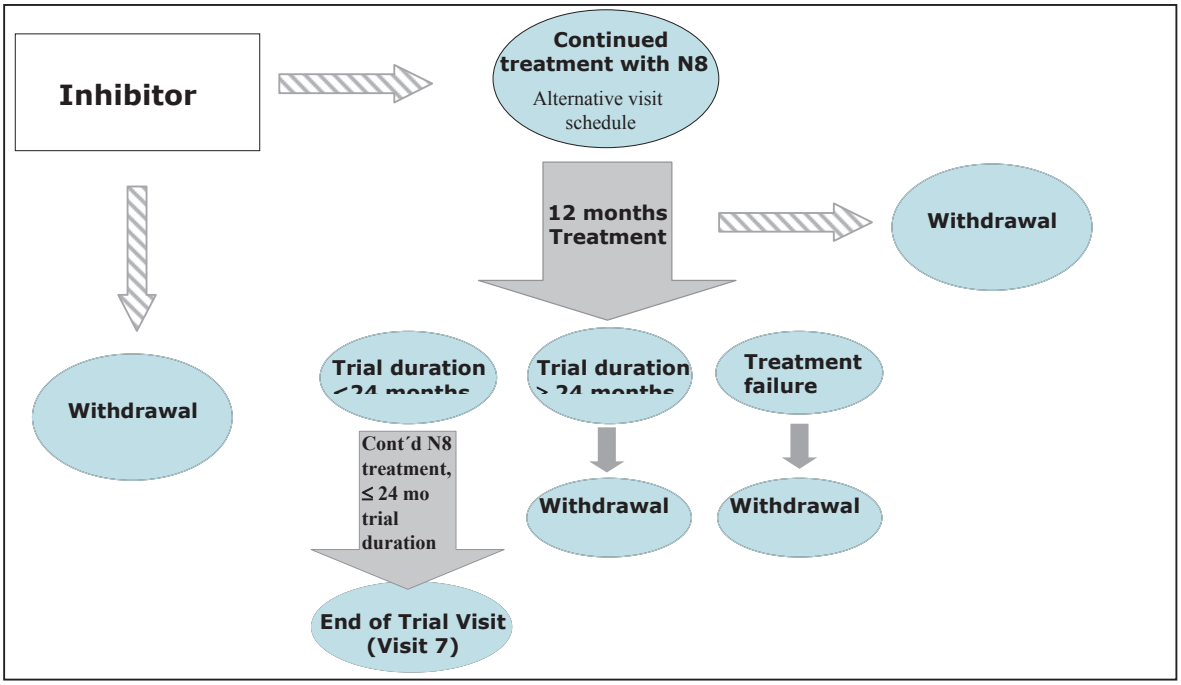
Inhibitor treatment failure is defined as persistence of inhibitor with no consistent decline of the inhibitor titer from peak level within 12 months of the inhibitor diagnosis. If inhibitor treatment failure occurs, the patient must be withdrawn.

After completion of the inhibitor treatment, the patient will be called to an End of trial Visit (Visit 7).

Treatment of bleeds with by-passing agents i.e. FVIIa or activated prothrombin complex concentrate (APCC), is allowed for patients who develop inhibitors.

Please see Section 8.2.2 for definition and diagnosis of inhibitor.

Details on inhibitor management can be found in Figure 5–1



Patients who develop inhibitor will be offered to continue N8 treatment. The regular visit schedule will stop and an alternative schedule will be commenced. After 12 months treatment, patients will fall into three categories; a) total trial duration < 24 months –treatment may continue up to 24 months, b) total trial duration ≥ 24 months – patients will be withdrawn, c) treatment failure as defined in Section 5.3.4 - patients will be withdrawn. Patients may also at any time be withdrawn at the discretion of the Investigator or the parents/legal representative, or on the patient´s on will.

Figure 5–1 Inhibitor Management

Table 5–1 Overview of Treatment Regimens

Trial product	Dose				
	Treatment	**Type**	**Total daily Doses, IU/kg**	**Frequency**	**Targeted level of FVIII**
rFVIII (N8)	Preventive	Individual	15-50	Once weekly	Local practice & guidelines
rFVIII (N8)	Preventive	Individual	20-50	Once every second day	Local practice & guidelines
rFVIII (N8)	Preventive	Individual	20-60	3 times weekly	Local practice & guidelines
rFVIII (N8)	Treatment of bleeds	Individual	Max 2x100	Investigator's discretion	>0.50 IU/mL
rFVIII (N8)	Surgery	Individual	Max 2x100	Investigator's discretion	>0.50 IU/mL* Local practice & guidelines
rFVIII (N8)	Inhibitor	Individual	Investigator's discretion	Investigator's discretion	NA

* Pre-surgery treatment

5.4 Treatment after End of Trial

It is expected that N8 will be granted marketing authorisation and is commercially available when the patients complete this trial. Where no marketing authorisation has been granted, each patient will be offered to continue in the phase 3b extension trial (guardian™ 2), see Section 3.2.1, as applicable by local regulation and rules.

5.5 Rationale for Treatment

Based on the clinical and preclinical results for N8 presented in Section 3.1.1.1, it is expected that dosing will be the same as that of currently marketed recombinant FVIII products and the same potency and efficacy is expected for N8.

Please refer to the IB[9] and any updates hereof for further preclinical and clinical data.

6 Trial Population

6.1 Number of Patients to be Studied

Countries planned to participate: Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Greece, Hong Kong, Japan, South Korea, Malaysia, Romania, Russia, Serbia, Spain, Thailand, Turkey, UK and US.

Planned number of patients to be screened (i.e. documented informed consent):	150
Planned number of patients to be started on trial product(s):	120
Planned number of patients to complete the trial:	100
Planned number of trial sites:	80

6.2 Inclusion Criteria

1. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
2. Male patients with congenital severe haemophilia A (FVIII level ≤1%)
3. Age < 6 years
4. No prior use of purified clotting factor products (previous exposure to blood components is acceptable)

6.3 Exclusion Criteria

1. Known or suspected allergy to hamster protein or intolerance to trial product(s) or related products
2. Previous participation in this trial defined as withdrawal after administration of trial product
3. Congenital or acquired coagulation disorders other than haemophilia A
4. FVIII inhibitor (≥0.6 BU/mL) at screening
5. Ongoing or planned treatment during the trial with immunomodulatory agents (e.g. intravenous immunoglobulin (IVIG)), routine systemic corticosteroids)
6. Platelet count <50,000 platelets/µL
7. Any disease or condition which, judged by the Investigator, could imply a potential hazard to the patient, interfere with the trial participation or trial outcome including renal and/or liver failure
8. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents and/or legal representatives and child
9. The receipt of any investigational product within 30 days prior to inclusion in this trial

Patients who are non-compliant with any of the eligibility criteria, but included in the trial, should be withdrawn immediately. If extraordinary circumstances speak in favour of maintaining the

patient in the trial then this is only acceptable if justified and approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and if the regulatory authorities are notified according to local requirements.

6.4 Withdrawal Criteria

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

The patient may be withdrawn from the trial at the discretion of the Investigator or the sponsor due to a safety concern or if judged non-compliant with trial procedures.

A patient must be withdrawn if the following applies:

1. Haemostasis not achievable with N8: The bleed cannot be controlled after 48 hours using recommended doses of N8
2. Allergy/Anaphylaxis to the trial product
3. Treatment with FVIII products other than N8
4. For inhibitor patients – inhibitor treatment failure with N8 treatment (refer to Inhibitor Treatment Section 5.3.4).

Withdrawn patients should be scheduled for an End of Trial Visit (Visit 7) as soon as possible and within 28 days after the last N8 administration, and preferably prior to initiation of treatment with another FVIII product. The Investigator should aim to conduct all procedures as specified in the protocol for Visit 7.

6.5 Patient Replacement

Withdrawn patients may be replaced to ensure that 100 patients complete the trial with at least 100 ED. Assuming a drop-out rate of 20%, it is estimated that 120 patients must be started on N8 to obtain the 100 completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate.

6.6 Rationale for Trial Population

The inclusion and exclusion criteria are in line with previously studied recombinant FVIII products, reflect the general haemophilia A paediatric population that will receive N8 when marketed, and address the requirements of the EMA/CHMP draft guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products[1]. According to the EMA guideline, the clinical programme must include a paediatric trial in PUP demonstrating safety and clinical efficacy in at least 100 patients.

Rationale for Inclusion Criteria:

- Criterion no.1 is included in accordance with ICH-GCP[18].
- Criterion no. 2 is included to select patients who will potentially benefit the most from treatment with N8.
- Criteria nos. 3 and 4 are included to target the specific population required to meet the objectives of this trial.

Rationale for Exclusion Criteria:

- Criterion no. 1 is chosen to protect patient's safety
- Criterion no. 2 is chosen to exclude patients treated with N8 (FVIII product), who are not PUP anymore
- Criteria nos. 3 and 6 are chosen to exclude patients with endogenous abnormalities of the coagulation system other than haemophilia
- Criterion no. 4 is chosen to exclude patients with FVIII inhibitors before starting treatment with N8
- Criterion no. 5 is selected to minimise confounding effects of other drugs and treatments on the patient's coagulation and immune system
- Criteria nos. 7 and 8 are chosen to avoid exposing fragile patients to a new compound
- Criterion no. 9 is included in accordance with ICH-GCP

Rational for Withdrawal Criteria:

- Criteria nos. 1, 2 and 4 are included to protect the patient's safety.
- Criterion no. 3 is selected not to confound the effects of the investigational product.

7 Trial Schedule

Planned duration of recruitment period (FPFV-LPFV): 42 months

Planned date for FPFV: December 2011

Planned date for LPFV: June 2015

Planned LPLV: July 2016

The end of the clinical trial is defined as last visit of the last patient.

Planned completion of clinical trial report (CTR): Q3 2016

Protocol information for this trial will be subject to public disclosure at external web sites (www.clinicaltrials.gov and www.novonordisk-trials.com) according to international regulations e.g. the International Committee of Medical Journal Editors (ICMJE)[19] the Food and Drug Administration Amendments Act (FDAAA)[20] - as reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure. In Japan the trial data will be registered at Clinical Trials Information/JapicCTI.

8 Methods and Assessments

8.1 Visit Procedures

8.1.1 Overall Procedures, Assessments and Methods

Specific procedures, assessments and methods for the scheduled visits are described in the sections below, and the list of assessments for each visit is presented in the flow chart, see Table 2–1.

8.1.2 Visit 1, Screening Visit

For all patients with a signed Informed Consent Form (ICF), the Investigator will, through IV/WRS, assign a unique 6 digit patient number. The patient number is maintained throughout the trial and continuously maintained should the patient be enroled in the extension trial, see Section 5.4.

The patients will be registered as enroled via telephone or internet by use of the IV/WRS.

Patients should withhold and stop any anti-haemophilic treatment with blood components at least 48 hours prior to Visit 1.

At Visit 1 the patients' characteristics will be obtained and eligibility will be assessed. If the inclusion and exclusion criteria are fulfilled, the screened patient will be scheduled for Visit 2.

According to local practice, the Investigator should keep a list(s) of participating patients e.g. ICF signed, screened and/or enroled etc.

In case a patient is evaluated as not eligible for trial participation by the Investigator, the Screening Failure form in the eCRF must be completed. A screening failure call must also be made to the IV/WRS, see Section 10

As a minimum the following should be recorded for screening failures:

- existence of patient (date of birth, ICF-/Screening-/Enrolment List)
- informed consent
- confirmation of participation in the trial (i.e. notes in medical records, IV/WRS screening confirmation, ICF)
- AEs or sign and symptoms (description and duration)
- reason for screening failure.

Patients will also be provided with a trial card stating that they are participating in the trial. This will include the contact addresses and telephone numbers for the clinical center where the patient will be seen.

8.1.3 Visit 2

The visit will be scheduled 14 ± 7 days after Visit 1.

Patients should withhold and stop any anti-haemophilic treatment with blood components at least 48 hours prior to Visit 2.

The main purpose of Visit 2 is to administer N8 for the first time, if applicable, to eligible patients.

Another important purpose is to provide the patient and care giver training for home treatment.

The assessments to be performed at Visit 2 are listed in Table 2–1

8.1.4 Visit 3 to Visit 7

Visits 3 to 7 will be scheduled based on the number of accumulated ED. The planned visit intervals and the visit assessment are listed in Table 2–1.

Patients should withhold treatment with N8 at least 48 hours prior to the visits.

Visit 7 should also be completed for withdrawn patients.

8.1.5 Unscheduled Visit

The unscheduled visit can be performed after the enrolment into the trial until the End of Trial Visit (Visit7) as either telephone visit or a site visit. Unscheduled visits will also be performed during inhibitor treatment, see Section 8.1.5.2, and surgery procedures, Section 8.1.5.1. Please find listed in Table 2–1 the assessments, which should be performed at an unscheduled visit. The date and time of the visit should be recorded in the eCRF.

8.1.5.1 Surgery Visit

Patients undergoing surgery will continue the regular visit schedule, but additional visits may be performed in the peri-operative period as decided by the Investigator. Surgery visits will be documented as unscheduled visits.

For planned surgery patients, the following data should be collected:

- Type of surgery
- Date of surgery
- N8 doses and dosing schedule 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.

Emergency surgery is allowed in this trial if adequate supply of N8 is available to ensure haemostasis and wound healing. The Investigator will decide which trial assessments to be made in an emergency situation.

8.1.5.2 Inhibitor Treatment Visit

All patients, who develop inhibitors will follow an alternative visit schedule prescribed by the Investigator according to local standard of practice, irrespective of whether inhibitor treatment is being initiated or not, see Section 5.3.4. Monthly visits are recommended, at least initially, for patients who develop inhibitors.

These visits will be recorded as unscheduled visits and the following assessments should be performed.

- Assessment of withdrawal criteria
- Concomitant Medication
- Body measurements (weight)
- Bleeds including classification and site of bleeds
- Adverse Events
- Physical examination
- Collect and review diary
- Diary dispensing
- Dispensing of the product
- Drug accountability
- Administration of N8
- FVIII inhibitor test

Recovery test is required at the time of inhibitor diagnosis and for the confirmation of inhibitor treatment success, see Section 8.2.3.

Measurement of N8 pharmacokinetic plasma (T1/2) will be performed to confirm inhibitor treatment success, see Section 8.2.4.

When the last inhibitor treatment visit has been performed, the patient will be called to an End of Trial Visit (Visit 7).

8.2 Assessments for Safety

8.2.1 Adverse Events

Monitoring of Adverse Events will be performed from the first trial-related activity to the End of Trial Visit (Visit 7) and at potential follow-up visits, according to procedures described in Section 12.

8.2.2 FVIII Inhibitors

All patients will be examined regularly for the development of FVIII neutralising antibodies (inhibitors). The tests will be performed at Visit 1 and Visits 3-7. Additional laboratory assessment for FVIII neutralising antibodies can be done if inhibitor development is suspected during the course of the trial, or if more frequent testing is mandated i.e. during unscheduled visits.

Detection of FVIII inhibitors will be carried out at a central laboratory using the Nijmegen modified Bethesda[21] assay. A positive inhibitor test is defined as ≥ 0.6 Bethesda Unit (BU)/mL.

In the event of a positive inhibitor test, the patient should attend an (unscheduled) visit within a week after the result is available to take a blood sample for a confirmatory test.

- The diagnosis of inhibitor is made if the patient has been tested positive for inhibitors (BU >0.6/mL) at two consecutive tests (central lab), sampled preferably within 2 weeks. Inhibitors will be classified as low titre (≥0.6 BU/mL but <5 BU/mL), or high titre (≥5 BU/mL), and as clinically significant (recovery <66% of expected level, assessed at inhibitor diagnosis at the time of the confirmatory inhibitor test).

Blood sampling for FVIII inhibitor test should be performed at a trough level, i.e. with a minimum of 48 hours N8 treatment washout period.

In case of inhibitor development, a clinical evaluation will be performed as described in Section 18.2.2.

All per protocol inhibitor laboratory samples are to be analysed in the central laboratory, and only these results will be used in the trial data analysis.

For storage, handling, dispatch, and disposition of samples analysed for FVIII inhibitors at the central laboratory, please refer to detailed guidance in the Laboratory Manual.

8.2.3 FVIII Recovery

Recovery is the FVIII plasma level recorded 30 minutes after trial product administration and reported as [IU/mL]/[IU/kg]. Recovery assessment is mandatory at inhibitor diagnosis to identify clinical relevant inhibitors (see Sections 8.2.2). Likewise, recovery assessment is necessary when establishing inhibitor treatment success (see Sections 5.3.4). Additional recovery assessments may be requested at the discretion of the Investigator.

Samples for FVIII recovery will be sent to the central laboratory for analysis.

8.2.4 FVIII (N8) Pharmacokinetic T1/2

The T1/2 of N8 will be based on FVIII activity and the procedures should be according to local guidelines. The N8 washout period should be at least 72 hrs. It is recommended that at least three time points for blood sampling is chosen, and it should be within 48 hrs of N8 administration. The samples should be sent to the central lab for analysis.

The N8 T1/2 will be used to evaluate inhibitor treatment success, see Section 5.3.4.

8.2.5 FVIII Trough Level Assessment

The Investigator can at his/her discretion perform trough level assessments at Visit 3-6. 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.

Trough levels need only to be recorded in the eCRF if it is the reason for dose adjustments.

8.2.6 Haematology

The assessment will be performed at Visit 1 and Visit 7 according to practice of the local laboratory and includes:

- Haemoglobin (mmol/L)
- Red cell count (erythrocytes) ($x10^{12}$/L)
- Mean corpuscular volume (MCV) (fL)
- Packed cell volume (haematocrit)(PCV)(%)
- Mean corpuscular haemoglobin (MCH) (fmol/L)
- White blood cell count (leucocytes) ($x10^{9}$/L)
- Differential white blood cell count (%)
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils
- Platelet count (thrombocytes) ($x10^{9}$/L)

It is recommended that the haematology values are reported in the above listed units. However, in the eCRF it will be possible to enter values in other units accepted by Novo Nordisk.

8.2.7 Biochemistry

The assessment will be performed at Visit 1 and Visit 7 according to practices of the central laboratory and includes:

- Sodium (mmol/L)
- Potassium (mmol/L)

- Urea (mmol/L)
- Creatinine (micromol/L)
- Total Proteins (g/L)
- Albumin (g/L)
- Total Bilirubin (micromol/L)
- Cholesterol and LDL (mmol/L)
- Chloride (mmol/L)
- Total calcium (mmol/L)
- Aspartate aminotransferase (AST) (IU/L)
- Alanine aminotransferase (ALT) (IU/L)
- Gamma-glutamyl Transferase (GGT) (IU/L)
- Alkaline phosphatase (ALP) (IU/L)

8.2.8 Laboratory Tests

8.2.8.1 General Considerations

The collection of all blood samples for the laboratory tests will be performed before administration of N8, except the recovery samples which must be collected 30 minutes after administration of N8.

Please find below a summary of the assessments and procedures for the local and central laboratories, respectively.

The laboratory equipment used by central and local laboratories may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the trial database, but may be reported to the Investigator according to specifications in the laboratory standard operating procedures and requirements. The additional data should be specified in the trial specific laboratory manual. The Investigator must review all laboratory results for concomitant illnesses and adverse events and report these according to this protocol.

8.2.8.2 Local Laboratory Tests

Assessments of haematology and FVIII trough levels will be done at the local laboratory as per standard of practice at the participating site. Laboratory results from the local laboratory will be recorded in the eCRF.

If the local laboratory is used for analysis of inhibitors and/or FVIII recovery, duplicate sample must also be sent to the central laboratory for analysis. The data from the central laboratory will then be used in the official analysis.

An Investigator must sign, date and categorise the local laboratory results. Categorisation will be either “normal”, “out of normal range, not clinically significant” or “out of normal range, clinically

significant". Clinically significant findings must be recorded as concomitant illness (blood samples during visit 1) or as an Adverse Event (blood samples taken at visit 2-7, unscheduled visits and potential follow-up visits). Abnormalities should only be recorded as AEs if not present or worsened from baseline/previous assessments. Laboratory results should be signed and dated. Laboratory reports (laboratory result) are considered source data and should be kept in patient file for source data verification (carried out by the monitor).

The local laboratory must be certified in performing laboratory tests and assessments as requested in this trial.

Storage, handling, and disposition of samples analysed at local laboratories, will be performed according to local laboratory procedures.

8.2.8.3 Central Laboratory Tests

A central laboratory will analyse and report all laboratory safety tests related to biochemistry, viral antibody assessments, FVIII inhibitor and FVIII activity tests performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained.

A one-stage FVIII clotting activity assay and a two-stage chromogenic assay will both be used to assess the FVIII activity at the central laboratory.

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 trial.

For descriptions of assay methods, particulars of instrumentation, procedures for obtaining samples/specimens, who will perform the assessments and the storage, handling conditions, and disposition of specimens, please refer to the Laboratory Manual.

8.2.8.4 Blood Sampling Volume

Blood samples for laboratory analysis of efficacy, safety and other parameters will be drawn as described for the individual visits. The total volume of blood drawn during the trial will be approximately 30 mL per patient. The blood volume collected from the patient for all tests should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days (see Appendix B). This is in accordance with European regulatory guidelines (Directive 2001/20/EC)[2,22]. During visits, when samples are taken, blood samples will be aliquoted to meet above mentioned requirements. Instructions will be provided in the Laboratory Manual.

8.2.9 Physical Examination

Physical examination should be performed at Visits 1-7 according to practice at the participating clinic including assessments of the following:

- Head, ears, eyes, nose, throat, and neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous systems
- Skin

Any changes in the examinations between the visits which fulfil the criteria of an Adverse Event must be recorded as such, see Section 12.1.

8.2.10 Vital Signs

Vital signs will be assessed at Visit 1 and Visit 7 and includes:

- Body temperature (assessed by measuring inner ear temperature or using an oral digital thermometer)
- Respiratory rate (resp./min.)
- Pulse: preferably supine
- Blood pressure (BP): preferably supine

BP (systolic and diastolic) and pulse rate will be measured according to local practice at the clinic; preferably after the patient has rested comfortably for at least 3 minutes.

Any changes in the vital signs between the two visits which fulfil the criteria of an Adverse Event must be recorded as such, see Section 12.1.

8.3 Assessments for Efficacy

8.3.1 Bleeds

During the entire trial period all bleeds treated with N8 will be entered in either the eCRF or in the patient's diary. For mild/moderate bleeds, the patient or caregiver must fill in the diary and at visits the diary data will be transcribed into the eCRF by trial site personnel. For severe bleeds (see definition in Section (8.3.1.1) the Investigator, or designated site staff, must be contacted without delay to prescribe the appropriate treatment and any follow-up procedures. It is recommended that these direct instructions are followed by, or given at, an unscheduled visit to the clinic. Documentation about the severe bleed should be entered in the medical records and eCRF by the trial personnel.

All bleeds should be reported to the clinic within 24 hours. However, if there is no haemostatic improvement within 8 h after one dose, immediate contact should be taken with the Investigator/site staff for advice.

Joint bleeds are either categorised as target joint or non-target joint bleeds. Target joint bleeds 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.[23]

For bleeds the following will be recorded in the patient diary:

- Date and time of onset of bleed
- Location of the bleeding (central nervous system (CNS), haemarthrosis (joint), gastrointestinal, subcutaneous, muscle, mucosal or other)
- Classification of bleed (spontaneous, traumatic)
- Haemostatic drug used for treatment (N8 or other drug if haemostasis cannot be achieved, i.e. bleed cannot be controlled with N8)
- Dose(s) and Time(s) of administration
- Other therapy used (compression/other)
- Date and time of stop of bleed
- The bleeds must be categorised as mild/moderate or severe, see Section 8.3.1.1.
- Clinical evaluation of the haemostasis (Excellent, Good, Moderate or None), see Section 8.3.1.2

8.3.1.1 Definition of Severity of Bleeds

Mild/Moderate: minor bleeds which are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal or subcutaneous bleeds

Severe: Major bleeds that require hospitalisation. All internal head and neck bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) will also be reported as severe and entered in the eCRF. All mild or moderate bleeds which are ongoing 24 hours after start will be redefined as severe.

8.3.1.2 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 an 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.

8.3.1.3 Bleed Classification

- Spontaneous
- Traumatic
- Re-bleed

Re-bleeds will be reported by the trial statistician based on the diary data. Re-bleed is defined as when after an initial period of improvement, worsening of bleeding site conditions either on treatment or within 72 hours after stopping of treatment (therefore, a new bleed is considered occurring later than 72 hours after stopping of treatment).

8.4 Other Assessments

8.4.1 FVIII genotype testing (not applicable to Brazil)

At Visit 2, all patients/parents/legally authorised representative (LAR) will be asked about documentation of previous FVIII genotype tests. If not available or if it needs to be re-tested FVIII genotype testing will be offered as allowed by local law. Investigator, parent(s) or LAR have the right to refuse to provide patient's FVIII genotype documentation or to refuse genotyping. This will not stop the patient to continue participation in the remainder of the study.

Applicable for Japan only: If documentation of the patient´s genotype already exists, the patient is offered to provide his data for the trial. If no previous data exists and genotyping consent is obtained, FVIII genotype analysis is performed at the laboratory in Bonn, Germany, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than FVIII. Samples will be disposed appropriately after the test and all test results are kept strictly confidential.

8.4.2 Viral Antibody Information

At Visit 1 status of the following viral infections are assessed.

• HBsAg and/or anti-HCV antibodies if status is unknown or the Investigator considers there is an indication to test

• HIV 1 & 2 antibodies if status is unknown or the Investigator considers there is an indication to test.

If the patient is HIV positive the last value of CD4+ T-cells, and date of test, should be recorded. If not available a new cell count is required.

8.4.3 Demography

Following information will be collected at Visit 1 as allowed by local law.

- Date of birth
- Ethnicity
- Race

8.4.4 Body Measurements

Weight and height will be measured at Visit 1 and 7, for Visit 2-6 only weight is measured.

- Weight, light clothing only (kg/lbs) and without shoes

- Height without shoes (cm/inches)

8.4.5 Diaries

Diaries will be dispensed at Visits 2-6, and the following data will be collected:

- Treatment
  - Preventive or treatment of bleed
  - N8 dose
  - Date and time of dose administration
- Bleeds
  - Onset of bleed (date and time)
  - Stop of bleed (date and time)
  - Location of bleed
  - Classification of bleed, see Section 8.3.1.3.
  - Evaluation of haemostasis, see Section 8.3.1.2.
  - Other therapy used
  - Severity of bleed, see Section 8.3.1.1.

Trial product administration performed at the clinic by the Investigator will not be entered into the diary, but in the eCRF.

8.4.6 Medical and Haemophilia History

8.4.6.1 Medical History

Complete medical history is to be obtained during the Screening Visit (Visit 1) including other coagulation-related diseases. In the event that a diagnosis is unknown the description of symptoms will be recorded. All chronic illnesses should be recorded.

The following organ systems should be considered in medical history (if recorded in the medical charts):

- Central and peripheral nervous system
- Eyes-ears-nose-throat
- Cardiovascular
- Respiratory
- Endocrine-metabolic
- Musculoskeletal
- Dermatologic
- Gastrointestinal system
- Genitourinary system
- Haematopoietic-lymphatic including blood type parameter (O type or non-O) as allowed by local law and if available

The following conditions should be assessed:

- Drug allergies or sensitivities
- Non-drug allergies

8.4.6.2 Details of Haemophilia

Following information about the patients haemophilia to be obtained during the Screening Visit (Visit 1).

- Diagnosis of haemophilia A (date)
- Classification of haemophilia A and FVIII level (%)
- Underlying gene defect (if known)
- History of relatives with haemophilia A (as recalled by parent/guardian) including inhibitors

8.4.6.3 Haemophilia Treatment History (if applicable)

Following information about the patients haemophilia treatment to be obtained during the Screening Visit (Visit 1).

- Treatment
  - Any treatment with blood products
  - Number of bleeds prior to screening visit
  - Number of bleeds into the same joint prior to the screening visit

8.4.7 HE and PRO data

In this trial HE and PRO data will be collected. The HE data include assessments of resource utilization and patient/caregiver burdens associated with bleeds. The PRO data use a validated questionnaire to assess treatment satisfaction, Hemo-Sat.

Hemo-Sat is a treatment satisfaction survey for parents/caregivers (the P version). Dimensions measured include ease and convenience, efficacy, burden, specialists/nurses, centre/hospitals, general satisfaction.

The questionnaire was originally developed in UK English and has been translated and linguistically validated into other languages. However it might not be available for all countries. The questionnaire is to be filled in at Visits 1, 3, and 7, preferably before any other trial related procedures.

8.5 Patient Compliance

Assessment of patient compliance with the protocol procedures for determination of the continuation of the trial will be done by the Investigator. Full compliance with protocol procedures is expected in this trial.

Failure of compliance with scheduled visits and trial product administration may result in withdrawal in accordance with the protocol withdrawal criteria, see Section 6.4.

Compliance with N8 treatment should be addressed at each visit. If the Investigator considers the bleeds a patient experiences are due to exceeding the intended time between doses, the Investigator must retrain the patient/parent/caregiver.

9 Trial Supplies

9.1 Trial Products

The following products will be supplied by Novo Nordisk:

- N8, 2000 IU/vial
    - Sterile, freeze-dried powder
    - To be reconstituted with 4.3 mL of 0.9% Sodium Chloride (NaCl) for injection
    - After reconstitution each vial contains 500 IU/mL of N8
    - The reconstituted solution is colourless and clear/almost clear
- N8, 250 IU/vial
    - Sterile, freeze-dried powder
    - To be reconstituted with 4.3 mL of 0.9% Sodium Chloride (NaCl) for injection
    - After reconstitution each vial contains 62.5 IU/mL of N8
    - The reconstituted solution is colourless and clear/almost clear
- Sodium chloride 0.9%, 10 mL

N8 must not be further diluted, added to or mixed with other material.

A leaflet describing the reconstitution procedure will be translated into local language(s) and handed over to the patient together with the trial product.

Detailed instructions regarding reconstitution of N8 will be provided in the Trial Materials Manual (TMM).

9.2 Packaging and Labelling of Trial Products

Labelling will be in accordance with Annex 13[24], local law and trial requirements.

The trial products will be packed open labelled.

Each box will have a Dispensing Unit Number (DUN) for drug accountability and traceability.

9.3 Storage of Trial Products

In use time of the reconstituted N8 is 24 hours at 2-8 °C or 4 hours at 9-25 °C.

- N8
    - Store at 2-8°C

- Protect from direct sunlight
- Do not freeze

- NaCl
  - No special storage requirements.

The Investigator must ensure the availability of proper storage conditions and monitor and record and evaluate the temperature. A temperature log for daily temperature recording (actual, min., and max. temperature on working days) must be kept at the Investigator site.

The Investigator must contact the Monitor in case of deviation outside the acceptable temperature range during storage at the site.

Returned trial product(s) (partly used or unused including empty packaging material) must be stored separately from non-allocated trial product(s). Returned trial products can be stored at room temperature.

9.4 Dispensing and Drug Accountability of Trial Products

The IV/WRS will allocate a trial product DUN to the patient at each dispensing visit. The correct DUN must be dispensed to the patient.

- No trial product(s) should be dispensed to any person not enroled in the trial.
- Unused trial product must be stored separately from used trial product.
- Once a patient is dosed, all vials (used, partially used, unused, returned, and lost/damaged) must be recorded in the IV/WRS Drug Accountability module.

Trial product will be dispensed at the visits depicted in the flow chart, see Table 2–1. The patient is required to return both used and unused vials at the next visit to the clinic or at the End of Trial Visit, as appropriate.

The Investigator or delegated person e.g. trial nurse will perform drug accountability in the IV/WRS Drug Accountability module.

All trial products must be retained for inspection by the Monitor. The Monitor will, upon completion of drug accountability, arrange for the destruction of used, unused, and broken vials of the supplied trial product.

9.5 Trial Product Administration

The trial product should be administered as a slow bolus i.v. injection over approximately 2 min. (from start to completion of injection) for all trial product administrations.

These administrations will primarily be performed at home. All patients and/or parents/caregivers will be instructed by Investigator how to handle home administration before first dose.

9.6 Auxiliary supply

All auxiliary supply used in this trial such as syringes, butterflies, sterile swaps etc. will be provided by Novo Nordisk.

10 Randomisation, Breaking of Blinded Codes and Interactive Voice/Web Response System (IV/WRS)

10.1 Randomisation

NA

10.2 Breaking of Blinded Codes

NA

10.3 Interactive Voice/Web Response System (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time by the internet. Some sessions may be available through a toll-free telephone number. Accessibility to the IV/WRS must be restricted to and controlled by authorised persons. For a minimum, the system will be used for enrolment of patients, dispensing of trial product, controlling of expiry date of trial product, ordering of trial product, drug accountability and screening failure data and withdrawal information. An IV/WRS user manual will be provided to the site.

11 Concomitant Illnesses and Concomitant Medication

Definitions:

Concomitant illness: any illness that is present at the start of the trial (i.e. at the first visit).

Concomitant medication: any medication, other than the trial product(s), that is taken during the trial, including the screening and run-in periods. Vaccinations must also be recorded as concomitant medication.

(Vaccinations will be included in the evaluation of risk factors for inhibitor development, see Section 18.4)

Details of all concomitant illnesses and medication must be recorded at trial entry (i.e. at the first visit). Any changes in concomitant medication must be recorded at each visit. If a change is due to an AE this must be recorded and reported according to section 12. If the change influences the patient's eligibility to continue in the trial the Monitor must be informed.

The information collected for each concomitant medication includes (at a minimum) start date, stop date or continuation and indication.

The following concomitant medications are not permitted during the course of this trial:

- Treatment with FVIII concentrates other than N8, see Section 6.4.

In case these medications are used during the trial, the patient must be withdrawn.

12 Adverse Events

12.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

An AE can also be a clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity, and is of a severity that requires active management (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

A worsening in concomitant illness must be recorded as an AE. A worsening of an ongoing AE should be reported on a new AE form by making a new assessment for seriousness and/or severity.

The following should not be recorded as AEs:

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

Serious Adverse Event (SAE):

A SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience [a)]
- In-patient hospitalisation or prolongation of existing hospitalisation [b)]
- A persistent or significant disability/incapacity [c)]
- A congenital anomaly/birth defect

- Important medical events [d)] that may not result in death, be life-threatening [a)] or require hospitalisation may be considered a SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

a) The term "life-threatening" in the definition of SAE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were 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, trial related and social purposes do not constitute AEs and should therefore neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

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

d) The term "important medical events" means events which may jeopardise the patient or require intervention to prevent a seriousness criterion. It can be AEs which suggest a significant hazard or puts the patient or clinical investigation subject at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.

Non-Serious Adverse Event:

A non-serious AE is any AE which does not fulfil the definition of a serious AE.

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.

Relationship to Trial Product (N8) Assessment Definitions:

- 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 aetiology other than the trial product.

Outcome Categories and Definitions:

- Recovered* – Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the patient signed the informed consent
- Recovering – The condition is improving and the patient is expected to recover from the event. This term should only be used when the patient has completed the trial
- Recovered with sequelae – As a result of the AE the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). If the sequelae meets a seriousness criterion, the AE must be reported as a SAE
- Not recovered
- Fatal
- Unknown – This term should only be used in cases where the patient is lost to follow-up.

*In Japan "Remitted" will be used

12.1.1 Technical Complaints

A technical complaint is any written, electronic, or oral communication that alleges defects on trial products listed as trial supplies in this protocol (section 9). The technical complaint may be associated with an AE, but does not concern the AE itself.

A technical complaint may for example concern:

- the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)

- the packaging material (e.g. leakage, cracks, problems with rubber membrane in the cartridge or errors in labelling text).

12.1.2 Medical Event of Special Interest and other events for expedited reporting

A medical event of special interest (MESI) is an event in which, in the evaluation of safety, has special focus.

A MESI should be reported following the same reporting requirements and timelines as for SAEs, irrespective of the MESI fulfils a seriousness criterion.

The following events are defined as MESIs in this trial;

- Medication error
    - Administration of wrong drug
    - wrong route of administration such as intramuscular instead of intravenous
    - Administration of an accidental overdose ie dose which may lead to significant health consequence as judged by the Investigator irrespective of whether a SAE criterion is met.
    - Administration of a high dose with the intention to cause harm

- Inhibitor formation against FVIII
    - blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk and if positive (BU ≥0.6/mL) at two consecutive tests - sampled preferably within 2 weeks - this should be reported by the Investigator as a MESI

- Allergic reaction including Anaphylactic reaction as defined by Sampson et al 2006[25]. 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.[25]

- Thromboembolic events
    - clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion, see definitions)

Other events for expedited reporting;
- Suspected transmission of infectious agents via a trial product.

12.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported from screening (visit 1) until End of Trial and at potential Follow-Up visits. During each contact with the trial site (visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or site staff e.g. visits to the laboratory) the patient must be asked about adverse events, e.g. “Have you experienced any problems since the last contact?”

All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated. Novo Nordisk’ assessment of expectedness is done according to the reference documents: N8 Investigator’s Brochure (insert reference)

The Investigator should record the diagnosis, if available. If no diagnosis is available then the Investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the Investigator on the standard AE form. If more than one sign or symptom is to be reported use a separate AE form for each sign and symptom. For SAEs complete a safety information form for each event. However, if several symptoms or diagnosis occur as part of the same clinical picture only one set of safety information form pages can be used to describe all the SAEs.

MESIs and other events for expedited reporting must always be reported to Novo Nordisk on the AE form and the safety information form, irrespective of seriousness within the same timelines as for SAEs.

The Investigator must report initial information on all SAEs, MESIs and other events for expedited reporting to Novo Nordisk within **24 hours** of obtaining knowledge about the event.

The Investigator must complete and forward electronically in pdf format/fax copies to Novo Nordisk:

- AE form in the eCRF **within 24 hours**
- safety information form on the paper CRFs **within 5 calendar days**

of obtaining knowledge about the SAE.

If for some reason the EDC application is unavailable then the AE information should be reported to Novo Nordisk by fax, telephone or e-mail within the same timelines.

For US the Investigator, and for all other countries Novo Nordisk, must inform the regulatory authorities and IECs/IRBs in accordance with the local requirements in force and ICH GCP[8].

Novo Nordisk will notify the Investigator of trial product related suspected unexpected serious adverse reactions (SUSARs) in accordance with the local requirements. In addition, the Investigator will be informed of any trial related procedure SAEs that may warrant a change of any trial procedure.

Investigators will be notified of trial-related SAEs in accordance with the local requirements in force and ICH GCP[8]. In Japan, Novo Nordisk must inform the health authorities and the relevant parties of SAE information in accordance with the Japanese requirements in force and ICH GCP.[8]

The monitor must be informed accordingly.

12.2.1 Disease-related Bleeding

Bleeds and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection to bleeds that are evaluated by the Investigator as part of the underlying disease are AEs. However, they should only be reported as AEs if evaluated as related to trial product or trial procedure by the Investigator. Furthermore, fatal or life-threatening SAEs must be reported regardless of relatedness. All bleeds and other symptoms related to the underlying disease will be captured in the eCRF.

12.2.2 Follow-up of Adverse Events

During and following a patient's participation in a clinical trial, the Investigator should ensure that adequate medical care is provided to the patient for any AE, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for AE(s) of which the Investigator becomes aware.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information (corrections, new or additional information) should be reported **within 24 hours** of obtaining knowledge of the information for SAEs, and if previously non-serious AEs become SAEs.

All non-serious AEs classified as severe or possibly/probably related to the trial product must be followed until the patient has "recovered" or "recovered with sequelae", and all queries have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (i.e. patient dies from another AE) can be closed with an outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the post-trial follow-up period and is expected by the Investigator to recover.

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

The Investigator must ensure that the worst case severity and seriousness is kept consistent.

The Investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days, unless otherwise specified. The Investigator must forward follow-up information on SAEs, MESIs and other events for expedited reporting within 5 calendar days of obtaining the information. This must be done by updating the AE form in the eCRF and/or completing a new safety information form marked follow-up on paper CRF and forwarding these to Novo Nordisk. If for any reason the EDC application is unavailable, then fax, telephone or e-mail to Novo Nordisk.

All SAEs, MESIs and other events for expedited reporting must be followed up until the outcome of the event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (i.e. the patient dies form another AE) can be closed with the outcome of "recovered" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the trial and is expected by the Investigator to recover.

After access to update the AE form in EDC is removed the Investigator must record any follow-up information, if required, of SAE, MESI and other events for expedited reporting on the paper CRFs provided at trial closure.

12.3 Technical Complaints and Technical Complaint Samples

12.3.1 Collection and Reporting of Technical Complaints

All technical complaints, as defined in Section 12.1 - occurring from the time of first and until the last usage of trial supplies - must be collected and reported to Novo Nordisk.

The patient must be asked about technical complaints during each contact (visit or telephone) with the Investigator or trial site staff. This may be done by posing a simple question such as "have you experienced any problems since the last contact?".

The Investigator must assess whether the technical complaint is related to:

- AE(s), SAE(s), MESI(s) and/or other events for expedited reporting

The AE(s), SAE(s), MESI(s) and/or other events for expedited reporting related to technical complaint(s) must be reported by the Investigator following the same reporting requirements and timelines as for other AEs, SAEs, MESIs and other events for expedited reporting (see section 12.2).

Technical complaints must be reported on the technical complaint form by the Investigator, as described in the following:

One technical complaint form must be completed for each trial product, non-investigational medicinal product or auxiliary supply. If the technical complaint involves more than one batch number, a technical complaint form for each batch number must be completed.

The Investigator must fax the technical complaint form to *Customer Complaint Center, Novo Nordisk, fax: +45 44 42 13 70*, within the following timelines of the trial site obtaining knowledge of the technical complaint:

- technical complaint assessed as related to a **SAE and/or MESI within 24 hours**
- all other technical complaints within **5 calendar days**

12.3.2 Collection, Storage and Shipment of Technical Complaint Samples

The Investigator must collect the technical complaint sample from the patient. If the technical complaint sample is unobtainable, the Investigator must specify on the technical complaint form why it is unobtainable.

The **technical complaint sample** and a **paper copy of the technical complaint form** must be sent to Novo Nordisk within **5 calendar days** of receiving the technical complaint sample at trial site by using the following address:

Novo Nordisk A/S, Att.: Customer Complaint Center, Krogshøjvej 55, 2880 Bagsværd, Denmark

The Investigator must ensure that the technical complaint sample is labelled with the batch number and, if available, the DUN number.

Storage and shipment of the technical complaint sample should be done in accordance with the conditions prescribed for the product, see Section 9. For further details on the shipment conditions of technical complaints, please contact the local monitor.

12.4 Precautions/Over-Dosage

As with any protein injected i.v., hypersensitivity reactions may occur. This might include rash, pruritus, fever, nausea, headache, and vomiting; also changes in blood pressure may occur.

If any of the above events occur or if an overdose is suspected, further N8 administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines.

12.5 Safety Committee(s)

12.5.1 Internal Novo Nordisk Safety Committee

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance of N8. The safety committee works according to a written guideline and will meet regularly to discuss and evaluate the overall safety for N8 for this trial and all other N8 trials. The Novo Nordisk safety committee can take action with regard to the patient safety for the trial based upon observations of the overall information for N8. Pre-defined rules for setting the enrolment on hold is described in Section 12.5.2.

The safety committee might meet to evaluate data at any time point during the conduct of the trial if deemed necessary.

12.5.2 Rules for putting the enrolment on hold

There are two pre-planned safety interim analysis. At each interim all patients exposed at the pre-defined time points determined by number of patients exposed will be evaluated for inhibitor development.

- Safety interim 1: After the first 25 patients have been to Visit 4 (20-25 exposure days)
- Safety interim 2: After the first 50 patients have been to Visit 5 (50-55 exposure days)

The expected rate of inhibitors is 30–35% in previously untreated patients with severe haemophilia A.

The rules for putting the enrolment on hold are as follows;

Inhibitor formation in 12 or more of all exposed patients at safety interim 1, or 22 or more of all exposed patients at safety interim 2, will result in the N8 safety committee evaluation of all cases of inhibitor formation. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enroled in the trial. The evaluation will provide the basis for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial.

The diagnosis of inhibitor is made if the patient has been tested positive for inhibitors (BU ≥0.6/mL) at two consecutive tests at central laboratory, sampled preferably within 2 weeks.

During the evaluation the safety committee will evaluate risk factors for inhibitor formation such as ethnicity, family history of inhibitors, FVIII gene mutation type, age at first FVIII treatment, reason for first treatment, treatment duration after first treatment, the details of any surgery (including type of surgery, amount of product used, and outcome), any recent infection and any recent vaccination. Furthermore the time of occurrence of inhibitor formation (after how many exposures) and whether the inhibitor is a high or low titre will be evaluated

12.5.3 Data Monitoring Committee

No Data Monitoring Committee will be established for this trial as the trial is open-label, and the investigational drug is not expected to show toxicity.

Safety surveillance will be performed by the internal Novo Nordisk safety committee.

13 Case Report Forms

Novo Nordisk will provide a system for EDC. This system and support services to the system will be supplied by a vendor. The activities of this vendor will be under the direction and supervision of Novo Nordisk.

13.1 Rules for Completing eCRFs

Ensure that all relevant questions are answered, and that no empty data blocks exist.

If a test/assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable) indicate this according to the data entry instructions.

The Investigator must ensure that all information derived from source documentation is consistent with the source information. By signing the case book electronically, the Investigator confirms that the information is complete and correct.

13.2 Corrections to eCRFs

Corrections to the eCRF data will be made by the Investigator or the Investigator's authorised staff. An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the Investigator's authorised staff after the date of the Investigator's signature on the case book then the case book must be signed again by the Investigator.

13.3 eCRF Flow

The Investigator must ensure that data are recorded in the eCRFs as soon as possible after the visit (preferably within 3 days). When data are entered it will be available to Novo Nordisk for data verification activities.

Site specific CRF data (in an electronic readable format) will be provided to the Investigator site after the trial database is released and access to update the trial data on the EDC application is removed. These data will be retained by the site.

When the final clinical trial report (CTR) is available the data will be archived by Novo Nordisk.

13.4 Analysis Results

Laboratory reports from the Local Laboratory must be signed and dated by the Investigator on the day of the review of the analysis results. The results from the Local Laboratory should be entered in

the eCRF for each patient. A signed and dated copy of Local Laboratory report must be retained at the trial site.

Central laboratory results will be transferred electronically to Novo Nordisk.

Laboratory reports from the central laboratory will be provided to the Investigator.

14 Monitoring Procedures

During the course of the trial, the Monitor will visit the trial site to ensure that the protocol has been adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between visits must not exceed 8 weeks when there are patients ongoing in the trial at the site. When there are no trial active patients at the sites, intervals between visits must not exceed 12 weeks.

The Monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. In addition the Monitor should be available for discussions e.g. by telephone.

For Screening Failures: Data in respect to the Screening Visit will be entered in the eCRF within preferably 3 days after data are available. The Screening Failure Form will be completed. These data will go into the trial database.

For withdrawn patients: All data collected in the period the patient participated in the trial will be entered in the eCRF.

The following data can be recorded directly in the eCRF and will then be considered source data:
- Ethnic origin
- Race

For all other data in the eCRF, it must be possible to verify these against source documents.

Diaries on paper will be provided by Novo Nordisk. Information on treatment and bleeds will be collected in the diaries, please refer to Section 8.4.5. The completed diaries are considered source data. The original diary must be stored at site. The Monitor will verify and ensure that the eCRFs and diaries are completed.

For all data recorded the source document must be defined in a source document agreement at each site.

15 Data Management

Data management is the responsibility of Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or external clinical research organisation (CRO).

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. In cases where laboratory data are transferred via non-secure electronic networks, data will be encrypted during transfer. The electronic laboratory data will be source data.

The central and local laboratories will provide laboratory reports to the Investigator. The laboratory report must be signed and dated by the Investigator and stored at the trial site as source data.

Data will be entered and delivered in an Oracle Clinical (OC) file and loading into OC.

The patient and biological material obtained from the patient will be identified by patient number, trial site and trial identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements.

16 Computerised Systems

Novo Nordisk will capture and process clinical data using computerised systems which are described in NN Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data. Novo Nordisk will collect information on the practical use of these systems within the conduct of this clinical trial.

17 Evaluability of Patients for Analysis

All main descriptions and analyses of efficacy will be based on the Full Analysis Set, as defined in ICH E9 Guidelines (Statistical Principles for Clinical Trials)[18]. The Full Analysis Set includes all dosed patients with data after dosing.

The Safety Analysis Set also includes all dosed patients with data after dosing. The analyses of the safety endpoints will be based on the Safety Analysis Set.

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.

18 Statistical Considerations

Novo Nordisk will be responsible for the statistical analysis.

18.1 Sample Size Calculation

No formal sample size calculations have been performed. The sample size is based on the EMA guideline requirement.

18.2 Statistical Methods

18.2.1 General Considerations

No formal testing of statistical hypotheses will be performed. Evaluation of data will be based on estimated incidence rates and odds ratios, and confidence intervals for these, as well as descriptive statistics, i.e. summary tables, listings, and figures.

18.2.2 Primary Endpoint(s)

Incidence rate of inhibitors defined as inhibitor titres ≥ 0.6 Bethesda units/mL
The incidence rate of 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 while the denominator will include all patients with minimum of 50 ED plus any patients with less than 50 ED but with inhibitors.

Furthermore, the time to inhibitor development will be presented by a Kaplan Meyer plot.
The relationship between the incidence rate of inhibitors and different patient and treatment characteristics will be investigated
Patient characteristics include:

- Ethnicity (White, Asian, African, Other)
- Family history of inhibitors (Negative, Positive)
- FVIII gene mutation type (Low risk (small deletions/insertions of < 200 base pairs, missense mutations, and other including splite or promoter mutations), High risk (large deletions of over 200 base pairs, nonsense mutations, intron 22 or one inversions))

Treatment characteristics include:

- Age at first treatment (Older than 12 months, between 6-12 months, between 1-6 months, before 1 month)
- Reason for first FVIII treatment (Prevention, Bleed, Surgery)
- Treatment moment at first treatment (Less than five consecutive days, Five or more consecutive days)

The odds ratio for each patient and treatment characteristic will be calculated using a univariate

logistics regression model and presented together with a 95% confidence interval.
The incidence rate of inhibitors will be calculated and presented by the patient and treatment characteristics.

18.2.3 Confirmatory Secondary Endpoints

NA

18.2.4 Supportive Secondary Endpoints

For patients that develop inhibitors only the time period until the last negative inhibitor result is considered for the efficacy endpoints below. Sensitivity analyses will be made only including patients who do not develop inhibitors. Further, tables will be made including only inhibitor patients. For these patients the relevant time period is the time period after positive inhibitor test.

Secondary Efficacy Endpoints

- Haemostatic effect of N8 on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None.

The haemostatic effect of N8 will be will be summarised by frequency tables containing count and percentages of all bleeds.
The haemostatic effect of N8 will also be summarised by the following subgroups: Cause of bleed (Spontaneous, Traumatic, Re-bleed), Site of bleeding (Central nervous system, Haemarthrosis (Joint), Gastrointestinal, Subcutaneous, Muscular or other), Classification of bleeding (Mild/Moderate or Severe) and Time of bleeding (the day is divided into 6 time intervals, each of 4 hours). Details (cause, site, classification and time) about the bleeds will also be summarised and listed.

- Annualized bleeding rate during bleeding prevention period with N8

For this endpoint patients who develop inhibitors will only be included if they have been treated for minimum 1 month before the first positive inhibitor test. The reason to exclude these patients from the calculations is that if the treatment period is too short, the uncertainty introduced on the estimated annualized bleeding rate will be relatively large.

The annualized number of bleeds in total and by cause of bleeding (spontaneous or traumatic) will be estimated by a Poisson model allowing for over-dispersion and presented with a 95% confidence interval (CI).

In addition, the annualized number of bleeds in total and by cause of bleeding, excluding all bleeds occurring more than 72 hours after last N8 dose will be estimated by a Poisson model allowing for over-dispersion and presented together with a 95% CI.

The annualized number of bleeds in total and by cause of bleeding, excluding all bleeds occurring more than 48 hours after last N8 dose will also be estimated by a Poisson model allowing for over-dispersion and presented together with a 95% CI.

A sensitivity analysis will be made only including data related to the time periods where the patients are dosed three times weekly or every second day.

The time interval from last N8 dose to start of a bleed will be summarised. This will be done by a frequency tables dividing the time interval into the following 5 groups: ≤ 12 hrs, > 12 hrs and ≤ 24 hrs, > 24 hrs and ≤ 48 hrs, > 48 hrs ≤ 72 hrs, > 72 hrs. The time interval from last N8 dose to start of a bleed will also be illustrated graphically with time from last dose on the x-axis and number of bleedings on the y-axis.

- Number of N8 infusions required per bleed

The number of infusions of N8 required per bleed will be calculated as the number of infusions of N8 used in the time period from start of the bleed to stop of the bleed. The number of infusions will be presented using count and percentages of all bleeds.

- Total consumption of N8 per patient (prevention, treatment of bleeds and during surgery) per month and annualised value

Total consumption of N8 during the trial will be summarised and listed by patient.

- N8 consumption per bleed

The consumption of N8 (IU/kg BW/bleed) will be calculated as the consumption of N8 used from start of the bleed to stop of the bleed. The consumption will be summarised and listed by patient.

- N8 consumption during bleeding prevention period

The consumption of N8 during bleeding prevention period (IU/kg BW/month*)* will be calculated as the consumption of preventive N8 doses and summarised and listed by patient.

Secondary Safety Endpoints

- Frequency of adverse events and serious adverse events

All AEs and SAEs will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity and by causal relation to trial product will also be made.

Furthermore, listings will be provided displaying all AEs and SAEs including pertinent clinical information.

- Incidence rate of high-titre inhibitors defined as inhibitor titre ≥ 5 Bethesda units/mL

Incidence rate of high-titre 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.

- Incidence rate of clinically relevant inhibitors defined as an inhibitor titre (≥ 0.6 BU/mL) combined with a decreased recovery (<66% of expected level)

The incidence rate of clinically relevant 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 Furthermore, the time to inhibitor development and clinically inhibitor development will be presented by a Kaplan Meyer plot.

The relationship between the incidence rate of clinically relevant inhibitors and high-titre inhibitors and different patient and treatment characteristics will also be investigated.

Outcome of inhibitor treatment will be listed and summarised.

All additional safety parameters such as laboratory parameters and physical examinations will be listed and summarised by visit for all patients.

18.3 Interim Analysis

An interim analysis is planned to occur after the first 50 patients each have 50 ED. The interim analysis will include a full report of all data for the 50 patient until the cut-off date, which is the date the 50th patient had his exposure number 50.

The interim analysis is performed to file a marketing authorisation variation application to include PUP in the N8 label.

Furthermore, the interim will include a safety analysis for all patients exposed before the cut-off date. The safety analysis will include a Kaplan Meyer plot presenting the time to high titre inhibitor, clinically relevant inhibitor and inhibitor (≥0.6 BU/mL), respectively. All AEs, SAEs, MESIs and other abnormal safety parameters such as laboratory parameters and physical examinations will be presented for all patients.

18.4 Sequential Safety Analysis/Safety Monitoring

There are two pre-planned safety interim analysis. At each interim all patients exposed at the pre-defined time points determined by number of patients exposed will be evaluated for inhibitor development.

- Safety interim 1: After the first 25 patients have been to Visit 4 (20-25 exposure days)

- Safety interim 2: After the first 50 patients have been to Visit 5 (50-55 exposure days)

The expected rate of inhibitors is 30–35% in previously untreated patients with severe haemophilia A.

The rules for putting the enrolment on hold are as follows;

Inhibitor formation in 12 or more of all exposed patients at safety interim 1, or 22 or more of all exposed patients at interim 2, will result in the N8 safety committee evaluation of all cases of inhibitor formation. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enroled in the trial. The evaluation will provide the basis for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial.

During the evaluation the Safety Committee will evaluate risk factors for inhibitor formation such as ethnicity, family history of inhibitors, FVIII gene mutation type, age at first FVIII treatment, reason for first treatment, treatment duration after first treatment, the details of any surgery (including type of surgery, amount of product used, and outcome), any recent infection and any recent vaccination. Furthermore the time of occurrence of inhibitor formation (after how many exposures) and whether the inhibitor is a high or low titre will be evaluated.

18.5 Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

N/A

18.6 PK and/or PD Modelling

N/A

18.7 Health Economics and Patient Reported Outcomes

Health economic data will be collected in the eCRF in connection with severe bleeds. Patient reported outcomes will be collected using questionnaires at visits 1, 3, and 7. The health economic and PRO data will be summarised using descriptive statistics.

19 Ethics

The trial will be conducted in compliance with ICH GCP[18], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[26].

19.1 Informed Consent Form for Trial Patients

In seeking and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s), and adhere to the ICH GCP and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator must give the patient and/or the patient's LAR oral and written information about the trial 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 trial the notion of legal representative should be understood as both parents, or legal representative(s), as defined in Member States' national laws, who consents on behalf of the child.

Consent: As a child is unable to provide legally binding consent, informed consent must be sought from the parents/ legal representative (see definition above) on the child's behalf. The specific and written informed consent of the parents/legal representative must be sought prior to enroling a child in the trial. Information should be given by an experienced Investigator to each parent, or the legal representative, on the purpose of the trial and its nature.

Assent: When a patient deemed legally incompetent, such as a child, is able to give assent to decisions about participation in trial, the Investigator 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.

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

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

The responsibility for seeking informed consent must remain with the Investigator or an adequately medically qualified person delegated by the Investigator. The written informed consent must be signed and personally dated by the parents/LAR, including time by the person who seeks the informed consent.

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

FVIII Genotype Testing

A collection of samples for genotype testing is offered to the patients participating in this trial. Prior to any trial-related activity, the Investigator must provide the patient and/or the patient's LAR the possibility to abstain from the genetic testing but still be able to participate in the trial.

19.2 Data Handling

If the patient or the patient's LAR withdraws the previously given informed consent or refuses to consent to continue in the trial, if the patient dies and no consent is available from a patient's LAR, or if the patient is lost to follow up then the patient's data will be handled as follows:

- Data collected will be retained by Novo Nordisk and entered into the database
- Safety events will be reported to the department responsible for global product safety, Novo Nordisk/regulatory authorities according to local/national requirements.

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

19.3 Institutional Review Boards/Independent Ethics Committee

Prior to commencement of the trial the protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient, patient recruitment procedures (incl. advertisement), if any, Investigator's Brochure (IB), available safety information, information about payments and compensation available to patients if not mentioned in the patient information, the Investigator's current curriculum vitae (CV) and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify the trial identification number, version, EudraCT no., title and/or the date of the documents that have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the Investigator or sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial protocol amendments to the protocol, non-substantial protocol amendments 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 trial (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 trial status, and other documents as required by the local IRB/IEC.

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

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

19.4 Regulatory Authorities

Regulatory authorities will receive the clinical trial application (CTA)/clinical trial notification (CTN for Japan), substantial/non-substantial protocol amendments (notifications of protocol amendments for Japan), reports on SAEs, and the CTR according to national requirements.

20 Premature Termination of the Trial/Trial Site

Novo Nordisk, Investigator or a pertinent regulatory authority may decide to stop the trial/trial site or part of the trial at any time, but agreement on procedures to be followed must be obtained.

Two pre-planned safety interim analyses will be performed during the trial to monitor the inhibitor development. If the pre-determined limit of number of cases is reached, the N8 safety committee will evaluate all cases of inhibitor formation. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enroled in the trial. For further information, please see Section 18.4.

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Investigator and/or Novo Nordisk should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

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

21 Protocol Compliance

Deviations from the protocol should be avoided.

If deviations occur then the Investigator must inform the Monitor, and the implications of the deviation must be reviewed and discussed.

Protocol deviations must be documented stating the reason, date, the action(s) taken, and the impact for the patients and/or the trial except for protocol deviations where no corrections are required as described in the trial specific validation checks in the approved trial validation plan (TVP). The Investigator must approve these as outlined in the TVP.

The documentation for the protocol deviations must be kept in the Investigator's trial file and Novo Nordisk's trial master file.

21.1 Audits and Inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk internal Quality Audit System or an inspection from domestic or foreign regulatory authorities. The Investigator and the site staff as well as Novo Nordisk clinical staff have an obligation to cooperate and assist in such audits and inspections. This includes giving Auditors and Inspectors direct access to all source documents and other documents relevant to the conduct of the clinical trial at the site.

22 Critical Documents

Before the Investigator starts the trial (i.e. the site has green light for screening patients), the following documents must be available to Novo Nordisk:

- regulatory approval and/or notification as required
- curricula vitae of Investigator and sub-Investigator(s) (current, dated and signed and/or supported by an official regulatory document)
- signed receipt of IB
- signed and dated agreement on the final protocol
- signed and dated agreement on any substantial protocol amendment(s), if applicable
- approval/favourable opinion from IEC/IRB clearly identifying the documents reviewed: the protocol, any substantial protocol amendments, patient information/informed consent form and any other written information to be provided to the patient, patient recruitment procedures
- copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement
- list of IEC/IRB members/constitution
- financial agreement(s)
  - Verification under disclosures per CRF of Final Conflict of Interest[11] (US sites only)
- FDA financial disclosure form or local equivalent as applicable.
- laboratory reference ranges
- laboratory certification/QA scheme/other documentation
- laboratory methods
- Signed and dated FDA form 1572 for each US Investigator (and individual US clinical trial staff if directly involved in the treatment or evaluation of research making a direct and significant contribution to the data).
  - All Investigators outside the US will **not** sign FDA Form 1572. As documented in writing by protocol signature, all Investigators will fully comply with ICH GCP[18], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[26].

23 Responsibilities

All staff (Novo Nordisk, site, lab, CRO etc.) must conduct the trial in compliance with ICH GCP[8], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[26].

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

A qualified physician, who is an Investigator or a sub-Investigator for the trial, should be responsible for all trial-related medical decisions.

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

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

In case the Investigator is not able to fulfil the role as Investigator (e.g. retirement), a new Investigator must be appointed in collaboration with Novo Nordisk.

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

The following will be analysed at the local laboratory: haematology and FVIII trough level assessment.

A central laboratory will analyse and report all laboratory safety tests related to biochemistry, viral antibody assessments, FVIII activity and FVIII inhibitor assessments performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically. Laboratory data will be reported to Novo Nordisk in a manner that anonymity of patients will be maintained.

HE and PRO data will be analysed by Novo Nordisk.

24 Reports and Publications

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

Novo Nordisk will designate a trial Investigator with the responsibility to review and sign the CTR, the Signatory Investigator.

24.1 Communication and Publication

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials 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 to not release data until specified milestones, e.g. when the clinical trial report is available. This includes the right to not release interim results of clinical trials, because the release of such information can invalidate the results of the entire trial.

At the end of the trial, one or more manuscripts for publication will be prepared collaboratively between Investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for less than 60 days to protect intellectual property.

24.1.1 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[27]).

Not withstanding anything to the contrary in this protocol. Novo Nordisk acknowledges the Investigators' right to publish the entire results of the trial. Any such scientific paper, presentation, communication or other information concerning the investigation described in this protocol, must be submitted in writing to the Novo Nordisk International Trial Manager prior to submission for publication/presentation for comments. Comments will be given within four weeks from receipt of the manuscript.

24.1.2 Publications

The results of this trial will be subject to public disclosure at external web sites according to international regulations, which is reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

In all cases, the trial results shall be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the trial. 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 Investigators' and Novo Nordisk's opinions shall be fairly and sufficiently represented in the publication.

In a multi-centre trial based on the collaboration of all trial sites, any publication of results must acknowledge all trial sites.

Novo Nordisk maintains the right to be informed of any Investigator 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 Trial Manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

24.1.3 Site-Specific Publication(s) by Investigator(s)

For a multi-centre clinical trial, 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 trial.

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

24.2 Investigator Access to Data and Review of Results

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

Individual Investigator(s) will have access to their own research participants' data after the full clinical trial report is finalised.

25 Retention of Clinical Trial Documentation

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

The Investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The Investigator should not destroy any documents without prior permission from Novo Nordisk. If the Investigator cannot archive the documents at the trial site after trial completion, Novo Nordisk can refer the Investigator to an independent archiving provider who has a system in place that allows only the Investigator to access the files.

The Investigator must be able to get hold of his/her trial documents without involving Novo Nordisk in any way.

Clinical trial documentation must be retained until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Medicinal Product.

For Japan, the Clinical trial site should retain clinical trial documentation until approval, or 3 years after the date of premature termination or completion of the clinical trial. The sponsor should retain clinical trial documentation for 5 years after the approval (in case of drug subjected to re-examination, until re-examination is completed), or 3 years after the date of premature termination or completion of the clinical trial.

Novo Nordisk will maintain Novo Nordisk's documentation pertaining to the trial as long as the product is on the market plus 20 years. The files from the Investigator site/institution will be retained 15 years after the completion of the trial, or longer if required by national regulations. For Japan, the files from the Investigator/institution must be retained longer in accordance with national regulations.

26 Indemnity Statement

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

27 References

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Appendix A

Agreement on Final Protocol

Agreement on Final Protocol

Trial ID: NN7008-3809

The Investigator and Novo Nordisk agree to conduct the trial as outlined in this protocol with reference to current Good Clinical Practice (GCP), applicable regulatory requirements, and in accordance with the Declaration of Helsinki. Any modification to the protocol must be agreed upon by both the Investigator and Novo Nordisk and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorised individuals representing Novo Nordisk (including monitoring staff and auditors), to institutional review boards/independent ethics committees (IEC/IRB) and/or to regulatory authorities.

Investigator:

Name (printed)	Signature	Date

Head of medical/clinical research or Designee:

Name (printed)	Signature	Date

Appendix B

Whole Blood Volume Rules in the Paediatric Population

Whole Blood Volume Rules

The whole blood volume is used as a general guide in estimating reasonable volumes of blood that can be removed safely.

The table below shows values for mean blood volume in children, men and women

(Geigy Scientific Tables, 7th Ed; 1971):

Whole Blood Volume	**(mL/kg Body Weight)**
Newborn, 15-30 minutes of age	76.5
Newborn, 24 hours	83.3
Children, 3 months	87
Children, 6 months	86
Children, 1 year	80
Children, 6 years	80
Children, 10 years	75
Children, 15 years	71

Appendix C

Anaphylaxis

Definition and treatment of anaphylactic reactions

The patient must be monitored carefully for anaphylactic reactions according to the clinical criteria for diagnosing as defined by Sampson et al, 2006.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure[1]
   - Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Reference

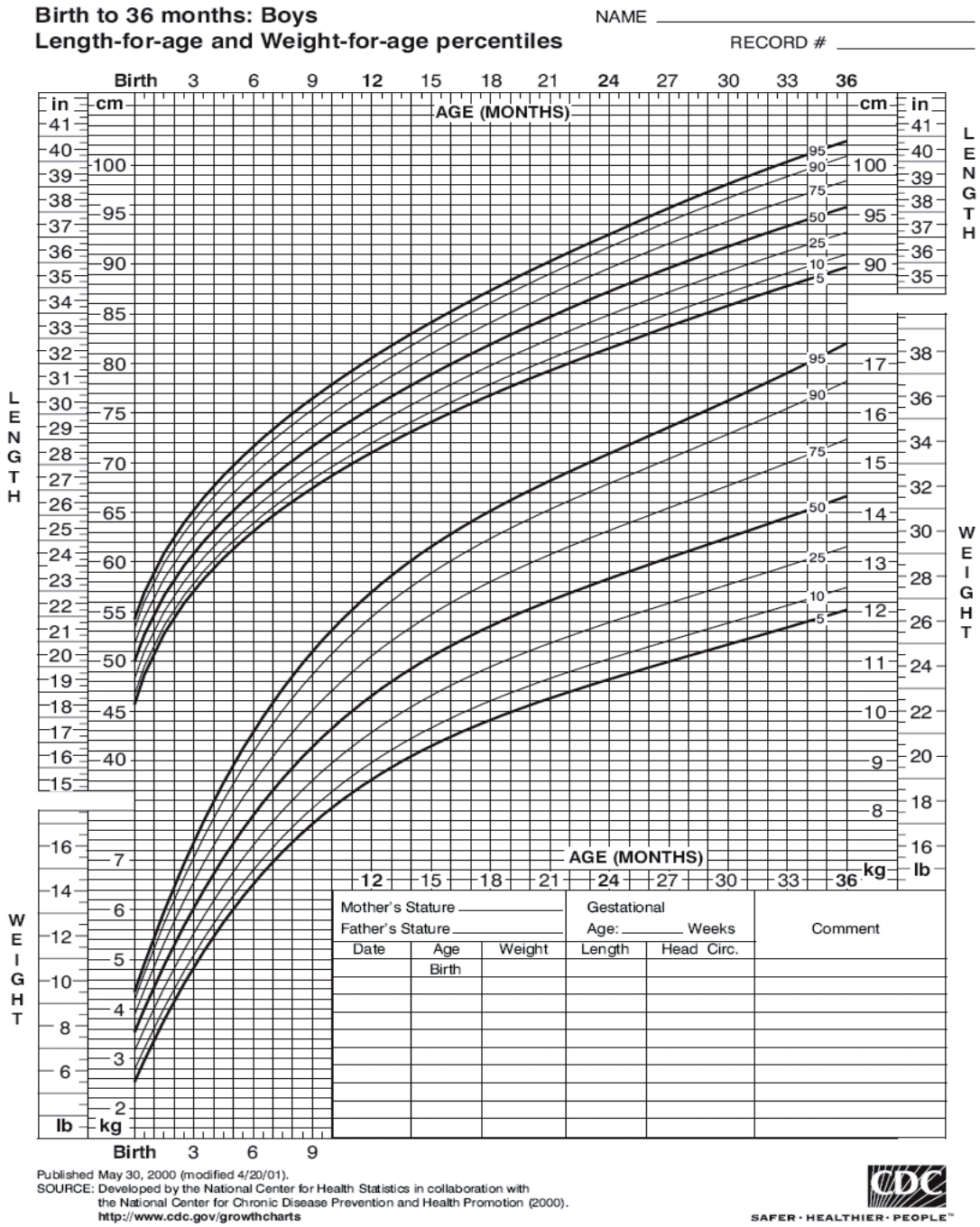
Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006; 47(4):373-380.

[1] Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Appendix D

Body Mass Index Charts

Body Mass Index Charts



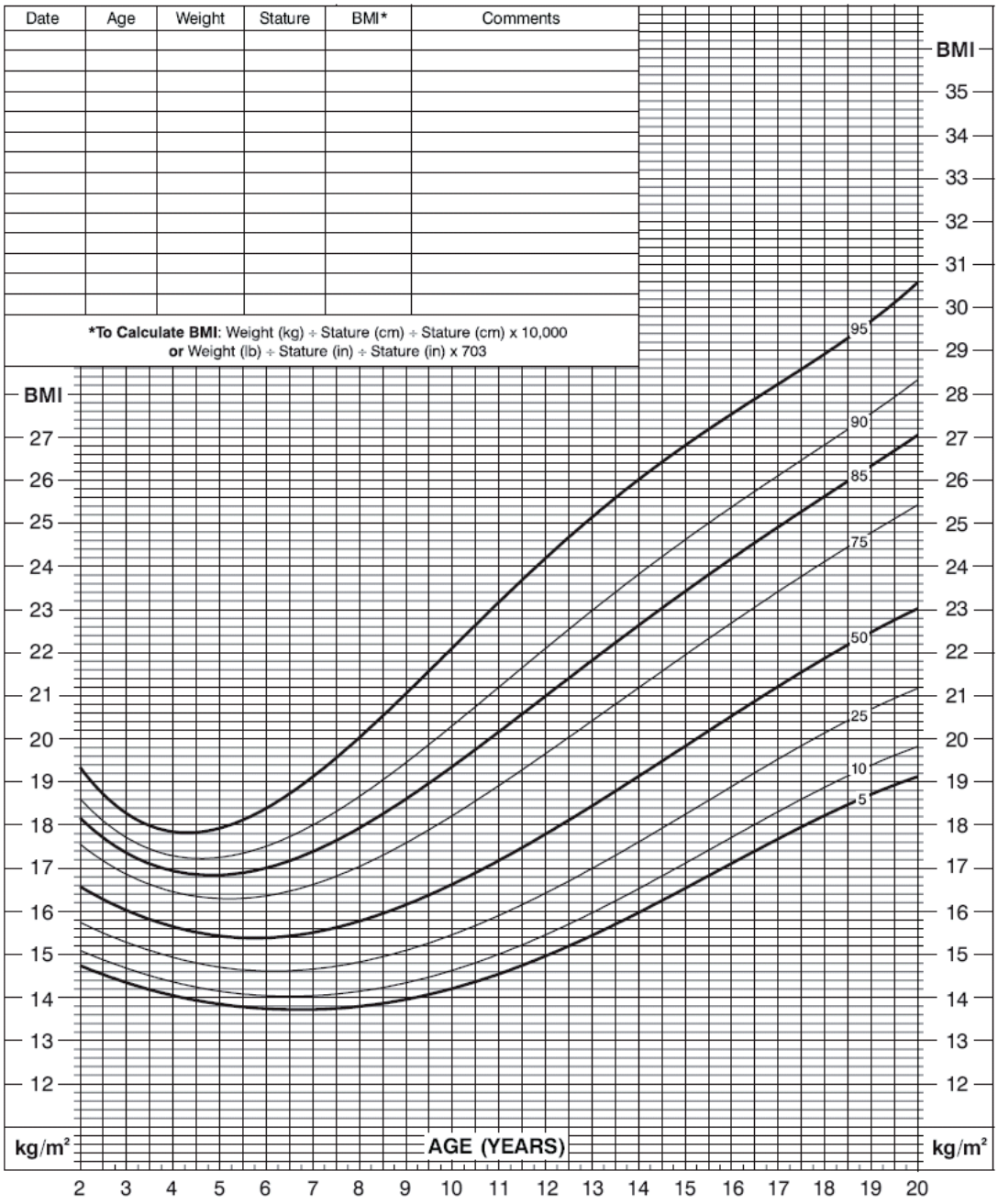
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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Appendix E

Patients Reported Outcome Questionnaires

Table of content

Trial ID: NN7008-3809

~~CONFIDENTIAL~~

VISIT X

Centre ID/No.: |_|_|_|

Subject No.: |_|_|_|_|_|_|

Hemo-Sat
Patient Satisfaction Scale

Hello there!

We would like to know how satisfied you are with your son's hemophilia treatment. We have a few questions that we would like you to answer. This questionnaire was made for parents of children with hemophilia.

- ⇨ Please read each question carefully.
- ⇨ Choose the answer that fits you best and check the appropriate box.
- ⇨ There are no right or wrong answers.
- ⇨ It's what you think that matters.

For example:	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
I'm satisfied with my son's life in general	☐	☒	☐	☐	☐

Date of completion: __ / __ / __ (month / day / year)

We would like to know how satisfied you are with the following aspects concerning YOUR SON'S HEMOPHILIA TREATMENT?

1. Ease and convenience

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. Treatment does not interfere with our everyday life	☐	☐	☐	☐	☐
2. I am satisfied with the number of doctor's appointments associated with my son's treatment	☐	☐	☐	☐	☐
3. It is easy to prepare the infusion	☐	☐	☐	☐	☐
4. I am satisfied with the volume of the infusion	☐	☐	☐	☐	☐
5. I am satisfied with the way that the medication is administered	☐	☐	☐	☐	☐
6. I am satisfied with the way that I have to store the medication	☐	☐	☐	☐	☐
7. I am satisfied with how often my son must be infused	☐	☐	☐	☐	☐
8. I feel that his medication is safe	☐	☐	☐	☐	☐
9. I worry about the risk of inhibitors associated with his medication	☐	☐	☐	☐	☐
10. I am bothered by side effects caused by his medication	☐	☐	☐	☐	☐
11. I worry about the risk of infection associated with his medication	☐	☐	☐	☐	☐

2. Efficacy

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the time needed for the medication to stop my son's bleed	☐	☐	☐	☐	☐
2. I am satisfied with the number of injections that are normally needed to stop a bleed	☐	☐	☐	☐	☐
3. I am confident that, if he takes the medication in advance, he can prevent a bleed	☐	☐	☐	☐	☐
4. I am satisfied with the ability of the medication to control my son's bleeds	☐	☐	☐	☐	☐
5. I am confident that he can have a normal life when he follows the prescribed treatment	☐	☐	☐	☐	☐
6. I am satisfied with the activities he is allowed to do with his treatment	☐	☐	☐	☐	☐

3. Burden

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. The medication does not cause my son any discomfort	☐	☐	☐	☐	☐
2. My son doesn't worry about receiving his medication	☐	☐	☐	☐	☐
3. I have full confidence in his medication	☐	☐	☐	☐	☐
4. I am pleased to be able to control his disease myself	☐	☐	☐	☐	☐

4. Specialist/Nurses

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the information that I received about my son's medication from his doctor	☐	☐	☐	☐	☐
2. I am satisfied with the information I received about his options for treatment	☐	☐	☐	☐	☐
3. I am satisfied with the quality of care that he receives	☐	☐	☐	☐	☐
4. I have confidence in the doctor's recommendations for my son's hemophilia treatment	☐	☐	☐	☐	☐
5. I am satisfied with the doctor's explanation of my son's health condition	☐	☐	☐	☐	☐
6. I am satisfied with the time my son's doctor spends with us	☐	☐	☐	☐	☐
7. I feel the doctor understands us and our problems	☐	☐	☐	☐	☐

5. Center/Hospital

How much do you agree with the following statements?	totally agree	somewhat agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am satisfied with the availability of the person on duty at the center/hospital	☐	☐	☐	☐	☐
2. We feel comfortable at the center/hospital	☐	☐	☐	☐	☐
3. I am satisfied with our relationship with his doctor	☐	☐	☐	☐	☐
4. I am satisfied with our relationships with the nurses	☐	☐	☐	☐	☐
5. I am confident that his center takes good care of him	☐	☐	☐	☐	☐

6. GENERAL SATISFACTION with the treatment

How much do you agree with the following statements?	totally agree	rather agree	neither agree nor disagree	somewhat disagree	totally disagree
1. I am generally satisfied with his treatment	☐	☐	☐	☐	☐
2. I am satisfied with his medication	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Substantial Protocol Amendment

no 1

to Protocol, final version 1.0

dated 29 June 2011

Trial ID: NN7008-3809

Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:

Name: [redacted]

Department: Haemostasis, Clinical Operations FVIII & FXIII

Table of Contents

Page

1 Introduction including rationale for the substantial protocol amendment

Novo Nordisk (NN) has produced a third generation rFVIII product (N8/turoctocog alfa) which is similar to other marketed rFVIII molecules of recombinant origin. Turoctocog alfa is produced without significant changes to either the molecular structure or manufacturing process of commonly derived rFVIII products.

The guardian™ 4/NN7008-3809 clinical trial is a prospective phase III paediatric trial intended to further investigate the safety and efficacy profile of turoctocog alfa in PUPs < 6 years of age with severe haemophilia A. The trial will continue until at least 50 subjects have received at least 50 ED to turoctocog alfa. The reduction in patient number reflects the industry standard for PUP trials taking into consideration haemophilia A being a rare disease.

This global substantial amendment has been prepared to:

- adapt the protocol to reduced number of patients and reduced number of exposure days
- clarify minor inconsistencies and ambiguities, and to correct apparent mistakes and misspellings.

In this substantial protocol amendment:

- Any new text is written **in italics**.
- Any text deleted from the protocol is written using ~~strike through~~.
- Any section referred from the protocol, which are not complete is depicted -------

2 Changes

2.1 General

Throughout the protocol the following changes will be made:

- ~~N8~~ *turoctocog alfa*
- ~~Visit 7~~ *Visit 5*
- Visit 5 and Visit 6 will be deleted.

2.2 Cover page

Department: Haemostasis Clinical Operations FVIII *& FXIII*

2.3 1 Summary

Primary Endpoint:
Incidence rate of FVIII inhibitors (≥0.6 BU/mL) will be evaluated from Visit ~~1~~ *2* to End of Trial Visit

---

Trial Design

The patients will receive preventive treatment with NNC 0155-0000-0004 until they reach a minimum of ~~100~~ *50* exposure days[1] (ED). The patients will stay in the trial for approximately ~~9~~*3*-24 months, and the estimated total duration of the trial is approximately ~~55~~ *50* months.

~~The trial is designed in accordance with European Medicines Agency (EMA) draft guideline from July 2009 on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products.~~[1]

Trial Population
Approximately ~~120~~ *60* PUP with severe (baseline level FVIII ≤1%) haemophilia A without inhibitors below 6 years of age in a non-bleeding state will be enroled to allow for at least ~~100~~ *50* patients to complete the trial.

Trial Product

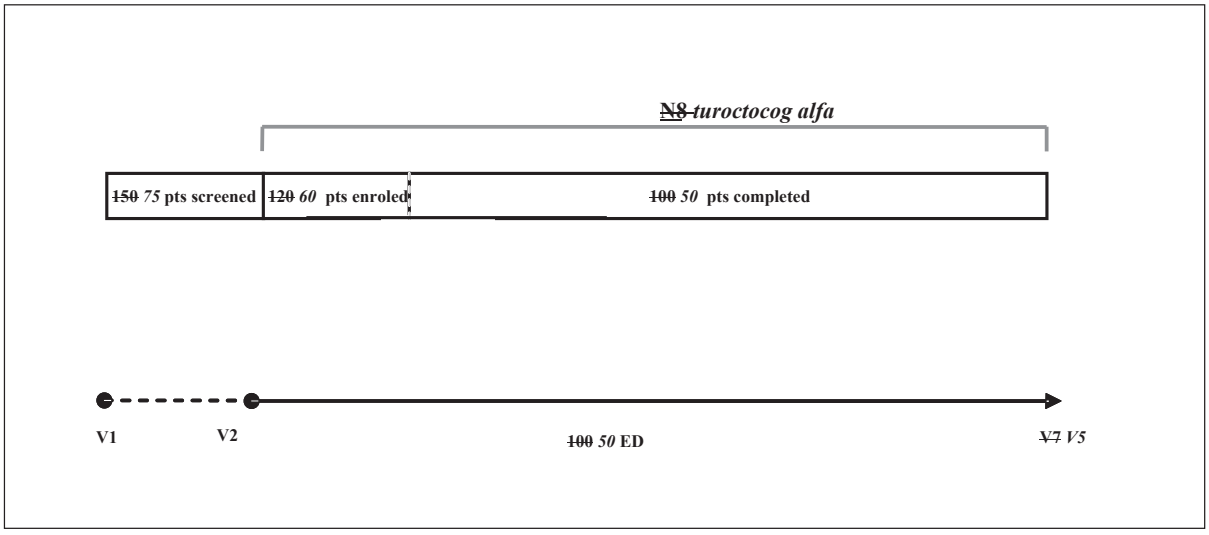
The maximum total daily dose of ~~N8~~ *turoctocog alfa,* for the treatment of bleeds *and/or during immune tolerance induction treatment for patients with inhibitors,* is 200 IU/kg with a maximum dose per infusion of 100 IU/kg. ~~This maximum limit does not apply during inhibitor treatment for patients with inhibitors~~.

2.4 2 Flow Chart

Following changes will be made in the flow chart:

- Columns labelled Visit 5 and Visit 6 will be deleted
- Column labelled Visit 7 will be re-named Visit 5
- Assessment "FVIII genotype test" will be moved to Visit 3, Visit 4 or unscheduled Visit. Table note "b" will be added and table note "f" moved to the "Assessments" column.
- Assessment "PRO questionnaire" will be removed from Visit 1
- ~~N8~~ *turoctocog alfa* administration will have table note "b" added to Visit 3 and Visit 4
- Assessment "FVIII recovery" will have table note "b" added to Visit 2, Visit 3 and Visit 4.
- Table note
    - c – mandatory to confirm clinical relevant inhibitors ~~and inhibitor treatment success~~
    - e – Visit 1 trial card only, Visit 2-*4* ~~6~~ diary card only

2.5 Figure 2-1 Trial Design



~~150~~ *75* patients are planned to be screened to get approximately ~~120~~ *60* enroled, and ~~100~~ *50* completers. Screening will be done at Visit 1, 14 ± 7 days prior to Visit 2. Preventive treatment with investigational product (~~N8~~ *turoctocog alfa*) starts at Visit 2 (may start after the first two bleeds, see Section 5.3*)*, and is completed at ~~V7~~ *V5*.

2.6 3.1.1.1 Pre-Clinical and Clinical Data

Recently ~~Currently three~~ *two major* clinical *trial* ~~studies~~ ~~are ongoing~~ *were completed* in the Novo Nordisk *turoctocog alfa* development program, the pivotal phase 3 trial (guardian™ 1*/NN7008-3543*)~~,~~ *and* the paediatric trial (guardian™ 3*NN7008-3545*), *and another large study is ongoing,* the extension trial (guardian™ 2*/NN7008-3568*).~~and~~ *T*he accumulated clinical experience with ~~N8~~ *turoctocog alfa* is now approaching ~~10000~~ *30000* exposure days (ED).

2.7 3.1.1.1 Risks and Benefits

After completing the present trial (guardian™ 4), *eligible* patients will be offered to continue with ~~N8~~ *turoctocog alfa* in an extension trial, see Section 5.4. This serves to minimise the patients' need of switching to other FVIII products.

2.8 3.2 Rationale for the Trial

~~In order to achieve marketing authorisation for this product, EMA draft guidelines on clinical investigation of plasma derived and recombinant FVIII products and review of relevant Food and Drug Administration (FDA) approvals of recombinant FVIII and FIX products[1,11,12] are applied in the clinical development programme (see further details in the IB[9]). According to the draft EMA guideline on clinical Investigation of new FVIII products, the clinical programme must include a paediatric trial in PUP demonstrating safety and clinical efficacy in at least 100 patients.~~

The guardian™ 4 trial is a prospective clinical phase 3~~a~~*b* trial intended at demonstrating safety and efficacy of ~~N8~~ *turoctocog alfa* in PUP < 6 years of age with severe haemophilia A. The trial will continue until at least ~~100~~ *50* patients have *reached a minimum of* ~~received at least 100~~ *50* ED to ~~N8~~ *turoctocog alfa*.

2.9 3.2.1 Clinical Development Programme

The overall clinical development programme for ~~N8~~ *turoctocog alfa* uses a stepwise approach, following the EMA ~~draft~~ guideline[1], by evaluating experience in older and previously treated patients (guardian™ 1) before investigating in younger children (guardian™ 3). *T*he present trial (guardian™ 4) *will support the programme scientifically with data on inhibitor development*~~and~~

~~finally~~ in previously untreated patients and contribute to the overall safety and efficacy profile of turoctocog alfa.~~ the study population of~~

2.10 5.1 Type of Trial

The trial comprises ~~7~~ *5* planned visits. Patients will attend a screening visit (Visit 1) in order to assess their eligibility. At Visit 2 eligible patient will receive their first dose and will be scheduled to attend ~~for 5~~ *3* more visits, if applicable. Details on the trial design can be found in Figure 2-1 and details on the individual visits can be found in Table 2-1.

The patients will be scheduled to receive treatment with ~~N8~~ *turoctocog alfa* for at least ~~100~~ *50* ED, which for the individual patient translates into a duration of approximately ~~9~~*3*-24 months depending on the dose regimens (and bleeding pattern). The total duration of the trial is estimated to be approximately ~~55~~ *50* months.

2.11 5.2 Rationale for Trial Design

This trial design (Figure 2-1) will provide documentation of the safety and efficacy of ~~N8~~ *turoctocog alfa* in prevention and treatment of bleeds in paediatric PUP with severe haemophilia A. ~~The trial design is in accordance with EMA draft guideline[1] from July 2009 for the development of rFVIII products.~~

~~Finally, the pivotal phase 3 trial (guardian™ 1) including at least 110 PTP above 12 years of age for at least 75 ED is planned to be completed before the initiation of the present trial.~~

2.12 5.3 Treatments of Patients

Approximately ~~120~~ *60* patients are expected to be enroled into the trial in order to have ~~100~~ *50* patients completing the trial (estimated drop out rate is 20%). For replacement of withdrawn patients, please refer to Section 6.5.

In most cases, treatment will be given at home with i.v. self-injection by the parent/caregiver/support person. However, on days when the patient is attending a trial visit, *if applicable* the dose ~~will~~ *may* be administered at the clinic by a health care professional.

Maximum dose

The maximum total daily dose of ~~N8~~ *turoctocog alfa,* for the treatment of bleeds *and/or during immune tolerance induction treatment for patients with inhibitors,* is 200 IU/kg with a maximum dose per infusion of 100 IU/kg~~. This maximum limit does not apply during inhibitor treatment for patients with inhibitors~~

2.13 5.3.4 Treatment of Patients with Inhibitors

Several genetic factors, such as FVIII gene mutation type, family history of inhibitors, ethnicity, have been associated with inhibitor development in patients with severe haemophilia.[15] Management of patients with inhibitors includes the treatment of bleeding episodes by the use of by-passing agents (rFVII*a* or activated prothrombin complex concentrates) and the permanent eradication of the inhibitor through immune tolerance induction therapy.

Patients who develop inhibitors, within this trial, will be offered continued treatment with ~~N8~~ *turoctocog alfa for 12 months*~~. The duration of the inhibitor treatment will be at least 12 months~~ from the time of diagnosis of inhibitor. ~~For patients who develop inhibitors during their first year in the trial (within 12 months) the inhibitor treatment may continue until a total trial duration of 24 months.~~

It may also be decided by the Investigator and/or parent/legal representative to withdraw the patient.

~~Transient inhibitors are defined in this trial as inhibitors which disappear within 3 months after two positive inhibitor tests.~~

~~Inhibitor treatment success is defined as (not applicable for patients with transient inhibitors):~~

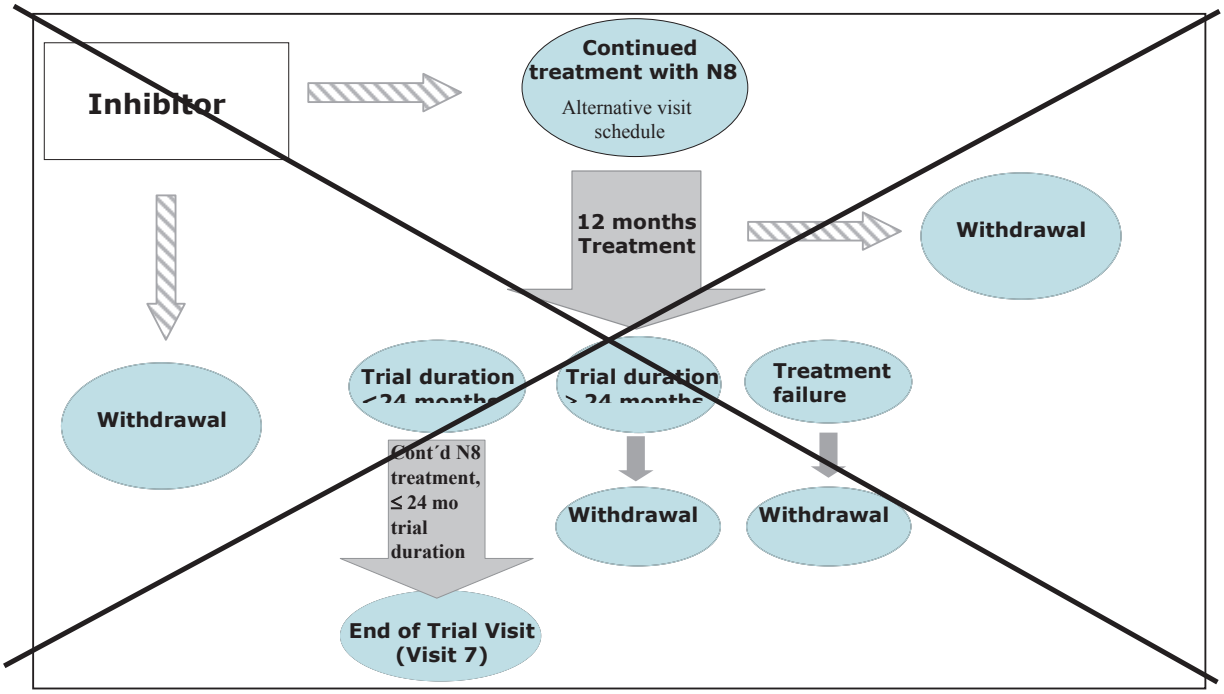
- ~~two consecutive blood samples showing inhibitor level <0.6 BU/mL~~
- ~~FVIII plasma recovery ≥66 % of expected level~~
- ~~N8 T1/2 of ≥6 h after a 72 h N8 washout period~~[17]

~~Inhibitor treatment failure is defined as persistence of inhibitor with no consistent decline of the inhibitor titer from peak level within 12 months of the inhibitor diagnosis. If inhibitor treatment failure occurs, the patient must be withdrawn~~.

After completion of the inhibitor treatment, *or if preventive treatment is resumed*, the patient will be called to an End of trial Visit (Visit *5* ~~7~~).

Treatment of bleeds with by-passing agents i.e. *r*FVIIa or activated prothrombin complex concentrate (APCC), is allowed for patients who develop inhibitors.

~~Details on inhibitor management can be found in~~ Figure 5.1



~~Patients who develop inhibitor will be offered to continue N8 treatment. The regular visit schedule will stop and an alternative schedule will be commenced. After 12 months treatment, patients will fall into three categories; a) total trial duration < 24 months – treatment may continue up to 24 months, b) total trial duration ≥ 24 months – patients will be withdrawn, c) treatment failure as defined in Section – patients will be withdrawn. Patients may also at any time be withdrawn at the discretion of the Investigator or the parents/legal representative, or on the patient´s on will.~~

2.14 5.4 Treatment after End of Trial

It is expected that ~~N8~~ *turoctocog alfa* will be granted marketing authorisation and is commercially available when the patients complete this trial. Where no marketing authorisation has been granted, ~~each~~ *eligible* patient*s* will be offered to continue in the phase 3b extension trial (guardian™ 2), see Section 3.2.1, as applicable by local regulation and rules.

2.15 6.1 Number of Patients to be Studied

Countries planned to participate: Austria, ~~Belgium~~, Brazil, ~~Canada~~, China, Croatia, Czech Republic, Greece, Hong Kong, Japan, ~~South Korea~~, Malaysia, ~~Romania~~, Russia, Serbia, Spain, ~~Thailand~~, Turkey, UK and US.

Planned number of patients to be screened (i.e. documented informed consent): ~~150~~*75*
Planned number of patients to be started on trial product(s): ~~120~~*60*
Planned number of patients to complete the trial: ~~100~~*50*

Planned number of trial sites: ~~80~~*50*

2.16 6.2 Inclusion criteria

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2. Male patient with congenital sever haemophilia A (FVIII level ≤1%)*

**based on the one-stage clotting assay*

---

5. Immunocompetent, defined as either HIV negative or if HIV positive, $CD4^+$ cells >200 cells/µl.

2.17 6.4 Withdrawal Criteria

~~4. For inhibitor patients – inhibitor treatment failure with N8 treatment (refer to Inhibitor Treatment Section 5.3.4.)~~

2.18 6.5 Patient Replacement

Withdrawn patients may be replaced to ensure that ~~100~~*50* patients complete the trial with at least ~~100~~*50* ED. Assuming a drop-out rate of 20%, it is estimated that ~~120~~*60* patients must be enroled ~~started on N8~~ to obtain the ~~100~~*50* completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate.

2.19 6.6 Rationale for Trial Population

The inclusion and exclusion criteria are in line with previously studied recombinant FVIII products, reflect the general haemophilia A paediatric population that will receive ~~N8~~ *turoctocog alfa* when marketed. ~~and address the requirements of the EMA/CHMP draft guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products[‡]. According to the EMA guideline, the clinical programme must include a paediatric trial in PUP demonstrating safety and clinical efficacy in at least 100 patients~~. *In addition, PUP in their immunological naïve state with regard to external FVIII protein, is the optimal population to investigate the development of inhibitors*.

Rationale for Withdrawal Criteria:

- Criteria nos. 1 *and* 2 ~~and 4~~ are included to protect the patient's safety.

2.20 7 Trial Schedule

Planned duration of recruitment period (FPFV-LPFV):	*39*~~42~~ months
Planned date for FPFV:	December 2011
Planned date for LPFV:	*March*~~June~~ 2015
Planned LPLV:	*April*~~July~~ 2016

2.21 8.1.2 Visit 1, Screening Visit

Patients should withhold ~~and stop~~ any anti-haemophilic treatment with blood components at least 48 hours prior to Visit 1.

2.22 8.1.5 Unscheduled Visit

The unscheduled visit can be performed after the enrolment into the trial until the End of Trial Visit (Visit~~7~~*5*) as either telephone ~~visit~~*contact* or a site visit. Unscheduled visits will also be performed during inhibitor treatment, see Section 8.1.5.2, and surgery procedures, Section. 8.1.5.1 Please find listed in Table 2-1 the assessments, which should be performed at an unscheduled visit. The date and time of the visit should be recorded in the eCRF.

2.23 8.1.5.2 Inhibitor Treatment Visit

All patients, who develop inhibitors *and continue treatment with turoctocog alfa,* will follow an alternative visit schedule prescribed by the Investigator according to local standard of practice~~, irrespective of whether inhibitor treatment is being initiated or not, see Section 5.3.4.~~ Monthly visits are recommended, at least initially~~, for patients who develop inhibitors~~.

~~Recovery test is required at the time of inhibitor diagnosis and for the confirmation of inhibitor treatment success, see Section 8.2.3.~~

~~Measurement of N8 pharmacokinetic plasma (T1/2) will be performed to confirm inhibitor treatment success, see Section 2.26.~~

When the last inhibitor treatment visit has been performed, the patient will be called to an End of Trial Visit (Visit *5* ~~7~~).

2.24 8.2.2 FVIII Inhibitors

All per protocol inhibitor laboratory sample~~s~~ analyses are to be ~~analysed~~ *coordinated by* ~~in~~ the central laboratory, and only these results will be used in the trial data analysis.

2.25 8.2.3 FVIII Recovery

Recovery is the FVIII plasma level recorded 30 ± 5 minutes after trial product administration and reported as [IU/mL]/[IU/kg]. Recovery assessment is mandatory at inhibitor diagnosis to identify clinical relevant inhibitors (see Sections 8.2.2~~). Likewise, recovery assessment is necessary when establishing inhibitor treatment success (see Sections 5.3.4)~~. Additional recovery assessments may be requested at the discretion of the Investigator.

2.26 ~~8.2.4 FVIII (N8) Pharmacokinetic T1/2~~

~~The T1/2 of N8 will be based on FVIII activity and the procedures should be according to local guidelines. The N8 washout period should be at least 72 hrs. It is recommended that at least three time points for blood sampling is chosen, and it should be within 48 hrs of N8 administration. The samples should be sent to the central lab for analysis.~~

~~The N8 T1/2 will be used to evaluate inhibitor treatment success, see Section 5.3.4.~~

2.27 8.2.5 FVIII Trough Level Assessment

The Investigator can at his/her discretion perform trough level assessments at visit*s* 3 *and 4* ~~6~~.

2.28 8.2.6 Haematology

- Mean corpuscular haemoglobin (MCH) (fmol~~/L~~)

2.29 8.2.8.1 General Consideration

The collection of all blood samples for the laboratory tests will be performed before administration of ~~N8~~ *turoctocog alfa*, except the recovery samples which must be collected after (*approximately* 30 minutes) administration of ~~N8~~ *turoctocog alfa*.

2.30 8.2.8.2 Local laboratory Tests

Assessments of haematology ~~and~~, FVIII trough levels *and CD4$^+$ T-cell count (if applicable)* will be done at the local laboratory* as per standard of practice at the participating site. Laboratory results from the local laboratory will be recorded in the eCRF.

**not applicable for Serbia*

2.31 8.2.8.3 Central Laboratory Tests

A central laboratory will *coordinate* analys~~e~~*is* and report*ing of* all laboratory safety tests related to biochemistry*,* viral antibody assessments *(except CD4$^+$ T-cell count)*, FVIII inhibitor and FVIII activity tests*, and genotyping* performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained.

A one-stage FVIII clotting activity assay and a two-stage chromogenic assay will both be used to assess the FVIII activity, *but only the one-stage clotting activity assay result will be reported to the Investigator.* ~~at the central laboratory~~.

For descriptions of ~~assay methods, particulars of instrumentation~~, procedures for obtaining samples/specimens, ~~who will perform the assessments~~ and the storage, handling ~~conditions~~, and disposition of specimens, please refer to the Laboratory Manual.

2.31.1.1 8.2.8.4 Blood Sampling Volume

Blood samples for laboratory analysis of efficacy, safety and other parameters will be drawn as described for the individual visits. The total volume of blood drawn during the trial will be approximately ~~30~~ *20-50* mL per patient *(the higher range is for patients in inhibitor treatment)*. The blood volume collected from the patient for all tests should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days (see Appendix B). This is in accordance with European regulatory guidelines (Directive 2001/20/EC)[2,22]. During visits, when samples are taken, blood samples will be aliquoted to meet above mentioned requirements. Instructions will be provided in the Laboratory Manual

2.32 8.4.1 **FVIII genotype testing** (not applicable to Brazil)

At Visit 2, all patients/parents/legally authorised representative (LAR) will be asked about documentation of previous FVIII genotype tests. If not available or if it needs to be re-tested FVIII genotype testing will be offered as allowed by local law. *The blood sample should be taken at Visit 3, Visit 4 or an unscheduled Visit.* Investigator, parent(s) or LAR have the right to refuse to provide

patient's FVIII genotype documentation or to refuse genotyping. This will not stop the patient to continue participation in the remainder of the study.

2.33 8.4.4 Body measurements

Weight and height will be measured at Visit 1 and ~~7~~*5*, for Visit 2-*4* ~~6~~ only weight is measured.

2.34 8.4.5 Diaries

Diaries will be dispensed at Visits 2-*4* ~~6~~, and the following data will be collected:

2.35 9.1 Trial Products

NNC 0155-0000-0004, N8 and turoctocog alfa are all synonym trial product names in this trial.

2.36 12.1.2 Medical Event of Special Interest and other events for expedited reporting

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Allergic reaction including Anaphylactic reaction as defined by Sampson et al 2006[25]. 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[25]. *All hypersensitivity reactions reported as MESI will be followed up with a hypersensitivity questionnaire*.

2.37 12.5.2 Rules for Putting the enrolment on hold

There ~~are two~~ *is one* pre-planned safety interim analysis. At ~~each~~ *this* interim all patients exposed at the pre-defined time point, determined by number of patients exposed, will be evaluated for inhibitor development.

- Safety interim ~~1~~: After the first 25 patients have been to Visit 4 (20-25 exposure days)
- ~~Safety interim 2: After the first 50 patients have been to Visit 5 (50-55 exposure days)~~

The expected rate of inhibitors is 30–35% in PUP ~~previously untreated patients~~ with severe haemophilia A.

The rules for putting the enrolment on hold are as follows;

Inhibitor formation in 12 or more of all exposed patients at *the* safety interim ~~1, or 22 or more of all exposed patients at interim 2,~~ will result in the ~~N8~~ *turoctocog alfa* safety committee evaluation of all cases of inhibitor formation. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enroled in the trial. The evaluation will provide the basis

for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial.

2.38 18.1 Sample Size Calculation

No formal sample size calculations have been performed, *but 50 patients are expected to give adequate precision for the estimate of inhibitor formation in PUP*. ~~The sample size is based on~~ ~~the EMA guideline requirement~~.

2.39 18.2.2 Primary Endpoints

Furthermore, the time to inhibitor development will be presented by a Kaplan Meyer plot.
The relationship between the incidence rate of inhibitors and different patient and treatment characteristics will be investigated
Patient characteristics include:

- Ethnicity (White, Asian, African, Other)
- Family history of inhibitors (Negative, Positive)
- FVIII gene mutation type (Low risk (small deletions/insertions of < 200 base pairs, missense mutations, and other including ~~splite~~ *splice* or promoter mutations), High risk (large deletions of over 200 base pairs, nonsense mutations, intron 22 or ~~one~~*1* inversions))

2.40 18.2.4 Supportive Secondary Endpoints

~~Outcome of inhibitor treatment will be listed and summarised.~~

2.41 ~~18.3~~ ~~Interim analysis~~

~~An interim analysis is planned to occur after the first 50 patients each have 50 ED. The interim analysis will include a full report of all data for the 50 patient until the cut-off date, which is the date the 50th patient had his exposure number 50.~~

~~The interim analysis is performed to file a marketing authorisation variation application to include PUP in the N8 label.~~

~~Furthermore, the interim will include a safety analysis for all patients exposed before the cut-off date. The safety analysis will include a Kaplan Meyer plot presenting the time to high titre inhibitor, clinically relevant inhibitor and inhibitor (≥0.6 BU/mL), respectively. All AEs, SAEs, MESIs and other abnormal safety parameters such as laboratory parameters and physical~~

~~examinations will be presented for all patients.~~

2.42 18.4 Sequential Safety Analysis/Safety Monitoring

There ~~are two~~ *is one* pre-planned safety interim analysis. At ~~each~~ *this* interim all patients exposed at the pre-defined time point, determined by number of patients exposed, will be evaluated for inhibitor development.

- Safety interim ~~1~~: After the first 25 patients have been to Visit 4 (20-25 exposure days)
- ~~Safety interim 2: After the first 50 patients have been to Visit 5 (50-55 exposure days)~~

The expected rate of inhibitors is 30–35% in previously untreated patients with severe haemophilia A.

The rules for putting the enrolment on hold are as follows;

Inhibitor formation in 12 or more of all exposed patients at *the* safety interim ~~1, or 22 or more of all exposed patients at interim 2,~~ will result in the ~~N8~~ *turoctocog alfa* safety committee evaluation of all cases of inhibitor formation. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enroled in the trial. The evaluation will provide the basis for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial.

2.43 18.7 Health Economics and Patient Reported Outcomes

Health economic data will be collected in the eCRF in connection with severe bleeds. Patient reported outcomes will be collected using questionnaires at visits ~~1,~~ 3, and ~~7~~*5*. The health economic and PRO data will be summarised using descriptive statistics.

2.44 27 References

Committee for medicinal products for human use (CHMP), Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products, (EMEA/CHMP/BPWP/144533/2009). ~~2009~~ *2011*.

2.45 Appendix B Whole Blood Volume Rules in the Paediatric Poulation

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The blood volume collected from the subject for all tests should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days. This requirement is in line with European regulatory requirements (Directive 2001/20/EC) and FDA requirements. The table below shows the estimated blood volume in children weighing from 6-25 kg and the blood volume that can be taken at any single time and in 28 days according to European regulatory requirements (Directive 2001/20/EC) and FDA requirements.

Total Blood volume according to Geigy Scientific Table
Children 1-5 years of age

Weight (kg)	*Blood volume (ml/kg)*	*Total Blood volume (ml)*	*Volume/blood sample (1%)*	*Volume /28 days (3%)*
6	*80*	*480*	*4,8*	*14,4*
7	*80*	*560*	*5,6*	*16,80*
8	*80*	*640*	*6,4*	*19,2*
9	*80*	*720*	*7,2*	*21,3*
10	*80*	*800*	*8.0*	*24.0*
11	*80*	*880*	*8.8*	*26.4*
12	*80*	*960*	*9.6*	*28.8*
13	*80*	*1040*	*10.4*	*31.2*
14	*80*	*1120*	*11.2*	*33.6*
15	*80*	*1200*	*12.0*	*36.0*
16	*80*	*1280*	*12.8*	*38.4*
17	*80*	*1360*	*13.6*	*40.8*

Weight (kg)	*Blood volume (ml/kg)*	*Total Blood volume (ml)*	*Volume/blood sample (1%)*	*Volume /28 days (3%)*
18	*80*	*1440*	*14.4*	*43.2*
19	*80*	*1520*	*15.2*	*45.6*
20	*80*	*1600*	*16.0*	*48.0*
21	*80*	*1680*	*16.8*	*50.4*
22	*80*	*1760*	*17.6*	*52.8*
23	*80*	*1840*	*18.4*	*55.2*
24	*80*	*1920*	*19.2*	*57.6*
25	*80*	*2000*	*20.0*	*60.0*

Substantial Protocol Amendment no. 2

to Protocol, final version 2.0 dated 01 February 2012

Trial ID: NN7008-3809

guardian™4

Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3

Applicable to Russia

Amendment originator:

[redacted]

[redacted]

Table of Contents

Page

1 Introduction including Rationale for the Substantial Protocol Amendment

The reason for this substantial protocol amendment is to change the Laboratory where $CD4^+$ T-cell count will be performed for investigator sites in Russia. $CD4^+$ T-cell count will be performed in the central laboratory.

In this substantial protocol amendment

- Any new text is written in *italic*.
- Any text deleted from the protocol is written with a ~~strike through.~~

2 Changes to the protocol

8 Methods and Assessments

...

8.2.7.2 Local Laboratory Tests

Assessments of haematology, FVIII trough levels ~~and CD4$^+$ T cell count (if applicable)~~ will be done at the local laboratory as per standard of practice at the participating site. Laboratory results from the local laboratory will be recorded in the eCRF.

8.2.7.3 Central Laboratory Tests

A central laboratory will coordinate analysis and report of all laboratory safety tests related to biochemistry, viral antibody assessments, *CD4$^+$ T-cell count*~~(except CD4$^+$ T cell count)~~, FVIII inhibitor and FVIII activity tests performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained.

Substantial Protocol Amendment

No.4-TR

to Protocol Attachment II-TR, final version 1.0

dated 26 September 2011

NN7008-3809

Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3

Applicable to Turkey

Amendment originator:

Name: [redacted]

Department: [redacted]

Table of Contents

Page

1 Introduction including rationale for the substantial protocol amendment

In this substantial protocol amendment:

- Any new text is written in **italics.**
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

In Turkey, the Priniciple Investigator of the site [redacted] - [redacted] changed in NN7008-3809 trial.

Previously, it was Assoc. Prof. [redacted]. The responsibility had been transferred to Assoc. Prof. [redacted]. There is no change in local laboratory informations.

Old text:

~~Investigator:~~	~~Title/ qualification~~	~~Assoc. Prof~~
	~~Name:~~	[redacted]
	~~Address:~~	[redacted]
	~~Tel:~~	
	~~Fax:~~	[redacted]
	~~Mobile:~~	[redacted]
	~~E-mail:~~	[redacted]

New text:

Investigator:	*Title/ qualification*	*Assoc. Prof*
	Name:	[redacted]
	Address:	[redacted]
	Tel:	
	Fax:	[redacted]
	Mobile:	[redacted]
	E-mail:	[redacted]

Substantial Protocol Amendment no 5

to Protocol, final version 2.0

dated 01 February 2012

Trial ID: NN7008-3809
(NNC0155-0000-0004)

Safety and Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3b

Applicable to all countries

Amendment originator:

Name: [redacted]

Department: Haemophilia, Clinical Operations FVIII & FXIII

Table of contents

Table of tables

Page

1 Introduction including rationale for the substantial protocol amendment

This global substantial amendment has been prepared to:

- change the treatment after end of trial
- introduce the concept of two different phases of the trial, a main phase and an extension phase
- present the results from previous trials in the guardian™ clinical programme
- extend the trial duration
- make it optional to conduct a phone "visit" for severe bleedings.

The current clinical trial, guardian™ 4 (NN7008-3809), includes Previously Untreated Patients (PUP), treated with turoctocog alfa for at least 50 exposure days (ED). To preserve the homogeneity of the patient cohort, patients will not be transferred to guardian™ 2 (NN7008-3568), which holds a trial population consisting of Previously Treated Patients (PTP) > 100 ED.

In this substantial protocol amendment:

- Any new text is written in **italics.**
- Any text deleted from the protocol is written using ~~strike through~~.

The below changes will not be disclosed in the following sections due to they are minor changes that do not affect the content of the text;

- minor inconsistencies and ambiguities, and typographical errors.

2 Changes

2.1 1 Summary

Objectives and Endpoints

Primary Endpoint:

- Incidence rate of FVIII inhibitors (≥0.6 BU/mL) will be evaluated *for the main phase of the trial* ~~from Visit 2 to End of Trial (EoT) Visit/Visit 5~~

Key Secondary Endpoints:

The secondary endpoints will be evaluated for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases.

- Haemostatic effect of NNC 0155-0000-0004 on treatment of bleeds assessed on a predefined four point scale: Excellent, Good, Moderate and None ~~will be evaluated from Visit 2 to EoT Visit/Visit 5~~
- Annualized bleeding rate ~~will be evaluated from Visit 2 to EoT Visit/Visit 5~~
- *Incidence rate of FVIII inhibitors (≥0.6 BU/mL)*

Trial Design

The trial consists of two phases. In the main phase ~~The~~ *an aggregated number of at least 50* patients will receive preventive treatment with NNC 0155-0000-0004 until they reach a minimum of 50 exposure days[2] (ED) *or until they develop inhibitors*. *After that the patient will continue in the extension phase, which will last for approximately 3.5 years*. ~~The patients will stay in the trial for approximately 3-24 months, and~~ The estimated total duration of the trial is approximately 5~~0 months~~ *years*.

~~The trial is designed in accordance with European Medicines Agency (EMA) guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products[1].~~

2.2 2 Flow Chart

(Clarification note: For Table 2-1 only information that are subjected to changes are presented.)

Table 2–1 Visit Flow Chart *main trial phase*

Visit number	Screen. Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Unscheduled Visit
Visit window	NA	14 ± 7 d post V1	10th -15thED	20th -25th ED	*50~~100~~th – 55~~110~~th* ED	
FVIII trough level			●b	●b	●*b*	
FVIII recovery		●b	●b	●b	●*b*	●b,c
T cells subset: CD4+	●*b,*h	●*b,h*				●*b,h*
turoctocog alfa administration		●b	●b	●b	●*b*	●b
Diary and Trial card dispensing and/or collection	●e	●e	●e	●e	●*e*	●b
Completion session in IV/WRS					~~●~~	
Drug dispensing and accountability		●g	●	●	●~~g~~	●b
~~**End of trial form**~~					~~●~~	

Table 2-2 presents the rolling visit schedule in the extension phase over the period of one year. It comes to effect after Visit 5 or after ITI treatment.

Table 2–2 Visit Flow Chart trial extension phase

Visit type	*Dispensing*		*Assessment& Dispensing*	*Dispensing*		*Assessment& Dispensing*	*End of Trial*	*Unsch Visit*
Visit number[#]	*6*	*7*	*8*	*9*	*10*	*11*		
Previous visit time(w)	*-8*	*-8*	*-10*	*-8*	*-8*	*-10*	*< 8*	
Visit window	*± 1w*	*± 1w*	*± 1w*	*± 1w*	*± 1w*	*± 1w*	*NA*	*NA*
ASSESSMENTS								
Withdrawal Criteria	●	●	●	●	●	●		
Concomitant medication	●	●	●	●	●	●	●	●*b*
Body measurements			●*c*			●*c*	●	
EFFICACY								
Bleed(s)	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*
SAFETY								
Adverse events	●	●	●	●	●	●	●	●*b*
Physical examination			●*a*			●*a*	●	
Vital signs			●*a*			●*a*	●	
FVIII inhibitors	●*a*	●*a*	●	●*a*	●*a*	●	●	●*a*
FVIII trough level			●*a*			●*a*		
FVIII recovery	●*a*	●*a*	●*a*	●*a*	●*a*	●*a*		●*a*
Biochemistry & Haematology			●			●	●	●*a*
OTHER ASSESSMENTS								
PRO questionnaire						●	●	
HE assessment	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*
Viral antibody test (if HIV, HBsAg and/or HCV status unknown)							●	●*b*
T cells subset: CD4+								●*b*
TRIAL MATERIAL								
turoctocog alfa administration	●*a*	●*a*	●*a*	●*a*	●*a*	●*a*		
Diary card dispensing and/or collection	●	●	●	●	●	●	●*d*	●*a*
Review of patient diary and entry of data in eCRF	●	●	●	●	●	●	●	●*a*
Completion session in IV/WRS							●	
Drug dispensing and accountability	●	●	●	●	●	●	●*e*	●*a*
EoT form							●	

 # - Presented numbers are for the first 12 months. Visit numbers for future years will be in consecutive order

a – Optional, at discretion of investigator

b – If applicable

c – Weight only
d – Collection only
e – Accountability only

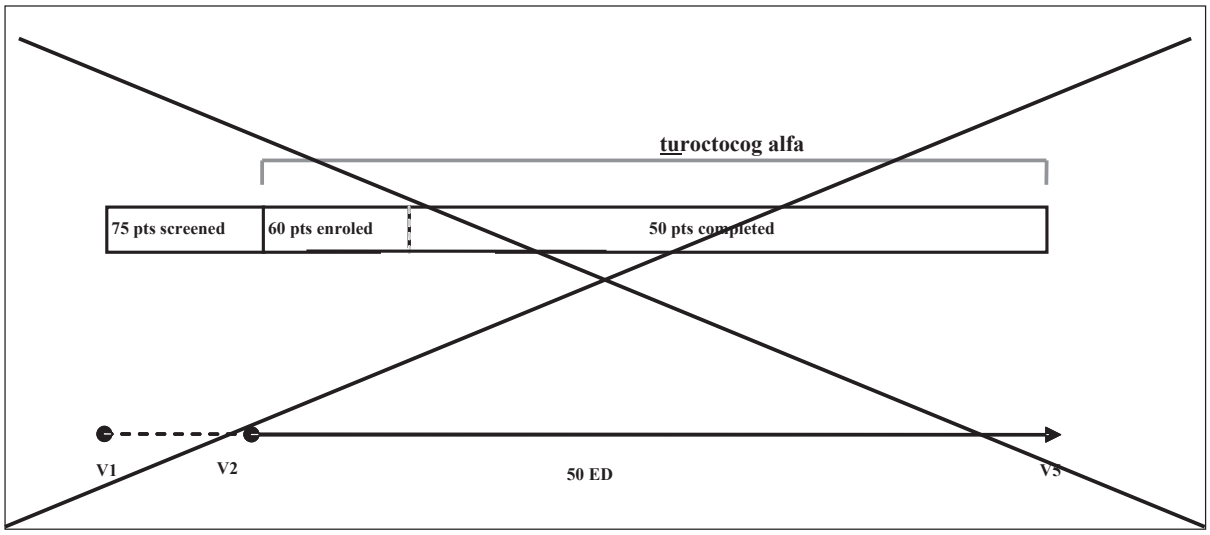
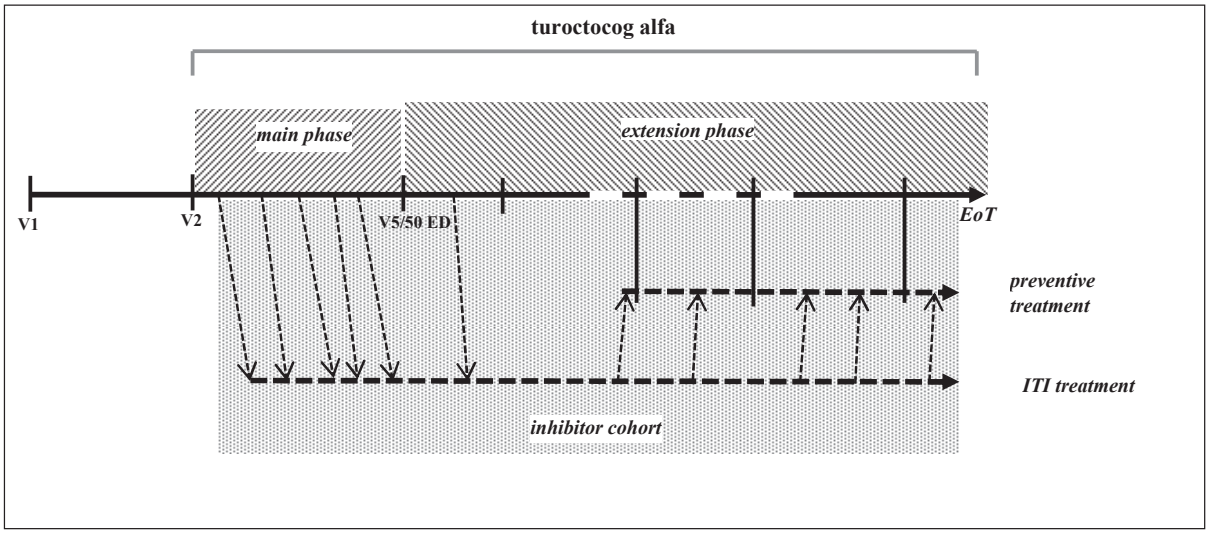


Figure 2-1 Trial Design



~~75 patients are planned to be screened to get approximately 60 enroled, and 50 completers.~~ Screening will be done at Visit 1, 14 ± 7 days prior to Visit 2. *At Visit 2 eligible patients are enroled and p*reventive treatment with investigational product (turoctocog alfa) starts *if applicable* ~~at Visit 2~~ (may start after the first two bleeds~~)., see Section 5.3 and is completed at V5~~. *At visit 5, after ≥ 50 ED, patients will leave the main phase of the trial and continue in the extension*

phase. Patients who develop inhibitors can continue with ITI treatment with an alternative visit schedule (down ward arrows). If ITI treatment is successful these patients can continue with preventive treatment according to the extension phase (upward arrows). The patients will belong to either of the groups main-phase, extension phase or inhibitor cohort.

2.3 3.1.1.1 Pre-Clinical and Clinical Data

Two phase 3 trials were completed in 2011, i.e. the pivotal trial guardian™ 1 (NN7008-3543) and the paediatric trial guardian™ 3 (NN7008-3545) in PTP with severe haemophilia A (FVIII≤1 %). In both trials, the primary objective was to assess safety, including the incidence rate of FVIII inhibitors (≥0.6 BU).

A total of 150 male patients aged 12 to 60 years were dosed in the guardian™ 1 trial, whereof 148 patients had at least 50 ED and 142 patients had at least 75 preventive ED in the trial. No clinically significant safety issues were identified and no FVIII inhibitors were detected. The success rate for treatment of bleeds was 84.5% (excluding bleeds for which there was no outcome reported).

A total of 63 male patients below 12 years of age were dosed in guardian™ 3 whereof 59 patients (28 children [0–<6 years] and 31 children [6–<12 years]) had at least 50 ED in the trial. No clinically significant safety issues were identified and no FVIII inhibitors were detected. The success rate for treatment of bleeds was 94.3% (excluding bleeds for which there was no outcome reported).

Further PK data have been obtained in the NN7008-3600 trial with six Japanese patients and in the NN7008-3893 trial with four additional adult patients. Both these trials used two different lots of drug product. In the NN7008-3600 trial, the PK properties of a single dose of turoctocog alfa in the Japanese population of patients with severe haemophilia A were successfully characterised. In the NN7008-3893 trial, three of the patients were of Asian and 1 was of Caucasian racial origin, and all patients completed the trial. No safety concerns were observed.

After completing the guardian™ 1 and guardian™ 3 trials, 189 of the 206 completing patients have continued treatment with turoctocog alfa within the extension trial guardian™ 2 (NN7008-3568), and the total clinical experience as of Nov 21 2011 exceeds 30000 ED. Despite regular monitoring and testing, no safety concerns have yet been detected and no patient has developed a FVIII inhibitor within the trials.

~~Recently two major clinical trials were completed in the Novo Nordisk turoctocog alfa development program, the pivotal phase 3 trial (guardian™ 1/NN7008-3543), the paediatric trial (guardian™ 3/NN7008-3545), and another large study is on-going, the extension trial~~

~~(guardian™2/NN7008-3568). The accumulated clinical experience with turoctocog alfa is now approaching 30000 exposure days (ED).~~

2.4 3.1.1.2 Risks and Benefits

~~After completing the present trial (guardian™ 4), eligible~~*The* patients will ~~be offered to~~ continue ~~with turoctocog alfa~~ in ~~an extension~~ *the trial until product launch or until the end of trial, should market authorisation not be obtained*, see Section 7 ~~5.4~~ for details. This serves to minimise the patients' need of switching to other FVIII products.

2.5 3.2 Rationale for the Trial

The guardian™4 trial is a prospective clinical phase 3b trial intended at demonstrating safety and efficacy of turoctocog alfa in PUP < 6 years of age with severe haemophilia A. ~~The trial will continue until at least 50 patients have received at least 50 ED to turoctocog alfa.~~

2.6 4.2 Endpoint(s)

Primary Endpoint

- Incidence rate of FVIII inhibitors (≥0.6 BU/mL*) will be evaluated for the main phase of the trial*

Secondary Endpoint(s)

The secondary endpoints will be evaluated for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases..

Safety Endpoints:

- ---
- *Incidence rate of FVIII inhibitors (≥0.6 BU/mL).*

2.7 5.1 Type of Trial

The trial ~~comprises 5 planned visits~~ *consists of two phases i.e. main and extension, respectively. In the main phase the p*atients will attend a screening visit (Visit 1) in order to assess their eligibility. At Visit 2 eligible patient will receive their first dose, if applicable, and will be scheduled ~~to attend~~ for 3 more visits. *After Visit 5 the patients will enter the extension phase, and a rolling visit schedule will apply with 6 planned visits (including 4 dispensing visits) per year.*

The *main trial phase will be completed when the aggregated number of* patients ~~will be scheduled to~~ *, who have either* received treatment with turoctocog alfa for at least 50 ED *or developed inhibitors, are at least 50.* ~~which~~ *F*or the individual patient *it* translates into duration of *the main phase of* approximately 3-24 months depending on the dose regimens (and bleeding pattern). *The duration of the extension phase may be up to 3.5 years, and t*he total duration of the trial is estimated to be approximately 5~~0 months~~ *years*, *please see Section 7.*

Patients who develop inhibitors during the trial may continue treatment with turoctocog alfa and will follow an alternative visit schedule, see Section 5.3.4. *These patients will be considered as a separate cohort and will be evaluated accordingly, please refer to Section 18.2.2.*

Details on the trial design can be found in Figure 2-1 and details on the individual visits can be found in Table 2-1 *and 2-2, and in Section 8.*

2.8 5.3 Treatment of Patients

Approximately 60 patients are expected to be enroled into the trial in order to have 50 *evaluable* patients ~~completing~~ *in the main phase of* the trial (estimated dropout rate is *15* ~~20~~%). For replacement of withdrawn patients, please refer to Section 6.5.

The maximum duration of treatment of a patient from first to last turoctocog alfa administration is approximately ~~24~~ *4 years* ~~month~~.

2.9 5.3.2 Treatment of Bleeds and Dose Adjustment

During preventive treatment, break-through bleeds may occur and require extra doses of turoctocog alfa. Treatment should be started as soon as a bleed is identified. *All bleeds,* mild/moderate *and severe,* ~~bleeds~~ can be treated at home*.* ~~whereas~~ *For* severe bleeds (see Section 8.3.1.1) ~~must always be evaluated by~~ the Investigator should evaluate if the patient should be seen ~~preferably~~ at the clinic. ~~However, even with severe bleeds treatment should be started immediately at home if possible.~~ All bleeds must be reported to the clinic within 24 hours from onset of the bleed.

2.10 5.3.4 Treatment of Patients with Inhibitors

Patients who develop inhibitors, within this trial, will be offered continued treatment with turoctocog alfa for 12 months. It may also be decided by the Investigator and/or parent/legal representative to withdraw the patient.

The ~~initiation,~~ dose level and dosing frequency of inhibitor treatment will be decided by the Investigator based on clinical evaluation and local standards, and it should be documented in the eCRF. Within this trial, 'inhibitor treatment' includes Immune Tolerance Induction (ITI) as well as smaller dose adjustments with low responding and/or clinical insignificant inhibitors.

If needed and decided by the Investigator, the initiation of the inhibitor treatment with turoctocog alfa can be delayed for up to 6 months from the time of diagnosis of inhibitor.

If the inhibitor disappears (BU <0.6/mL) during the ITI treatment, the patient should resume preventive treatment as recommended in this protocol, see Table 5-1, following the visit schedule in the extension phase. For patients still with positive inhibitors after 12 months ITI treatment, continued trial participation will be evaluated based on the level of inhibitors. ~~After completion of the inhibitor treatment, or if preventive treatment is resumed, the patient will be called to an End of trial Visit (Visit 5).~~

2.11 5.4 Treatment after End of Trial

It is expected that turoctocog alfa will be granted marketing authorisation and is commercially available when the patients complete this trial. ~~Where no marketing authorisation has been granted, eligible patients will be offered to continue in the phase 3b extension trial (guardianTM 2), see Section 3.2.1, as applicable by local regulation and rules.~~

2.12 6.1 Number of Patients to be studied

Countries planned to participate: Austria, Brazil, China, Croatia, ~~Czech Republic~~, Greece, Hong Kong, Japan, ~~Malaysia~~, Russia, ~~Serbia~~, Spain, Turkey, ~~UK~~ and US.

Planned number of patients to be screened (i.e. documented informed consent): ~~75~~*65*

2.13 6.4 Withdrawal Criteria

~~1. Haemostasis not achievable with turoctocog alfa: The bleed cannot be controlled after 48 hours using recommended doses of turoctocog alfa~~

Withdrawn patients should be scheduled for an EoT Visit ~~(Visit 5)~~ as soon as possible and within 28 days after the last turoctocog alfa administration, and preferably prior to initiation of treatment with another FVIII product. The Investigator should aim to conduct all procedures as specified in the protocol for *the EoT* Visit ~~5~~.

2.14 6.5 Patient Replacement

Withdrawn patients may be replaced to ensure that 50 patients complete the trial with at least 50 ED. Assuming a drop-out rate of ~~20~~*15*%, it is estimated that 60 patients must be enroled to obtain the 50 completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate.

2.15 6.6 Rationale for Trial Population

Rational for Withdrawal Criteria:

- Criteri*on*~~a~~ no~~s~~. 1 is included to protect the patient's safety
- Criterion no. *2*~~3~~ is selected not to confound the effects of the investigational product.

2.16 7 Trial Schedule

Planned LPLV: ~~April~~ *QIII* 2016

The duration of the trial for the individual country is dependent upon the timelines of market authorisation and commercial availability of the trial product. Should market authorisation not be obtained, the maximum trial duration is approximately 5 years.

2.17 8.1.1 Overall Procedures, Assessments and Methods

Specific procedures, assessments and methods for the scheduled visits are described in the sections below, and the list of assessments for each visit is presented in the flow charts, see Table 2-1 *and 2-2*.

2.18 8.1.2 Visit 1, Screening Visit

For all patients with a signed Informed Consent Form (ICF), the Investigator will, through IV/WRS, assign a unique 6 digit patient number. The patient number is maintained throughout the trial ~~and continuously maintained should the patient be enroled in the extension trial, see Section 5.4~~.

2.19 8.1.4 Visit 3 to Visit 5

~~Visit 5 should also be completed for withdrawn patients.~~

2.20 8.1.5 Unscheduled Visit

The unscheduled visit can be performed after the enrolment into the trial until the EoT Visit (~~Visit5~~) as either telephone contact or a site visit. Unscheduled visits will also be performed during inhibitor treatment, see Section 8.1.5.2, and *for* surg~~ery~~*ical* procedures, Section 8.1.5.1. Please find listed in Table 2–1 *and Table 2-2* the assessments, which should be performed at an unscheduled visit. The date and time of the visit should be recorded in the eCRF.

2.21 8.1.5.2 Inhibitor Treatment Visit

The alternative visit schedule will remain as long as the patient is treated for inhibitor. ~~When the last inhibitor treatment visit has been performed, the patient will be called to an End of Trial Visit (Visit 5)~~.

2.22 8.1.6 Extension phase Visits

These are visits to be performed for patients, who have completed the main phase and after Visit 5 continue in the extension phase. Patients, who resume preventive treatment after completed ITI treatment, will also follow the visit schedule in the extension phase. The patients will be called to the visits according to a rolling visit schedule, which runs over one year. There are two kinds of visits, Dispensing (4) and Assessment&Dispensing (2), and the aggregated planned number of visits over one year is 6.

Please also see Table 2-2 for your reference.

2.23 8.1.7 EoT Visit

Within 8 weeks of the last scheduled visit in the extension phase the patient should be called to an EoT Visit. For patients, who discontinue the trial, an EoT visit should be performed within 28 days.

2.24 8.2.1 Adverse Events

Monitoring of Adverse Events will be performed from the first trial-related activity to the EoT Visit ~~(Visit 5)~~ and at potential follow-up visits, according to procedures described in Section 12.

2.25 8.2.2 FVIII Inhibitors

All patients will be examined regularly for the development of FVIII neutralising antibodies (inhibitors). The tests will be performed at Visit 1 and Visits 3-5 *in the main phase of the trial, and at the Assessment&Dispensing Visits in the extension phase, i.e. at least twice annually.*

2.26 8.2.3 FVIII Recovery

Samples for FVIII recovery will be sent to the central laboratory for analysis*, see Section 8.2.7.2.*

2.27 8.2.4 FVIII Trough Level Assessment

The Investigator can at his/her discretion perform trough level assessments at any time during the trial. ~~Visit 3-4~~

2.28 8.2.5 Haematology

The assessment will be performed at Visit 1 and Visit 5 *in the main phase, the Assessment&Dispensing Visits in the extension phase, EoT Visit and optionally at unscheduled visits. It is performed* according to practice of the local laboratory and includes:

2.29 8.2.6 Biochemistry

The assessment will be performed at Visit 1 and Visit 5 *in the main phase, the Assessment&Dispensing Visits in the extension phase, EoT Visit and optionally at unscheduled visits. It is performed* according to practice of the central laboratory and includes:

2.30 8.2.7.2 Local Laboratory Test

Assessments of haematology, FVIII trough levels and $CD4^+$ T-cell count (if applicable) will be done at the local laboratory* as per standard of practice at the participating site. Laboratory results from the local laboratory will be recorded in the eCRF.

**in Russia and Hong Kong, $CD4^+$ T-cell count is done centrally*

~~not applicable for Serbia~~

Clinically significant findings must be recorded as concomitant illness (blood samples during visit 1) or as an Adverse Event (blood samples taken *during the course of the trial.* ~~at visit 2-5, unscheduled visits and potential follow-up visits~~)

2.31 8.2.7.3 Central Laboratory Tests

A central laboratory will coordinate analysis and report of all laboratory safety tests related to biochemistry, viral antibody assessments (except CD4+ T-cell count), FVIII inhibitor, FVIII activity and *genotyping* ~~tests~~ performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained.

2.32 8.2.7.4 Blood Sampling Volume

Blood samples for laboratory analysis of efficacy, safety and other parameters will be drawn as described for the individual visits. The total volume of blood drawn during the trial will be approximately ~~20~~*40*- ~~50~~*65* mL per patient (the higher range is for patient in inhibitor treatment

and/or for patient, who stay in the trial for a longer duration of time). *According to the* European regulatory guidelines (Directive 2001/20/EC)[2,19] the *recommended* blood volume collected from the patient ~~for all tests~~ should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days (see Appendix B). ~~. This is in accordance with~~ *Where this guideline is not applicable, local guidelines for blood sampling volumes will apply.* During visits when *multiple* samples are taken, blood samples will be aliquoted to meet above mentioned requirements. Instructions will be provided in the Laboratory Manual and in Appendix B.

2.33 8.2.8 Physical Examination

Physical examination should be performed at Visits 1-5 *and at EoT (additional examinations can be performed as appropriate)* according to practice at the participating clinic including assessments of the following:

2.34 8.2.9 Vital Signs

Vital signs will be assessed at Visit 1 ~~and~~ ,Visit 5 *and at EoT (additional assessments can be performed as needed)* and includes:

- Body temperature (assessed by measuring inner ear temperature or using an oral digital thermometer)
- Respiratory rate (resp./min.)
- ~~Pulse: preferably supine~~
- ~~Blood pressure (BP): preferably supine~~

~~BP (systolic and diastolic) and pulse rate will be measured according to local practice at the clinic; preferably after the patient has rested comfortably for at least 3 minutes.~~

Any changes in the vital signs between the two visits which fulfil the criteria of an Adverse Event must be recorded as such, see Section 12.1.

2.35 8.3.1 Bleeds

During the entire trial period all bleeds ~~treated with turoctocog alfa~~ will be entered in either the eCRF or in the patient's diary. For ~~mild/moderate~~ bleeds *treated at home*, the patient or caregiver must fill in the diary and during visits the diary data will be transcribed into the eCRF by trial site personnel. ~~For severe bleeds (see definition in Section (8.3.1.1) the Investigator, or designated site staff, must be contacted without delay to prescribe the appropriate treatment and any follow-up procedures. It is recommended that these direct instructions are followed by, or given at, an unscheduled visit to the clinic.~~ Documentation about ~~the severe~~ bleed*s treated at the clinic* should be entered in the medical records and eCRF by the trial personnel.

2.36 8.4.1 FVIII genotype testing ~~(not applicable to Brazil)~~

At Visit *1* ~~2~~, all patients/parents/legally authorized representative (LAR) will be asked about documentation of previous FVIII genotype tests. If not available or if it needs to be re-tested FVIII genotype testing will be offered as allowed by local law. The blood sample should be taken at Visit 3, 4 or an unscheduled Visit. *The FVIII genotype analysis is performed at the laboratory in Bonn, Germany.* Investigator, parent(s) or LAR have the right to refuse to provide patient's FVIII genotype documentation or to refuse genotyping. This will not stop the patient to continue participation in the remainder of the ~~study~~ trial.

2.37 8.4.2 Viral Antibody Information

At Visit 1 *and at EoT* status of the following viral infections are assessed.

2.38 8.4.4 Body Measurements

Weight and height will be measured at Visits 1, 5 and EoT. For Visits 2-4 *and for the Assessment&Dispensing Visits in the extension part* only weight is measured.

2.39 8.4.5 Diaries

Diaries will be dispensed *and reviewed* at *all v*isits ~~2-4~~, *except Visits 1, 2 and EoT.* The following data will be collected.

2.40 8.4.7 HE and PRO data

The questionnaire is to be filled in at Visits ~~1,~~ 3 *and* 5 *in the main phase*, *annually in the extension phase and at EoT Visit* preferably before any other trial related procedures.

2.41 9.4 Dispensing and Drug Accountability of Trial Products

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•No trial product(s) should be dispensed to any person not enroled in the *trial (excluding parents/LAR)*

Trial product will be dispensed at the visits depicted in the flow chart, see Table 2-1 *and 2-2.* The patient is required to return both used and unused vials at the next visit to the clinic or at the End of Trial Visit, as appropriate.

2.42 14 Monitoring Procedures

During the course of the trial, the Monitor will visit the trial site to ensure that the protocol has been adhered to, that all issues have been recorded, to perform source data verification and to monitor

drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP*, but* ~~The intervals between visits must not exceed 8 weeks when there are patients ongoing in the trial at the site. When there are no trial active patients at the sites, intervals between visits~~ must not exceed 12 weeks.

2.43 18.2.2 Primary Endpoint(s)

- Incidence rate of inhibitors defined as inhibitor titres ≥ 0.6 Bethesda units/mL *for the main phase of the trial*

The incidence rate of 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 *number of* all patients with inhibitors while the denominator will include *number of* all patients with *confirmed inhibitors during the main phase of trial or completed the main phase without confirmed* ~~minimum of 50 ED plus any patients with less than 50 ED but with~~ inhibitors.

2.44 18.2.4 Supportive Secondary Endpoints

All the below efficacy endpoints will be evaluated for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases. Sensitivity analyses will be made only including patients who do not develop inhibitors during the main phase of the trial and during the extension phase of the trial. ~~For patients that develop inhibitors only the time period until the last negative inhibitor result is considered for the efficacy endpoints below. Sensitivity analyses will be made only including patients who do not develop inhibitors. Further, tables will be made including only inhibitor patients. For these patients the relevant time period is the time period after positive inhibitor test~~.

Secondary Efficacy Endpoints

- Annualized bleeding rate during bleeding prevention period with turoctocog alfa

For this endpoint patients who develop inhibitors will only be included if they have been treated *with at least two doses of trial product* ~~for minimum 1 month~~ before the first positive inhibitor test. The reason to exclude these patients from the calculations is ~~that if the treatment period is too short,~~ that the *information from the treatment with one dose is too small and* the uncertainty introduced on the estimated annualized bleeding rate will be relatively large.

Separate reports and listings will be made for the above efficacy endpoints for patients developing inhibitors. Data used in these reports and listings will include data from the first time patient is confirmed with inhibitors until the end of the main phase of trial as well as until the end of trial. Furthermore, each of these reports will also be generated for different method for management of patients with inhibitors.

Secondary Safety Endpoints

- *Incidence rate of inhibitors defined as inhibitor titres ≥ 0.6 Bethesda units/mL for the extension part of trial and the combined main and extension phases of the trial.*

The incidence rate of inhibitors will be calculated and analyzed in the similar way as the primary endpoint.

Furthermore, Kaplan Meyer plots and the additional analyses outlined in Section 18.2.2 for the primary endpoint will be generated using data from the extension phase and the combined main and extension phases of the trial.

- Frequency of *AEs* ~~adverse events~~ and *SAEs* ~~serious adverse events~~

AEs and SAEs will be analyzed for the main phase of the trial and the combined main and extension phases.

Separate reports and listings will be made for AEs and SAEs for patients developing inhibitors. Data used in these reports and listings will include data from the first time patient is confirmed with inhibitors until the end of the main phase of trial as well as until the end of trial.

The incidence rate of clinically relevant inhibitors and high-titre inhibitors will be evaluated for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases.

All additional safety parameters such as laboratory parameters and physical examinations will be listed and summarized by visit for all patients *for the main phase of trial, for the extension phase of trial, and for the combined main and extension phases*

Separate reports and listings will be made for the above safety endpoints for patients developing inhibitors. Data used in these reports and listings will include data from the first time patient is confirmed with inhibitors until the end of the main phase of trial as well as until the end of trial.

2.45 18.6 Health Economics and Patient Reported Outcomes

Health economic data will be collected in the eCRF in connection with severe bleeds. Patient reported outcomes will be collected using questionnaires at Visits 3 and 5 *in the main phase, and annually during the extension phase.*

2.46 23 Responsibilities

The following will be analysed at the local laboratory: haematology, FVIII trough level assessment *and CD4+ T-cell (excluding Russia)*.

~~A~~Central *and specialized* laborator~~y~~*ies* will analyse and report all laboratory safety tests related to biochemistry, viral antibody assessments, FVIII activity, FVIII inhibitor assessments and *potential genotyping* performed in this trial.

2.47 27 References

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9 Investigator's Brochure. N8: Recombinant Factor VIII, ~~3~~*4th* edition. ~~10-12-~~*000915 May 2012*

2.48 Appendix B

The blood volume collected from the subject ~~for all tests~~ should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days *according to* ~~This requirement is in line with~~ European regulatory *guidelines* ~~requirements~~ (Directive 2001/20/EC)[2,19] ~~and FDA requirements~~*, or it should be according to local guidelines for blood sampling volumes. As a reference,* the table below shows the estimated blood volume in children weighing from 6 -25 kg and the blood volume that can be taken at any single time and *with*in 28 days*, respectively,* according to *EMA,* ~~European regulatory requirements (Directive 2001/20/EC)~~ and *over a 24h period according to* FDA ~~requirements~~ guidelines.

Total Blood volume *~~according to Geigy Scientific Table~~ and maximum blood sampling volume according to EMA and FDA.*

Weight (kg)	Blood volume (ml/kg)	Total Blood volume (ml)	Volume/blood sample (1%) ***EMA***	Volume/28 days (3%) ***EMA***	*Volume/ 24h* ***FDA***
6	**80**	**480**	**4.8**	**14.4**	

7	**80**	**560**	**5.6**	**16.8**	***14***
---	**---**	**---**	**---**	**---**	
10	**80**	**800**	**8.0**	**24.0**	***20***
---	**---**	**---**	**---**	**---**	
15	**80**	**1200**	**12.0**	**36.0**	***30***
---	**---**	**---**	**---**	**---**	
20	**80**	**1600**	**16.0**	**48.0**	***40***
---	**---**	**---**	**---**	**---**	
25	**80**	**2000**	**20.0**	**60.0**	***50***

Substantial Protocol Amendment no 6

to Protocol, final version 3.0

dated 27 August 2012

Trial ID: NN7008-3809
(turoctocog alfa)

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3b

Applicable to all countries

Amendment originator:

Name: [redacted]

Department: Haemophilia, Clinical Operations FVIII & FXIII

Table of contents

Page

Table of tables

Page

1 Introduction

1.1 Substantial protocol amendment

This global substantial amendment has been prepared to:

- enable performing Visit 1 and Visit 2 at the same day
- revise inclusion criterion no.2 and exclusion criterion no. 4
- delete inclusion criterion no.5 and exclusion criterion no. 6
- extend the number of required exposure days (ED) from 50 to 100
- analyse haematology samples at the central lab.

In this substantial protocol amendment:

- any new text is written in *italics*
- any text deleted from the protocol is written using ~~strike through~~.

Minor changes that do not affect the content of the protocol will not be disclosed in the following sections e.g.:

- the substance code NNC 0155-0000-0004 will be exchanged for turoctocog alfa
- minor inconsistencies and ambiguities
- typographical errors.

1.2 Rationale for amendment No. 6

The main focus of this amendment is enabling performing Visits 1 and 2 at the same day. The current clinical trial includes Previously Untreated Patients (PUP), and the protocol demands blood sampling at the first visit in the trial. This constitutes a risk for bleeds. For the safety of these untreated patients, we will make it possible to administer trial product already at the first visit to the clinic. This can be accomplished if Visit 1 and Visit 2 are performed at the same time, without waiting for lab result from screening assessments.

Changes to the eligibility criteria, i.e. deletion of inclusion criterion #5 and exclusion criteria and #6, and revising inclusion criterion #2 and exclusion criterion #4, are following considerations of relevance. Immune competency will be present in the vast majority of PUPs and inclusion criterion #5 can thus be regarded as unnecessary. Presence of FVIII inhibitors, $0.6 \geq$ BU, (exclusion criterion #4) can be considered as highly improbable in a true PUP population. Similarly, thrombocytopenia with platelets $\leq 50000/\mu l$ (exclusion criterion #6) will also very rarely, if ever, be seen in these haemophilic patients. The above mentioned parameters will be captured as baseline characteristics,

but not for eligibility.
It is our strong opinion that changing the above criteria will in not compromise the safety of the patients enrolled in the trial. Patients with any disease or condition which might pose a potential hazard are not eligible according to the unchanged exclusion criterion #7.

2 Changes

2.1 1 Summary

Trial Design

The trial consists of two phases. In the main phase, an aggregated number of at least 50 patients will receive preventive treatment with *turoctocog alfa* ~~NNC 0155-0000-0004~~ until they reach a minimum of 50 exposure days (ED) or until they develop inhibitors. After that the patient will continue in the extension phase *until at least 100 ED has been achieved*, which will *translate into a maximum of* ~~last for approximately~~ 3.5 years. The estimated total duration of the trial is approximately 5 years.

Trial Population

Approximately 60 PUP with severe (~~baseline level~~ FVIII ≤1%) haemophilia A with~~out~~ *no history of* inhibitors below 6 years of age in a non-bleeding state will be enroled to allow for at least 50 patients to complete the trial.

Key Inclusion Criteria:

- ---
- Male patients *diagnosed* with congenital severe haemophilia A (~~baseline level~~ FVIII ≤ 1%)

Key exclusion Criteria:

- ---
- *Any history of* FVIII inhibitor ~~(≥ 0.6 BU/mL) at screening~~
- ---
- ~~Platelet count <50,000 platelets/µL~~

2.2 2 Flow Chart

(Clarification note: For Table 2-1 and 2-2 only information that is subjected to changes is presented.)

Table 2–1 Visit Flow Chart main trial phase

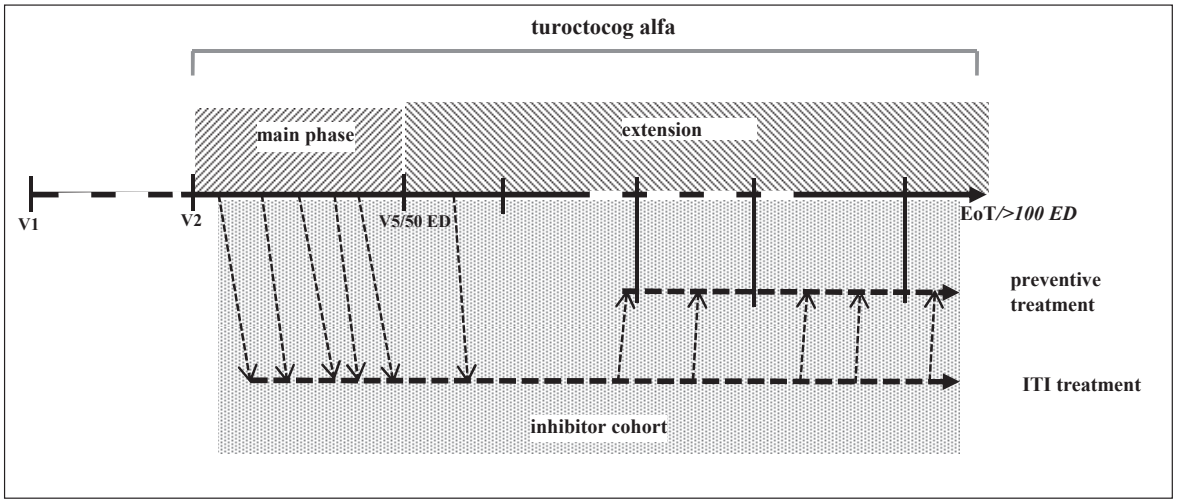
Visit number	Screen. Visit 1	Visit 2#	Visit 3	Visit 4	Visit 5	Unscheduled Visit
Visit window	NA	*<21~~14 ± 7~~* d post V1	10th -15thED	20th -25th ED	*50~~100~~th – 55~~110~~th* ED	

 # Visit 2 can be performed at the same day as Visit 1

Table 2–2 Visit Flow Chart trial extension phase

Visit type	Dispensing		Assessment& Dispensing	Dispensing		Assessment& Dispensing	End of Trial	Unsch Visit
Visit number#	6	7	8	9	10	11		
Previous visit time(w)	-8	-8	-10	-8	-8	-10	< 8	
Visit window	± 1w	± 1w	± 1w	± 1w	± 1w	± 1w	NA	NA
ASSESSMENTS								
SAFETY								
FVIII trough level	●*a*	●*a*	●a	●*a*	●*a*	●a		●*a*

a – optional, at discretion of investigator



Screening will be done at Visit 1.~~, 14 ± 7 days prior to~~ Visit 2 *will be performed within 21 days post Visit 1, and it could be the same day as Visit 1*. At Visit 2 eligible patients are enrolled and preventive treatment with investigational product (turoctocog alfa) starts if applicable (may start after the first two bleeds). At Visit 5, after ≥ 50 ED, patients will leave the main phase of the trial and continue in the extension phase. Patients who develop inhibitors can continue with ITI treatment with an alternative visit schedule (down ward arrows). If ITI treatment is successful these patients can continue with preventive treatment according to the extension phase (upward arrows). The patients will belong to either of the groups main-phase, extension phase or inhibitor cohort.

Figure 2–1 Trial Design

2.3 3.1.1.2 Risks and Benefits

After the patients *have achieved the required number of ED, they may* ~~will~~ continue in the trial until product launch or until the end of trial, should market authorisation not be obtained, see Section 7. This serves to minimise the patients' need of switching to other FVIII products

2.4 5.1 Type of Trial

The trial consists of two phases i.e. main and extension, respectively. In the main phase the patients will attend a screening visit (Visit 1) in order to assess their eligibility. At Visit 2 eligible patients will receive their first dose, if applicable. *It is an option to perform Visit 1 and Visit 2 at the same day for the purpose of immediate administration of the trial product. After Visit 2 the patients* ~~and~~ will be scheduled for 3 more visits *in the main phase.* After Visit 5 the patients will enter the extension phase, and a rolling visit schedule will apply with 6 planned visits (including 4 dispensing visits) per year.

The main trial phase will be completed when the aggregated number of patients, who have either received treatment with turoctocog alfa for at least 50 ED or developed inhibitors, are at least 50. *In the extension phase the patients will be followed until at least 100 ED has been achieved*. For the individual patient it translates into duration of the main phase of approximately 3-24 months depending on the dose regimens (and bleeding pattern). The duration of the extension phase may be up to 3.5 years, and the total duration of the trial is estimated to be approximately 5 years, please see Section 7.

2.5 ~~5.3~~ Treatment of Patients

Approximately 60 patients are expected to be enrolled *(trial drug administered)* into the trial in order to have 50 ~~evaluable~~ patients*, who complete* in ~~the main phase of~~ the trial (estimated drop-out rate is 15%). For replacement of withdrawn patients, please refer to Section 6.5.

2.6 ~~6.2~~ Inclusion Criteria

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2. Male patients *diagnosed* with congenital severe haemophilia A (FVIII level ≤1%)~~*~~

~~5. Immunocompetent, defined as either HIV negative or if HIV positive, $CD4^{+}$ cells > 200 cells/µl.~~

~~*based on the one-stage clotting assay~~

2.7 ~~6.3~~ Exclusion Criteria

4. *Any history of* FVIII inhibitor ~~(≥ 0.6 BU/mL) at screening~~

~~6. Platelet count <50,000 platelets/µL~~

2.8 ~~6.5~~ Patient Replacement

Withdrawn patients may be replaced to ensure that 50 patients complete the trial with at least ~~50~~ *100* ED. Assuming a drop-out rate of 15%, it is estimated that 60 patients must be enroled to obtain the 50 completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate.

2.9 ~~6.6~~ Rationale for Trial Population

Rational for Exclusion Criteria:

- Criteria~~a~~on no~~s~~. 3 and ~~6 are~~ is chosen to exclude patients with endogenous abnormalities of the coagulation system other than haemophilia

2.10 7 Trial Schedule

Planned completion of clinical trial report (CTR): ~~Q3 2016~~ *Q1 2017*

2.11 8.1.3 Visit 2

The visit will be scheduled *within 21* ~~14 ± 7~~ days after *Visit* 1.

The main purpose of Visit 2 is to administer turoctocog alfa for the first time, if applicable, *or alternatively dispense the trial product* to eligible patients.

2.12 8.1.3.1 Combining Visit 1 and Visit 2

Visit 1 and Visit 2 can be performed at the same day. It will allow for immediate administration of trial product should, this be preferred or deemed necessary.

Please ensure that all assessments required for Visit 1 and Visit 2 are performed and that all required blood samples for the central laboratory is taken before the administration of the trial product.

2.13 8.2.2 FVIII Inhibitors

All patients will be examined regularly for the development of FVIII neutralising antibodies (inhibitors). The tests will be performed at Visit 1 *(baseline characteristics)* and Visits 3-5 in the main phase of the trial, and at the Assessment&Dispensing *and EoT* Visits in the extension phase, i.e. at least twice annually. Additional laboratory assessment for FVIII neutralising antibodies can be done if inhibitor development is suspected during the course of the trial, or if more frequent testing is mandated i.e. during unscheduled visits.

2.14 8.2.3 FVIII ~~Recovery~~ *Assessments*

2.15 *8.2.3.1* *FVIII Activity*

In order to establish patient characteristics, baseline FVIII activity will be taken at Visit 1. Any anti-haemophilic treatment with blood components should be withdrawn at least 48 hours prior to blood sampling.

2.16 ~~8.2.3~~ *8.2.3.2* FVIII Recovery

Recovery is the FVIII plasma level recorded 30 ± 5 minutes after trial product administration and reported as [IU/mL]/ [IU/kg]. Recovery assessment is mandatory at inhibitor diagnosis to identify

clinical relevant inhibitors (see Section 8.2.2). Additional recovery assessments may be requested at the discretion of the Investigator.

Samples for FVIII recovery will be sent to the central laboratory for analysis, see Section 8.2.7.2.

2.17 ~~8.2.4~~ *8.2.3.3* FVIII Trough Level Assessment

The Investigator can at his/her discretion perform trough level assessments at *any visit during the trial, except* Visit ~~3-4~~ *1-2*. 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.

Trough levels need only to be recorded in the eCRF if it is the reason for dose adjustments.

2.18 8.2.5 Haematology

The assessment will be performed at Visit 1 and Visit 5 in the main phase, the Assessment&Dispensing Visits in the extension phase, EoT Visit and optionally at unscheduled visits. It is performed according to practice of the *central* ~~local~~ laboratory and includes:

~~It is recommended that the haematology values are reported in the above listed units. However, in the eCRF it will be possible to enter values in other units accepted by Novo Nordisk.~~

2.19 8.2.7.2 Local Laboratory Tests

Assessments of ~~haematology~~, FVIII trough levels ~~and CD4^{+} T-cell count (if applicable)~~ will be done at the local laboratory* as per standard of practice at the participating site. Laboratory results from the local laboratory will be recorded in the eCRF.

~~*in Russia and Hong Kong, CD4+ T-cell count is done centrally~~

2.20 8.2.7.3 Central Laboratory Tests

A central laboratory will coordinate analysis and report ~~of~~ all laboratory safety tests related to biochemistry, viral antibody assessments ~~except CD4^{+} T-cell count~~, FVIII inhibitor, FVIII activity and genotyping performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained.

2.21 8.4.5 Diaries

Diaries will be dispensed and reviewed at all visits~~, except visits 1, 2 and EoT~~ *starting from Visit2*.

2.22 12.1.2 Medical Event of Special Interest and other events for expedited reporting

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- Inhibitor formation against FVIII
    - *Inhibitor formation is always considered a MESI*. Blood samples for measurements of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk. *However, if an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, it should be reported as MESIs*.
      The diagnosis of inhibitor is made, if the patient has been tested positive for inhibitors (BU≥0.6/mL) at two consecutive tests *at the central laboratory,* sampled preferably within 2 weeks. ~~this should be reported by the Investigator as a MESI~~
      However, if the first inhibitor test is positive, it should also be reported as a MESI even though the confirmatory test is negative.

2.23 23 Responsibilities

The following will be analysed at the local laboratory: ~~haematology,~~ FVIII trough level assessment ~~and CD4+ T-cell (excluding Russia).~~

Central and specialized laboratories will analyse and report all laboratory safety tests related to biochemistry, *haematology,* viral antibody assessments, FVIII activity, FVIII inhibitor assessments and potential genotyping performed in this trial. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically. Laboratory data will be reported to Novo Nordisk in a manner that anonymity of patients will be maintained.

2.24 Appendix D Body Mass Index Charts

Appendix D will be deleted.

Protocol Amendment

no 7
to Protocol, final version 4
dated 30 November 2012

Trial ID:NN7008-3809

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to all countries

Amendment originator:

Name: [redacted]

Department: Haemophilia, Clinical Operations 1

Table of contents

Table of figures

Page

Table of tables

Page

1 Introduction including rationale for the protocol amendment

The main reasons for this amendment is to re-define the duration and conditions for treatment of patients with inhibitors, restrict the number of previous exposures to blood components (to keep a homogenous PUP population), re-define the trial duration and revise the date of end of trial. In addition, the possibility to further investigate immunogenicity of turoctocog alfa e.g. non-neutralising antibodies assessment and Human Leucocyte Antigen *(*HLA) genotyping will be introduced. Some changes are administrative to align with updated guidelines and Novo Nordisk Standard Operation Procedures e.g. the requirement to list the participating countries has been removed.

The Patient Information and Informed Consent will be adapted accordingly.

In this protocol amendment:

- Any new text is written ***in italics.***
- Any text deleted from the protocol is written using ~~strike through~~.
- Corrections of minor inconsistencies and ambiguities, and typographical errors will not be listed.

2 Changes

2.1 1 Summary

Trial Design

The trial consists of two phases. In the main phase, an aggregated number of at least 50 patients will receive preventive treatment with turoctocog alfa until they reach a minimum of 50 exposure days[2] (ED) or until they develop inhibitors. After that the patients will continue in the extension phase ~~until~~ *where at least 50 patients should achieve* at least 100 ED ~~has been achieved~~, which will translate into a ~~maximum~~ *trial duration* of *up to* ~~3.5~~ *5* years *(including any potential inhibitor treatment)*. The estimated total duration of the trial is approximately ~~5~~ *7* years.

Trial Population

Approximately 60 PUP with severe (FVIII ≤ 1%) haemophilia A with no history of inhibitors below 6 years of age ~~in a non-bleeding state~~ will be enrolled to allow for at least 50 patients to complete the trial

Key Inclusion Criteria

- ---
- No prior use of purified clotting factor products (previous exposure, *equal to or less than 5 ED* to blood components, *e.g. cryoprecipitate, fresh frozen plasma* is accepted)

2.2 2 Flow Chart

(Clarification note: For Table 2-1 and 2-2 only information that is subjected to changes is presented.)

Table 2–1 Visit Flow Chart main trial phase

Visit number[#]	Screen. Visit 1	Visit 2[#]	Visit 3	Visit 4	Visit 5	Unscheduled Visit
Visit window	NA	≤ 21 d post V1	10th -15thED	20th -25th ED	50th -55th ED	
SAFETY						
Consent for ~~FVIII~~ genotype test	●					
Antibodies **- FVIII inhibitors** ***- FVIII non-neutralising antibodies***	●a		●a	●a	●a	●a, b
Trial Material						
Diary and Trial card dispensing and/or collection[e]	●~~e~~	●~~e~~	●~~e~~	●~~e~~	●~~e~~	●b
Drug dispensing and accountability		●g	●	●	●	●b
Diary card training		●				

- Visit 2 can be performed at the same day as Visit 1

a – minimum 48 hours washout period of turoctocog alfa (or blood component products at Visit 1)

b – if applicable

---

e - Visit 1 trial card only, Visit ~~2-4~~ *2-5* diary card only

---

g - Visit 2 dispensing only~~, Visit 5 accountability only~~

Table 2–2 Visit Flow Chart trial extension phase

Visit type	Dispensing		Assessment& Dispensing	Dispensing		Assessment& Dispensing	End of Trial	Unsch Visit
Visit number[#]	6	7	8	9	10	11		
Previous visit time(w)	-8	-8	-10	-8	-8	-10	< 8	
Visit window	± 1w	± 1w	± 1w	± 1w	± 1w	± 1w	NA	NA
SAFETY								
Antibodies **- FVIII inhibitors** ***- FVIII non-neutralising antibodies***	●a	●a	●	●a	●a	●	●	●a

- Presented numbers are for the first 12 months. Visit numbers for future years will be in consecutive order

a – optional, at discretion of investigator

Caption text (Figure 2–1 Trial Design)
Screening will be done at Visit 1. Visit 2 will be performed within 21 days post Visit 1, and it could be the same day as Visit 1. At Visit 2 eligible patients are enrolled and preventive treatment with investigational product (turoctocog alfa) starts if applicable (may *be delayed, see section 5.3.1* ~~start after the first two bleeds~~). At Visit 5, after ≥ 50 ED, patients will leave the main phase of the trial and continue in the extension phase. Patients who develop inhibitors can continue with ITI treatment with an alternative visit schedule (down ward arrows). If ITI treatment is successful these patients can continue with preventive treatment according to the extension phase (upward arrows). The patients will belong to either of the groups main phase, extension phase or inhibitor cohort.

2.3 5.1 Type of Trial

The main trial phase will be completed when the aggregated number of patients, who have either received treatment with turoctocog alfa for at least 50 ED or developed inhibitors, are at least 50. In the extension phase*, at least 50* ~~the~~ patients will be followed until at least 100 ED has been achieved. For the individual patient it translates into duration of the main phase of approximately 3-24 months depending on the dose regimens (and bleeding pattern). The duration of the extension phase may be up to 3.5 years, and the total duration of the trial is estimated to be approximately ~~5~~ *7* years, please see Section 7.

2.4 5.3 Treatment of Patients

Patients will enter a bleeding preventive regimen as described below, see Section 5.3.1. ~~Preventive treatment can be postponed until a maximum of two bleeding episodes have occurred.~~ For prevention one single bolus dose of turoctocog alfa is administered intravenously (i.v.) at each administration day. Turoctocog alfa should preferably be administered in the morning. The maximum duration of treatment of a patient from first to last turoctocog alfa administration is approximately 4 years.

2.5 5.3.1 Preventive Treatment and Dose Adjustment

The decision to initiate preventive treatment will be made by the Investigator and the child's parent or legal representative with due consideration for the child's own wishes (if they are capable to express these wishes). *However, the preventive treatment has to be commenced no later than when the patient reaches 24 months old, or after a maximum of two treatment requiring bleeding episodes (joint, muscle or severe bleeding episode) have occurred, whatever comes first. Should a patient be older than 24 months of age at enrolment, preventive treatment needs to start immediately.*

2.6 5.3.2 Treatment of Bleeds and Dose Adjustments

~~If a haemostatic response of bleeds cannot be achieved (i.e. the bleed does not stop) after 48 hours using doses of turoctocog alfa up to 200 IU/kg BW per day, another FVIII product may be selected at the discretion of the Investigator. The use of other FVIII products will result in withdrawal of the patient from the trial.~~

2.7 5.3.4 Treatment of patients with Inhibitors

Patients who develop inhibitors, within this trial, will be offered continued treatment with turoctocog alfa ~~for 12 months~~, *including ITI treatment for a maximum period of 24 months.* It may also be decided by the Investigator and/or parent/legal representative to withdraw the patient.

Patients will be evaluated after 12 months of ITI treatment, based on the level of inhibitors. If inhibitors are still positive after 12 months, but the decline from peak titer level is ≥ 20%, ITI may continue for a maximum period of 24 month in totals.

If needed and decided by the Investigator, the initiation of the inhibitor treatment with turoctocog alfa can be delayed, ~~for up to~~ *but it has to start within* 6 months from the time of diagnosis of inhibitor.

If the inhibitor disappears (BU <0.6/mL) during the ITI treatment, the patient ~~should~~*will continue in the extension phase at a time point decided by the Investigator,* resuming/*starting* preventive treatment as recommended in this protocol, see Table 5–1. *However, if the inhibitor persists after 24 months of ITI treatment, the patient will be withdrawn from the trial.* ~~following the visit schedule in the extension phase. For patients still with positive inhibitors after 12 months ITI treatment, continued trial participation will be evaluated based on the level of inhibitors.~~

Treatment of bleeds with by-passing agents i.e. FVIIa or activated prothrombin complex concentrate (APCC) *according to local label*, is allowed for patients who develop inhibitors. *Bypassing agents are not considered trial medication*

2.8 5.4 Treatment after End of Trial

When discontinuing trial product, patients should be switched to a suitable marketed product at the discretion of the Investigator. It is expected that turoctocog alfa will be granted marketing authorisation and is commercially available when the patients complete this trial. *However, this cannot be guaranteed.*

Novo Nordisk will not provide any patient with trial medication after the end of the trial unless required in accordance with local law or regulation.

2.9 6.1 Number of patients to be Studied

~~Countries planned to participate: Austria, Brazil, China, Croatia, Greece, Hong Kong, Japan, Russia, Spain, Turkey, and US.~~

Planned number of patients to complete the main phase of the trial: 50

2.10 6.2 Inclusion Criteria

---
4. No prior use of purified clotting factor products (previous exposure, *equal to or less than 5 ED* to blood components*, e.g. cryoprecipitate, fresh frozen plasma,* is accepted)

2.11 6.4 Withdrawal criteria

A patient must be withdrawn if the following applies:
1. Not in use
2. Allergy/Anaphylaxis to the trial product
3. Treatment with FVIII products other than turoctocog alfa
4. Not in use
5. *Inhibitor treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (BU ≥ 0.6/mL)*
6. *FVIII inhibitor titer decline from peak level is less than 20% after 12 months of inhibitor treatment*
7. *FVIII inhibitor is positive (BU ≥ 0.6/mL) after 24 months of inhibitor treatment.*
8. *After completed inhibitor treatment (maximum 24 months), preventive treatment as described in the protocol is not resumed/started.*

2.12 6.6 Rationale for Trial Population

Rational for Withdrawal Criteria

- *Criterion no. 5-8 are selected for the safety of patients, who do not benefit from inhibitor treatment with turoctocog alfa*

2.13 7 Trial Schedule

Planned *date for* LPLV: ~~QIII~~ *30 June* ~~2016~~*2018*

~~The duration of the trial for the individual country is dependent upon the timelines of market authorisation and commercial availability of the trial product. Should market authorisation not be obtained, the maximum trial duration is approximately 5 years.~~

The duration of turoctocog alfa treatment in this trial is a minimum total 100 EDs for a particular patient. Once a patient has achieved 100 EDs, they may be offered the option to continue in the trial until either turoctocog alfa is commercially available in the relevant country or until the marketing authorisation application for turoctocog alfa is rejected in the relevant country unless the trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the LPLV for the trial will be no later than 30 June 2018 whether or not the product is commercially available in the relevant country.

The following exceptions will be made to the date for LPLV:

- *patients will be allowed to achieve at least 100 ED with trial product.*
- *patients with inhibitor will be allowed to receive ITI treatment for up to 24 months.*

Planned completion of *main* clinical trial report (CTR): Q1 ~~2017~~ *2016*

Planned completion of updated clinical trial report: Q4 2018

2.14 8.1.3 Visit 2

Other~~Another~~ important purposes are to provide the patient and care giver training for home treatment *and training for how to fill out the diary.*

2.15 8.1.5. Unscheduled Visit

If the patient visits the site for additional dispensing of trial product and/or auxiliary supplies, or if a scheduled visit is postponed, it is not considered as an unscheduled visit.

2.16 8.2.2 FVIII antibodies ~~Inhibitors~~

2.17 8.2.2.1 FVIII Inhibitors

2.18 8.2.2.2 Non-neutralising antibodies

Plasma samples for analysis of non-neutralising antibodies against FVIII will be taken at the same time point as for inhibitor testing. The results will be used to characterise the underlying immunogenicity towards FVIII. The samples will be frozen and stored and the analysis will be carried out by a validated antibody assay. The samples may be used for further FVIII antibody characterisations (e.g. isotyping, binding properties).

It will not be possible to review the results of non-neutralising antibody measurements in relation to potential AEs because the results will be available after LPLV.

Determination of non-neutralising antibodies against FVIII will be performed by Novo Nordisk A/S or by a laboratory appointed by Novo Nordisk A/S.

If requested by the regulatory authorities antibody samples may be stored for a longer period until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

2.19 8.2.4 Haematology

- Haemoglobin (~~mmol~~g/L*)*

2.20 8.2.6.1 General Considerations

Laboratory results should be signed and dated by the Investigator. Laboratory reports (laboratory result) are considered source data and should be kept in patient file for source data verification

(carried out by the monitor). Clinically significant findings must be recorded as concomitant illness (blood samples during visit 1) or as an Adverse Event (blood samples taken during the course of the trial). Abnormalities should only be recorded as AEs if not present or worsened from baseline/previous assessments.

2.21 8.2.6.2 Local Laboratory Tests

~~An Investigator must sign, date and categorise the local laboratory results. Categorisation will be either "normal", "out of normal range, not clinically significant" or "out of normal range, clinically significant". Clinically significant findings must be recorded as concomitant illness (blood samples during visit 1) or as an Adverse Event (blood samples taken during the course of the trial). Abnormalities should only be recorded as AEs if not present or worsened from baseline/previous assessments. Laboratory results should be signed and dated. Laboratory reports (laboratory result) are considered source data and should be kept in patient file for source data verification (carried out by the monitor).~~

2.22 8.2.6.3 Central Laboratory Tests

A central laboratory will coordinate ~~analysis and report of~~ all laboratory ~~safety~~ tests *and will perform* ~~related to~~ the biochemistry*, haematology and* viral antibody assessments. FVIII inhibitor, *turoctocog alfa antibodies*, FVIII activity and genotyping *assessments will be* performed *by different specialized laboratories.* ~~in this trial.~~ Laboratory data from the central *and specialized* laboratories will be reported to Novo Nordisk electronically, and in a manner that *ensures* anonymity of patients~~will be maintained~~.

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

2.23 8.3.1 Bleeds

- Dose(s) *(trial product volume and vial strength)* and Time(s) of administration

2.24 8.3.1.1 Definition of Severity of Bleeds

Severe: Major bleeds that require hospitalisation. All internal head and neck bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) will also be reported as severe and entered in the eCRF.~~All mild or moderate bleeds which are on-going 24 hours after start will be redefined as severe.~~

2.25 8.3.1.3 Bleed Classification

Re-bleeds will be reported by the trial statistician based on the diary data. Re-bleed is defined as *a bleed*~~when after an initial period of improvement,~~ *(*worsening of bleeding site conditions *e.g. swelling, pain)* ~~either on treatment or~~ within 72 hours after stopping of *a previous bleed at the same anatomical location.*~~treatment (therefore, a new bleed is considered occurring later than 72 hours after stopping of treatment~~.

2.26 8.4.1 ~~FVIII~~ Genotype testing

At Visit 1, all patients/parents/legally authorised representative (LAR) will be asked about documentation of previous FVIII *and Human Leucocyte Antigen (HLA)* genotype tests. If not available or if it needs to be re-tested, *based on the Investigators discretion*, FVIII *and HLA* genotype testing will be offered as allowed by local law. The blood sample should be taken at Visit 3, 4 or an unscheduled Visit. The ~~FVIII~~ genotype analysis is performed at the laboratory in Bonn, Germany.

Investigator, parent(s) or LAR have the right to refuse to provide patient's ~~FVIII~~ genotype documentation or to refuse genotyping. This will not ~~stop~~ *prevent* the patient's ~~to~~ continued participation in the remainder of the trial.

Applicable for Japan only: If documentation of the patient´s genotype already exists, the patient is offered to provide his data for the trial. If no previous data exists and genotyping consent is obtained,~~ FVIII~~ genotype analysis is performed at the laboratory in Bonn, Germany, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than FVIII *and HLA*. Samples will be disposed appropriately after the test and all test results are kept strictly confidential.

2.27 9.1 Trial Products

Novo Nordisk will not supply any non-investigational products (NIMPs).

2.28 9.4 Dispensed and Drug Accountability of Trial Products

Once a patient is dosed, *the* ~~all~~vials (used,~~ partially used,~~ unused, returned, and lost/damaged) must be recorded in the IV/WRS Drug Accountability module.

2.29 11 Concomitant Illnesses and Concomitant Medication

Concomitant medication: any medication, other than the trial product(s), that is taken during the trial, including the screening and run-in periods. Vaccinations must also be recorded as concomitant medication, *and it should include vaccinations performed 1 year prior to Visit 1.*

NB Vaccinations planned ahead of trial participation should be postponed to 3 months after the first turoctocog alfa treatment, as vaccination activates the immune system of the patient, thereby potentially increasing the risk of inhibitor development

2.30 12.1 Definitions

Serious Adverse Event (SAE):

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- Important medical events~~d)~~ that may not result in death, be life-threatening[a)] or require hospitalisation[b] may be considered a SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition *SAE*[d]. *Suspicion of transmission of infectious agents via trial product and formation of inhibitory antibodies must always be considered an SAE.*

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d) ~~The term "important medical events" means events which may jeopardise the patient or require intervention to prevent a seriousness criterion. It can be AEs which suggest a significant hazard or puts the patient or clinical investigation subject at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.~~ *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.*

~~**Relationship to Trial Product (turoctocog alfa) Assessment Definitions**~~ ***Causality assessment***
The following terms are used when assessing the relationship between an AE and the relevant trial product(s):

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 aetiology other than the trial product.

~~**Outcome Categories and Definitions**~~ ***Final outcome of an AE***

- **Recovered/*resolved*** [*] – Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the patient signed the informed consent.
- **Recovering/*resolving*** – The condition is improving and the patient is expected to recover from the event. This term should only be used when the patient has completed the trial *or has died from another AE*.
- **Recovered/*resolved* with sequelae** – ~~As a result of the AE the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed).~~*The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure* If the sequelae meets a ~~seriousness~~ *SAE* criterion, the AE must be reported as a SAE
- **Not recovered/*not resolved* -** *The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known*
- **Fatal -** *This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved","recovering/resolving","recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE*.
- **Unknown** – This term should only be used in cases where the patient is lost to follow-up.

[*] ~~In Japan "Remitted" will be used~~

2.31 12.1.2 Medical Event of Special Interest and other events for expedited reporting

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- Medication error
    - Administration of wrong drug
    - Wrong route of administration such as intramuscular instead of intravenous
    - Administration of an accidental ~~overdose i.e. dose which may lead to significant health consequence as judged by the Investigator irrespective of whether a SAE~~

~~criterion is met~~ *lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen as judged by the Investigator, although not necessarily did happen.*

- Administration of a high dose with the intention to cause harm (*e.g. suicide attempt)*

2.32 12.2 Collection, Recording and Reporting of Adverse Event

All events meeting the definition of an AE must be collected and reported; ~~from screening (visit 1)~~ *this includes events from the first trial related activity after the patient has signed the informed consent* until End of Trial and at potential Follow-Up visits. *The events must be recorded in the applicable CRF forms in a timely manner, see timelines below and Figure 12.1*

During each contact with the trial site *staff*(~~visit or telephone, excluding safety visits, where the patient is not seeing the Investigator or site staff e.g. visits to the laboratory~~) the patient must be asked about adverse events, e.g. "Have you experienced any problems since the last contact?"

MESIs and other events for expedited reporting must always be reported to Novo Nordisk on the AE form and the safety information form, irrespective of seriousness. ~~within the same timelines as for SAEs.~~

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:
~~The Investigator must report initial information on all SAEs, MESIs and other events for expedited reporting to Novo Nordisk within **24 hours** of obtaining knowledge about the event.~~

The Investigator must complete *the following forms in the CRF/eCRF within the specified timelines* ~~and forward electronically in pdf format/fax copies to Novo Nordisk~~:

- ***SAEs:*** *The* AE form ~~in the eCRF~~ **within 24 hours** *and the paper safety information form within 5 calendar days of the Investigator's first knowledge of the SAE.*
  The AE form in the eCRF must be signed within 7 calendar days from the date the information was entered in the eCRF.
- ***Non-serious AE fulfilling the MESI criteria:*** *The AE form and safety information form* **within *14 calendar days*** *of the Investigator's first knowledge of the event***.**
- ~~safety information form on the paper CRFs **within 5 calendar days**~~

The paper safety information form must be forwarded to NovoNordisk either by fax, email or courier.

Contact details (fax, telephone, e-mail and address) are provided in the Investigators trial file.

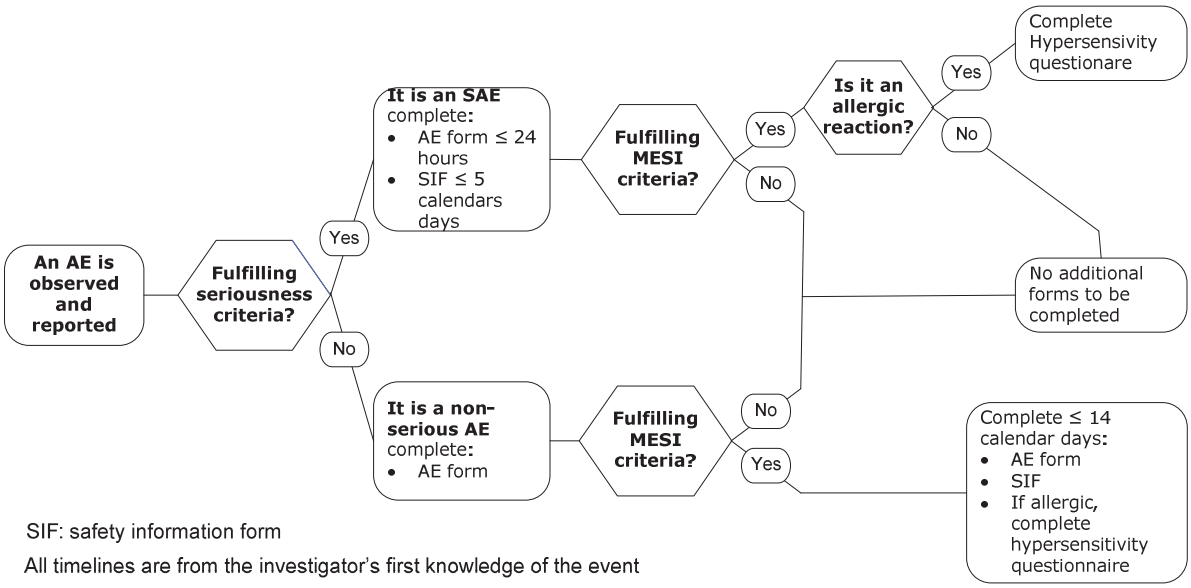

Figure 12–1

Reporting of trial product-related SUSARs by the sponsor:
~~For US the Investigator, and for all other countries Novo Nordisk, must inform the regulatory authorities and IECs/IRBs in accordance with the local requirements in force and ICH GCP[8].~~

Novo Nordisk will notify the Investigator of trial product related suspected unexpected serious adverse reactions (SUSARs) in accordance with the local requirements. In addition, the Investigator will be informed any trial related SAEs that may warrant a change of any trial procedure.

~~Investigators will be notified of trial related SAEs in accordance with the local requirements in force and ICH GCP[8]. In Japan, Novo Nordisk must inform the health authorities and the relevant parties of SAE information in accordance with the Japanese requirements in force and ICH GCP.~~

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and GCP, unless locally this is an obligation of the Investigator.

2.33 12.2.2. Follow-up of Adverse Events

~~During and following a patient's participation in a clinical trial, the Investigator should ensure that adequate medical care is provided to the patient for any AE, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for AE(s) of which the Investigator becomes aware.~~

~~The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.~~

The Investigator must record follow-up information updating the forms in the eCRF, and/or as corrections to the original paper CRF or by using a new paper form marked as follow-up.

Follow up information must be reported to Novo Nordisk according to the following:

- ***SAEs***: All SAEs~~, MESIs and other events for expedited reporting~~ must be followed until the outcome of the event is "recovered/*resolved*", "recovered/*resolved* with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs on-going at time of death (where death is due to another AE) ~~can~~ *may* be closed with the outcome "~~recovered~~recovering/resolving" or "not recovered/*not resolved*". Cases can be closed with the outcome of "recovering*/resolving*" when the patient has completed the ~~trial~~ *follow-up period* and is expected by the Investigator to recover.

  The SAE follow-up information should only include new (*e.g.* corrections, or additional) information ~~should~~ *must* be reported **within 24 hours** of ~~obtaining knowledge~~the Investigator's first knowledge of the information ~~for SAEs~~. *This is also the case for* previously non-serious AEs *which subsequently* become SAEs.
- ***Non-serious AEs***: ~~All~~Non-serious AEs ~~classified as severe or possibly/probably related to the trial product~~ must be followed until the~~ patient has~~ *outcome of the event is "recovering/resolving*", "recovered*/resolved*" or "recovered*/resolved* with sequelae" *or until the end of the follow-up period stated in the protocol, whichever comes first,* and *until* all queries *related to these AEs* have been resolved. Cases of chronic conditions or cancer or AEs on-going at time of death (where death is due to another AE) ~~can~~ *may* be closed with an outcome of "recovering*/resolving*" or "not recovered*/not resolved*". Cases can be closed with an outcome of "recovering*/resolving*" when the patient has completed the ~~post-trial~~ follow-up period and is expected by the Investigator to recover.

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

- ***Non-serious AE fulfilling the MESI criteria****: Follow-up information on MESIs should only include new (e.g. corrections or additional) information and must be reported* ***within 14 calendar days*** *of the Investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.*

~~The Investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.~~

The Investigator must ensure that the worst case severity and seriousness *of an event* is kept ~~consistent~~*throughout the trial*. *A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.*

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** *from the date of receipt of the request*, unless otherwise specified *in the follow-up request*. ~~The Investigator must forward follow-up information on SAEs, MESIs and other events for expedited reporting within 5 calendar days of obtaining the information. This must be done by updating the AE form in the eCRF and/or completing a new safety information form marked follow-up on paper CRF and forwarding these to Novo Nordisk.If for any reason the EDC application is unavailable, then fax, telephone or e-mail to Novo Nordisk~~.

2.34 12.3.1 ~~Collection and~~ Reporting of Technical Complaints

---

~~The patient must be asked about technical complaints during each contact (visit or telephone) with the Investigator or trial site staff. This may be done by posing a simple question such as "have you experienced any problems since the last contact?".~~

~~The AE(s), SAE(s), MESI(s) and/or other events for expedited reporting related to technical complaint(s) must be reported by the Investigator following the same reporting requirements and timelines as for other AEs, SAEs, MESIs and other events for expedited reporting (see section 12.2).~~

The Investigator must fax the technical complaint form to Customer Complaint Center, Novo Nordisk, fax: +45 44 42 13 70, within the following timelines of the trial site obtaining knowledge of the technical complaint:

- technical complaint assessed as related to a **SAE ~~and/or MESI~~ within 24 hours**

- all other technical complaints within **5 calendar days**

2.35 13.4 Analysis Results

Laboratory reports from the *central, specialized and* local laboratories must be signed and dated by the Investigator on the day of the review of the analysis results. ~~The~~ *Potential* results from the local laboratory should be entered in the eCRF for each patient. A signed and dated copy of ~~Local~~ *the* laboratory reports must be retained at the trial site.

2.36 14 Monitoring Procedures

During the course of the trial, the Monitor will visit the trial site to ensure that the protocol has been adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. *The first monitoring visit will be performed as soon as possible after FPFV and no later than 4 weeks after.* The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate*,* and the compliance of the trial site to the protocol and GCP, ~~but~~ *and* must not exceed 12 weeks *after preventive treatment has been commenced. Prior to initiation of preventive treatment monitoring should be performed when a patient has been screened and after each treatment requiring bleed.*

2.37 18.2.1 General Considerations

The main CTR will be conducted when at least 50 patients have completed the main phase of the trial (completed visit 5 or has a confirmed inhibitor). The main CTR will present data for the main phase, the extension phase and the combined main and extension phases of the trial. An updated CTR will be conducted when all patients have completed the extension phase of the trial. The updated CTR will also present data for the main phase, the extension phase and the combined main and extension phases of the trial.

2.38 18.4 Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

The data from genotyping and immunogenicity assessment will be summarised using descriptive statistics.

2.39 19.1 Informed Consent Form for Trial Patients

Prior to any trial-related activity, the Investigator must give the patient and/or the patient's LAR oral and written information about the trial 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 trial the notion of~~

~~legal representative should be understood as both parents, or legal representative(s), as defined in Member States' national laws, who consents on behalf of the child.~~

~~**Consent**: As a child is unable to provide legally binding consent, informed consent must be sought from the parents/ legal representative (see definition above) on the child's behalf. The specific and written informed consent of the parents/legal representative must be sought prior to enrolling a child in the trial. Information should be given by an experienced Investigator to each parent, or the legal representative, on the purpose of the trial and its nature.~~

The patients or the patient's LAR must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The Investigator must ensure the patient or the patient's LAR ample time to come to a decision whether or not to participate in the trial.

2.40 19.4 Regulatory Authorities

Regulatory authorities will receive the clinical trial application (CTA)/clinical trial notifications (CTN for Japan), substantial/non-substantial protocol amendments ~~(notifications of protocol amendments for Japan)~~, reports on SAEs, and the CTR according to national requirements.

2.41 20 Premature Termination of the Trial/Trial Site

~~Two~~ *One* pre-planned safety interim analysis will be performed during the trial to monitor the inhibitor development.

2.42 23 Responsibilities

Central and specialized laboratories will analyse and report all laboratory safety tests related to biochemistry, haematology, viral antibody assessments, FVIII activity, FVIII ~~inhibitor~~ *antibody* assessments and potential genotyping performed in this trial. Laboratory data from the central *and specialized* laboratories will be reported to Novo Nordisk electronically. Laboratory data will be reported to Novo Nordisk in a manner that anonymity of patients will be maintained.

2.43 25 Retention of Clinical Trial Documentation

The Investigator must be able to ~~get hold of~~ *access* his/her trial documents without involving Novo Nordisk in any way. *Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the Investigator before access is revoked to the systems supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (e.g. the CD-ROM) is not readable during the entire storage period, the Investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.*

~~Clinical trial documentation must be retained until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Medicinal Product.~~

~~For Japan, the Clinical trial site should retain clinical trial documentation until approval, or 3 years after the date of premature termination or completion of the clinical trial. The sponsor should retain clinical trial documentation for 5 years after the approval (in case of drug subjected to reexamination, until re-examination is completed), or 3 years after the date of premature termination or completion of the clinical trial.~~

2.44 Attachment I – Global

List of Key Staff, Relevant Departments and CRO(s)

Sponsor´s medical expert	Name	[redacted]
	Address	Novo Allé DK-2880 Bagsvaerd
	Tel:	[redacted]
	Fax:	+45 44436740
	E-mail:	[redacted]
International Trial Manager:	Name:	[redacted]
	Address:	Novo Allé DK-2880 Bagsvaerd

Tel: [redacted]

Fax: +45 44436740

E-mail: [redacted]

Special Laboratory

Name: *NovoNordisk Laboratory*

Contact person: [redacted]

Address: *Cell and Antibody Analysis*
Novo Nordisk Park G8 S.10

DK-2760 Måløv
Denmark

Tel: [redacted]

E-mail: [redacted]

IVRS vendor:

Name: [redacted]

Program Manager: [redacted]

Address: [redacted]

[redacted]

[redacted]

Tel: [redacted]

Fax: [redacted]

E-mail: [redacted]

Protocol Amendment

No 08_AT
to Protocol, final version 5.0
dated 11 Nov 2013

Trial ID: NN7008-3809

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to Austria

Amendment originator:

Name: [redacted]

Department: [redacted]

Table of contents

Page

1 Introduction including rationale for the protocol amendment

In this protocol amendment: A new site will be added.

2 Changes

An additional site will be opened:

[redacted]

Protocol Amendment

no 9
to Protocol, final version 5
dated 11 November 2013

Trial ID:NN7008-3809

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

Haemophilia, Clinical Operations 1

Table of contents

Table of figures

Table of tables

1 Introduction including rationale for the protocol amendment

1.1 Overview of changes:

1. Clarified that commercially available FVIII must not be infused prior to enrolment
2. Added withdrawal criteria: Preventive treatment not initiated at age of 24 months
3. Recruitment period has been prolonged
4. Added a new laboratory test: Lupus Anticoagulant
5. Added long term retention of remaining blood samples (Biospecimens)
6. Changed the timing of interim analysis by including inhibitor patients in the "25 patients who need to completed visit 4 before the interim analysis".
7. Added a new preventive treatment frequency of twice weekly
8. Number of planned sites increased
9. Added monitoring visits every 12 weeks also before patients have been recruited at a site
10. Changed definition of disease related bleedings from being AEs to not being AEs
11. Clarification that the maximum of 2 treatment requiring bleeding episodes, before preventive treatment must start, must be treated with trial product (turoctocog alfa)
12. Clarified dosing for treatment of bleeds
13. Clarified publications of results
14. Clarified dosing guidelines for ITI treatment
15. Clarified timing of CD4+T cells sampling
16. Changed minor inconsistencies, ambiguities and typographical errors

Subject information/Informed consent:

17. Changed minimum mandatory safety text
18. Changed inconsistencies. These changes are considered minor and do not affect the content of the SI/IC and thus will not be listed in this amendment:

- your treatment changed to your child's treatment
- investigator changed to trial doctor
- drug changed to medication
- doctor changed to trial doctor

1.2 Rational for the changes:

1. The trial product (turoctocog alfa) will be commercially available during the conduct of this trial and must not be used prior to trial enrolment due to that potentially patients that are excluded due to inhibitor developed using turoctogoc alfa will bias the primary endpoint
2. It has previously been stated in the protocol that preventive treatment must be initiated before the age of 24 months. This has now been emphasised by adding this to the withdrawal criteria.

3. To ensure possibility of recruiting Chinese patients as the CTA in China has been delayed
4. To align with other PUP trials in haemophilia and to ensure better evaluation of inhibitor patients
5. To ensure a possibility of exploratory analysis in the future on remaining blood samples and to align with other PUP trials in haemophilia
6. To ensure timely interim analysis independent of number of inhibitor patients
7. The gap from once weekly to 3 times weekly infusion of preventive treatment was to big so sites have requested twice weekly frequency to avoid overdosing of patients
8. To ensure the number of planned recruited patients are fulfilled the number of sites are increased
9. 12 weeks between monitoring visits even if there are no patients at site have been reintroduced to ensure a check of trial supplies at site and thus possibility to enrol patients
10. To align with other guardian protocols and Global Safeties current definition of disease related bleedings
11. Ensure no misunderstanding regarding treatment requirering bleeds must be treated with trial product (turoctocog alfa)
12. Sites have requested a guideline for treatment of bleeding episodes
13. Align with current procures for publication of results
14. To guide sites if dosing during ITI treatment
15. Align flow chart with text in protocol
16. Enhance quality of protocol

Subject information/Informed consent:

17. Minimum mandatory safety text has been updated
18. Enhance quality of SI/IC

In this protocol amendment:

- Any new text is written ***in italics.***
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

1 Summary

….

Primary Endpoint:

Incidence rate of FVIII inhibitors (~~>~~≥0.6 BU~~/ml~~) will be evaluated for the main phase of the trial

Key Secondary Endpoints:

….

Incidence rate of FVIII inhibitors (~~>~~≥0.6 BU)

Key Inclusion Criteria:

….

- No prior use of purified clotting ~~factor~~ *FVIII* products (previous exposure, equal to or less than 5 ED to blood components, e.g. cryoprecipitate, fresh frozen plasma is accepted) *including commercially available NovoEight® /Novoeight®*

Trial Product

…

~~The dose for treatment of bleeds is decided by the Investigator but should be approximately 25-50 IU/kg in accordance with Guidelines for the Management of Haemophilia[1]. The maximum total daily dose of turoctocog alfa for the treatment of bleeds is 200 IU/kg with a maximum dose per infusion of 100 IU/kg.~~

2 Flow chart

Table 2-1 Visit Flow Chart main trial phase

Visit number	**Screen. Visit 1**	**Visit 2[#]**	**Visit 3**	**Visit 4**	**Visit 5**	**Unscheduled Visit**
Visit window	**NA**	**~~<~~≤ 21 d post V1**	**10th - 15thED**	**20th -25th ED**	**50th -55th ED**	
PATIENT RELATED INFO / ASSESSMENTS						
Consent for genotype test	●,*b*					
Biospecimen consent	●,*b*					
~~FVIII g~~Genotype test [f]			●b	●b		●b
Lupus Anticoagulant						●*b*
HE assessment		●	●	●	●	●*b*
Viral antibody test ~~(if HIV, HBsAg and /or HCV status unknown)~~	●i ,~~b~~					●*b*
T cells subset: CD4+	●~~b,~~h	●~~b,~~h				●b,h
TRIAL MATERIAL						
~~Completion session in IV/WRS~~						
Diary ~~card~~ training		●				

- Visit 2 can be performed at the same day as Visit 1

a – minimum 48 hours washout period of turoctocog alfa (or blood component products at Visit 1)

b – if applicable *or optional*

c – mandatory to confirm clinical relevant inhibitors

d – weight only
e – Visit 1 trial card only, Visit 2-5 diary ~~card~~ only
f – if *previous tests are* not available, if allowed by *local* law and after consent
g – Visit 2 dispensing only
h – if HIV positive, last value of CD4+ T-cells (if available), or new cell count
i - *if HIV, HBsAg and/or HCV status unknown*

Table 2-2 presents the rolling visit schedule in the extension phase over the period of one year. It comes to effect after Visit 5 or after ~~ITI~~ inhibitor treatment.

Table 2-2 Visit Flow Chart trial extension phase

Visit type	Dispensing		Assessment & Dispensing	Dispensing		Assessment & Dispensing	End of Trial	Unsch Visit
Visit number[#]	6	7	8	9	10	11		
Previous visit time(w)	-8	-8	-10	-8	-8	-10	< 8	
Visit window	± 1w	± 1w	± 1w	± 1w	± 1w	± 1w	NA	NA
ASSESSMENTS								
Withdrawal Criteria	●	●	●	●	●	●		●*b*
Body measurements			●c			●c	●	●*a*
SAFETY								
Lupus Anticoagulant								●*b*
FVIII trough level	●a	●a	●a	●a	●a	●a		●a
FVIII recovery	●a	●a	●a	●a	●a	●a		●a
Biochemistry ~~& Haematology~~			●			●	●	●a
Haematology			●			●	●	●*a*

OTHER ASSESSMENTS								
HE assessment	●~~b~~	●~~b~~	●~~b~~	●~~b~~	●~~b~~	●~~b~~	●~~b~~	●b
Viral antibody test ~~(if HIV, HBsAg and /or HCV status unknown)~~							●	●*a,~~b~~*
T cells subset: CD4+							●	●*b*
TRIAL MATERIAL								
turoctocog alfa administration	●a	●a	●a	●a	●a	●a		●*a*
Diary ~~card~~ dispensing and/or collection	●	●	●	●	●	●	●d	●*b*
Review of patient diary and entry of data in eCRF	●	●	●	●	●	●	●	●*b~~,a~~*
Drug dispensing and accountability	●	●	●	●	●	●	●e	●*b~~,a~~*

- Presented numbers are for the first 12 months. Visit numbers for future years will be in consecutive order

a – optional, at discretion of investigator

b – if applicable

c – weight only

d – collection only

e – accountability only

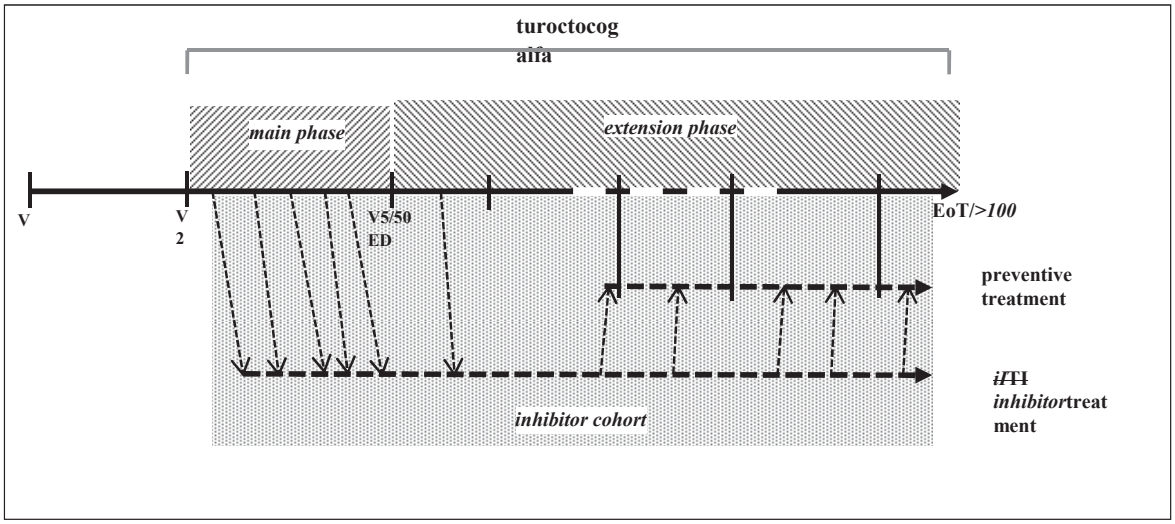

Figure 2–1 Trial Design

3.2 Rationale for the Trial

…

The guardian™ 4 trial is a prospective clinical phase 3*a*~~b~~ trial intended at demonstrating safety and efficacy of turoctocog alfa in PUP < 6 years of age with severe haemophilia A.

4.2 Endpoint

…..

Primary Endpoint

1. Incidence rate of FVIII inhibitors (≥0.6 BU~~/ml~~) will be evaluated for the main phase of the trial.

…….

Safety Endpoints:

……

- Incidence rate of clinically relevant inhibitors defined as an inhibitor titre (≥0.6 BU~~/mL~~) combined with a decreased recovery (<66% of expected level)

- Incidence rate of high-titre inhibitors defined as inhibitor titre ≥ 5 BU~~/mL~~.
- Incidence rate of FVIII inhibitors (~~>~~≥0.6 BU~~/mL~~)

5.3.1 Preventive Treatment and Dose Adjustment

The preventive treatment regimens are meant to reflect the different dosing regimens applied globally for initial and continued treatment of PUP. The recommended dose is 15-50 IU/kg BW once weekly at the start of preventive treatment, but ~~higher and~~ more frequent doses may be necessary depending on the clinical situation. The regimen should then be gradually increased towards 20-50 IU/kg BW every second day or 20-60 IU/kg BW *two or* three times weekly.[14]

The decision to initiate preventive treatment will be made by the Investigator and the child's parent or legal representative with due consideration for the child's own wishes (if they are capable to express these wishes). However, the preventive treatment has to be commenced no later than when the patient reaches 24 months old, or after a maximum of two ~~treatment requirering~~ bleeding episodes *have occurred which require treatment with turoctocog alfa* ~~(joint, muscle or severe bleeding episode) have occurred~~, whatever comes first. Should a patient be older than 24 months of age at enrolment, preventive treatment needs to start immediately

5.3.2 Treatment of Bleeds ~~and dose adjustment~~

…….

The dose for treatment of bleeds should aim at providing a post injection level of FVIII of at least 0.50 IU/mL *or 50 IU/dL*. ~~The bleeding pattern of the individual patient, as well as low trough levels described above, should be considered in adjustments of the preventive dose and at the Investigator's discretion.~~

The individual dose is determined by the investigator, using the recommendations in the World Federation of Haemophilia (WFH) guidelines.[10]

The required dosage can be determined using the following formula

Dose (IU) = weight (kg) x desired factor level (IU/dL) x 0.5

The WFH guideline[10] *may be used to guide dosing. FVIII activity should not fall below the lower range for the given plasma activity level (in % of normal or IU/dl) until the bleeding episode is resolved. As the guidelines are recommendations non-compliance with them will not require protocol deviations. The maximum dose per injection mentioned in this protocol must though be followed.*

Table 5-1 Guide for dosing in bleeding episodes[1]

Degree of haemorrhage	***FVIII level required (%) (IU/dl)***	***Frequency of doses (hours)/ Duration of therapy (days)***
Early haemarthrosis, muscle bleeding or oral bleeding	*20-40*	*Repeat every 12 to 24 hours until the bleeding episode as indicated by pain is resolved or healing achieved*
More extensive haemarthrosis, muscle bleeding or haematoma	*30-60*	*Repeat injection every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved*
Life-threatening haemorrhages	*60-100*	*Repeat injection every 8 to 24 hours until threat is resolved*

X[1] Novo Nordisk company core data sheet for turoctocog alfa

This formula may be used to calculate resulting factor levels:

IU/dL (or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 [IU/dL]/[IU/kg]

……

Each administered dose (mL ~~IU~~ given, *vial strength* and time of day) as well as efficacy in treatment of bleeds will be registered in the diary and in the eCRF.

5.3.3 Treatment during surgery

……..

Doses should aim at securing haemostasis without reaching super-physiological FVIII levels.

5.3.4 Treatment of patients with inhibitors

……

An ITI protocol with high-dose or low-dose regimen can be chosen by the Investigator, depending on the patient's peak inhibitor titre and the titre before the start of the ITI. International consensus guidelines and local practice guidelines should be used when selecting optimal ITI regimen.[15],[16],[17]

……

Patients will be evaluated after 12 months of ~~ITI~~ *inhibitor* treatment, based on the level of inhibitors. If inhibitors are still positive after 12 months, but the decline from peak titer level is ≥ 20%, ~~ITI~~ *inhibitor treatment* may continue for a maximum period of 24 months in total.

The dose level and dosing frequency of inhibitor treatment will be decided by the Investigator based on clinical evaluation and local standards, and it should be documented in the eCRF. Within this trial, 'inhibitor treatment' includes Immune Tolerance Induction (ITI) as well as smaller dose adjustments with ~~low responding and/or~~ clinical insignificant inhibitors.

If needed and decided by the Investigator, the initiation of the inhibitor treatment with turoctocog alfa can be delayed, but it has to start within 6 months from the time of diagnosis of inhibitor.

Inhibitor treatment with turoctocog alfa will be included in the overall count of ED.

If the inhibitor disappears (~~BU~~<0.6 *BU*/~~mL~~) during the *inhibit*or ~~ITI~~ treatment, the patient will continue in the extension phase at a time point decided by the Investigator, resuming/starting preventive treatment as recommended in this protocol, see Table 2–1. However, if the inhibitor persists after 24 months of ~~ITI~~ *inhibit*or treatment, the patient will be withdrawn from the trial.

Table 2–1 Overview of Treatment Regimens

Trial product	Dose				
	Treatment	Type	Total daily Doses, IU/kg	Frequency	Targeted level of FVIII
rFVIII (turoctocog alfa)	Preventive	Individual	15-50	Once weekly	Local practice & guidelines
rFVIII (turoctocog alfa)	*Preventive*	*Individual*	*20-60*	*Two times weekly*	*Local practice & guidelines*

rFVIII (turoctocog alfa)	Preventive	Individual	20-60	3 times weekly	Local practice & guidelines
rFVIII (turoctocog alfa)	Preventive	Individual	20-50	Once every second day	Local practice & guidelines
rFVIII (turoctocog alfa)	Treatment of bleeds	Individual	*Investigator's discretion* **. See section ~~max 2x100~~	Investigator's discretion	>0.50 IU/mL
rFVIII (turoctocog alfa)	Surgery	Individual	*Investigator's discretion*** ~~max 2x100~~	Investigator's discretion	>0.50 IU/mL* Local practice & guidelines
rFVIII (turoctocog alfa)	Inhibitor	Individual	Investigator's discretion**	Investigator's discretion	NA

* Pre-surgery *and during surgery* treatment
** *Please see section 5.3 for the maximum allowed dose*

6 Trial population

6.1 Number of Patients ~~to be studied~~

……

Planned number of trial sites: 5~~0~~*5*

6.2 Inclusion Criteria

……

4. No prior use of purified clotting ~~factor~~ *FVIII* products (previous exposure, equal to or less than 5 ED to blood components, e.g. cryoprecipitate, fresh frozen plasma, is accepted) *including commercially available NovoEight® /Novoeight®*

2.4 Withdrawal criteria

……

5. Inhibitor treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (~~BU~~≥ 0.6 *BU/*~~mL~~)

6. FVIII inhibitor titer decline from peak level is less than 20% after 12 months of inhibitor treatment

7. FVIII inhibitor is positive (~~BU~~ ≥ 0.6 *BU*/~~mL~~) after 24 months of inhibitor treatment.

8. After completed inhibitor treatment (maximum 24 months), preventive treatment as described in the protocol is not resumed/started.

9. Preventive treatment not initiated at the patient's age of 24 months.

6.6 Rationale for Trial Population

……

Rational for Withdrawal Criteria:

- Criterion no. *2*~~1~~ is included to protect the patient's safety.
- Criterion no. *3* ~~2~~ is selected not to confound the effects of the investigational product

7 Trial schedule

Planned duration of recruitment period (FPFV-LPFV):	39 months
Planned date for FPFV:	December 2011
Planned date for LPFV:	*31 December*M~~arch~~ 2015

……

- patients with inhibitor will be allowed to receive inhibitor ~~ITI~~ treatment for up to 24 months

8.1.2 Visit 1, Screening Visit

……

The assessments to be performed at Visit 1 are listed in Table 2-1

8.1.5.1 Surgery Visit

Patients undergoing surgery will continue the regular visit schedule, but additional visits may be performed in the peri-operative period as decided by the Investigator. Surgery visits will be documented as unscheduled visits.

For planned surgery patients, the following data should be collected:

- Type of surgery
- Date of surgery
- turoctocog alfa doses and dosing schedule 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
- *Concomitant medication*
- *Adverse events*
- *Assessment of withdrawal criteria*

8.1.5.2 Inhibitor Treatment Visit

All patients, who develop inhibitors and continue treatment with turoctocog alfa, will follow an alternative visit schedule prescribed by the Investigator according to local standard of practice, Monthly visits are recommended, at least initially, for patients who develop inhibitors.

These visits will be recorded as unscheduled visits and the following assessments should be performed.

- Assessment of withdrawal criteria
- Concomitant Medication
- Body measurements (weight)
- Bleeds including classification and site of bleeds
- Adverse Events
- Physical examination
- Collect and review diary
- Diary dispensing
- Dispensing of trial product
- Drug accountability
- Administration of turoctocog alfa*, if applicable*
- FVIII inhibitor test
- *Performing drug accountability*

8.1.6 Extension phase Visits

These are visits to be performed for patients, who have completed the main phase and after Visit 5 continue in the extension phase. Patients, who ~~resume preventive treatment after~~ complete~~d ITI~~ *inhibitor* treatment, will also follow the visit schedule in the extension phase. The patients will be

called to the visits according to a rolling visit schedule, which runs over one year. There are two kinds of visits, Dispensing (4) and Assessment & Dispensing (2), and the aggregated planned number of visits over one year is 6.

8.1.7 EoT Visit

Within 8 weeks of the last scheduled visit in the extension phase the patient should be called to an EoT Visit. For patients, who discontinue the trial, an EoT visit should be performed within 28 days.

Please also see Table 2-2 for your reference.

8.2.2.1 FVIII inhibitors

Detection of FVIII inhibitors will be carried out at a central laboratory using the Nijmegen modified Bethesda[21] assay. A positive inhibitor test is defined as ≥ 0.6 Bethesda Unit (BU)~~/mL~~.

In the event of a positive inhibitor test, the patient should attend an (unscheduled) visit *preferably* within ~~a~~ *2* week*s of the first blood sample* ~~after the result is available~~ to take a *new* blood sample for a confirmatory *inhibitor* test.

- The diagnosis of inhibitor is made if the patient has been tested positive for inhibitors (~~></~~≥0.6 *BU*~~/mL~~) at two consecutive tests (central lab), sampled preferably within 2 weeks. Inhibitors will be classified as low titre (≥0.6 BU~~/mL~~ but <5 BU~~/mL~~), or high titre (≥5 BU~~/mL~~), and as clinically significant (recovery <66% of expected level, assessed at inhibitor diagnosis at the time of the confirmatory inhibitor test).

8.2.2.2 Non neutralising antibodies

Plasma samples for analysis of non-neutralising antibodies against FVIII will be taken at the same time point as for inhibitor testing. The results will be used to characterise the underlying immunogenicity towards FVIII. The samples will be frozen and stored and the analysis will be carried out by a validated antibody assay. The samples may be used for further FVIII antibody characterisations (e.g. isotyping, binding properties), *see section 25.2*

It *might* ~~will~~ not be possible to review the results of non-neutralising antibody measurements in relation to potential AEs because *some of* the results ~~will~~ *may* be available after LPLV.

Determination of non-neutralising antibodies against FVIII will be performed by Novo Nordisk A/S or by a laboratory appointed by Novo Nordisk A/S.

~~If requested by the regulatory authorities antibody samples may be stored for a longer period until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).~~

8.2.3.2 FVIII Recovery

……

Samples for FVIII recovery will be sent to the central laboratory for analysis, see Section *8.2.7.3* ~~**8.2.6.2**~~

8.2.6 Lupus Anticoagulant

Lupus Anticoagulant will be sampled together with the confirmatory inhibitor test at an unscheduled visit.

In the event that a patient has both a positive Lupus Anticoagulant and a positive confirmatory inhibitor test Lupus Anticoagulant must be taken at every consecutive inhibitor test thereafter until the inhibitor test is negative (<0.6 BU).

8.2.7.3 Central Laboratory Tests

For descriptions of procedures for obtaining samples/specimens, and the storage, handling and disposition of specimens, please refer to the Laboratory Manual*, and section 25.2*

8.3.1.3 Bleed Classification

Re-bleeds will be reported by ~~the trial statistician~~ Novo Nordisk based on the diary data. Re-bleed is defined as a bleed (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping of a previous bleed at the same anatomical location.

8.4.1 Bleed Classification

At Visit 1, all patients/parents/legally authorised representative (LAR) will be asked about documentation of previous FVIII and Human Leucocyte Antigen (HLA) genotype tests. If not available or if it needs to be re-tested, based on the Investigators discretion, FVIII and HLA genotype testing will be offered as allowed by local law. The blood sample should be taken at Visit 3, 4 or an unscheduled Visit. ~~The genotype analysis is performed at the laboratory in Bonn, Germany.~~

Investigator, parent(s) or LAR have the right to refuse to provide patient's genotype documentation or to refuse genotyping. This will not prevent the patient's continued participation in the remainder of the trial.

Applicable for Japan only: If documentation of the patient´s genotype already exists, the patient is offered to provide his data for the trial. If no previous data exists and genotyping consent is obtained, genotype analysis is performed ~~at the laboratory in Bonn, Germany,~~ using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than FVIII and HLA. Samples will be disposed appropriately after the test and all test results are kept strictly confidential.

8.4.2 Viral Antibody Information

At Visit 1 and at EoT status of the following *tests* ~~viral infections~~ are assessed.

- HBsAg and/or anti-HCV antibodies ~~if status is unknown or the Investigator considers there is an indication to test~~
- HIV 1 & 2 antibodies ~~if status is unknown or the Investigator considers there is an indication to test.~~

At Visit 1 the above tests are only mandatory in case the patient's status is unknown or the Investigator considers there is an indication to test. ~~If the patient is HIV positive the last value of CD4+ T-cells, and date of test, should be recorded. If not available a new cell count is required~~

8.4.2.1 CD4+T cells

If the patient is HIV positive at Visit 1 the most recent value in the medical records of CD4+ T-cells, and date of test, should be recorded at either Visit 1 or Visit 2. If this is not available a new cell count is required.

At the EoT visit CD4+T cell count must be obtained.

8.4.4 Body measurements

Weight and height will be measured at Visits 1, 5 and EoT. For Visit 2-4 and for the Assessment & Dispensing Visits in the extension part only weight is measured. *Additional assessments can be performed as needed*

8.4.6.2 Details of haemophilia

Following information about the patient's haemophilia to be obtained during the Screening Visit (Visit 1):

- Diagnosis of haemophilia A (date)
- Classification of haemophilia A and FVIII level (%)
- Underlying gene defect (if known *and patients/LAR's consent has been obtained*)
- History of relatives with haemophilia A (as recalled by parent/guardian) including inhibitors

8.4.7 HE and PRO data

In this trial HE and PRO data will be collected.

The HE data include assessments of resource utilization and patient/caregiver burdens associated with bleeds. *HE questions are available in the eCRF. The HE assessments should be completed at every scheduled and every inhibitor unscheduled visit in case the patient has had a bleed between visits. In case of a severe bleed additional HE questions should be completed.*

The PRO data use a validated questionnaire to assess treatment satisfaction, Hemo-Sat. *(See Appendix E)*. Hemo-Sat *questionnaire* is a treatment satisfaction survey for parents/caregivers (the P version). Dimensions measured include ease and convenience, efficacy, burden, specialists/nurses, centre/hospitals, general satisfaction. The *HEMO-Sat* questionnaire was originally developed in UK English and has been translated and linguistically validated into other languages. However it might not be available for all countries. The *HEMO-Sat* questionnaire is to be filled in at Visits 3 and 5 in the main phase, annually in the extension phase and at EoT Visit, preferably before any other trial related procedures.

9.3 Storage of Trial Products

……

~~NaCl~~*Sodium chloride*

……

Returned trial product(s) (*used,* partly used or unused *vials* including empty packaging material) must be stored separately from non-allocated trial product(s). Returned trial products can be stored at room temperature.

9.4 Dispensing and Drug Accountability of Trial Products

Drug accountability is the responsibility of the investigator.

The IV/WRS will allocate a trial product DUN to the patient at each dispensing visit. The correct DUN must be dispensed to the patient.

- No trial product(s) should be dispensed to any person not enrolled in the trial (excluding parents/LAR).
- Unused trial product must be stored separately from used trial product.
- Once a patient is dosed, the vials (~~used,~~ unused~~,returned~~ and lost~~/damaged~~) must be recorded in the IV/WRS Drug Accountability module.

9.5 Trial Product Administration

The IV/WRS will report the dosing volume of turoctocog alfa to be injected based on the patient's weight and dose IU/kg.

10.3 Interactive Voice/Web Response System (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time by the internet. Some sessions may be available through a toll-free telephone number. Accessibility to the IV/WRS must be restricted to and controlled by authorised persons. For a minimum, the system will be used for enrolment of patients, ~~dispensing~~ *allocation* of trial *product with sufficient expiry until the next scheduled visit, facilitation of expiry monitoring dosing volume calculation of turoctocog alfa*, ~~controlling of expiry date of trial product~~, ordering of trial product, drug accountability and screening failure data and withdrawal information. An IV/WRS user manual will be provided to the site.

11 Concomitant Illnesses and Concomitant Medication

……

- Treatment with FVIII concentrates other than the ~~turoctocog alfa~~ *the trial product*, see Section 6.4.

12.1.1 Technical Complaint

……
the packaging material (e.g. leakage, cracks, problems with rubber membrane ~~in the cartridge~~ or errors in labelling text).

12.1.2 Medical Event of Special Interest and other events for expedited reporting

……

- Inhibitor formation against FVIII
  - Inhibitor formation is always considered a MESI. Blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk. However, if an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, it should be reported as MESIs.
    The diagnosis of inhibitor is made, if the patient has been tested positive for inhibitors (~~BU~~ ≥0.6 *BU*/~~mL~~) at two consecutive tests at the central laboratory, sampled preferably within 2 weeks. However, if the first inhibitor test is positive, it should also be reported as a MESI even though the confirmatory test is negative.

……

All AEs, either observed by the Investigator or reported by the patient, must be recorded by the Investigator and evaluated. Novo Nordisk' assessment of expectedness is done according to the reference documents: turoctocog alfa Investigator's Brochure[7] ~~(insert reference)~~

……

- **SAE:** The AE form **within 24 hours** and the paper safety information form within 5 calendar days of the Investigator's first knowledge of the SAE.
  The AE form in the eCRF must be signed *by the Investigator* within 7 calendar days from the date the information was entered in the eCRF. *The AE form must be signed regardless of how complete it is. If the AE form is updated after it has been signed it must be signed again by the principal Investigator.*

12.2.1 Disease related Bleeding

Disease related b~~B~~leeds and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection to bleeds that are evaluated by the Investigator as part of the underlying disease *should not be reported as* ~~are~~ AEs *or SAEs unless* .~~However, they should only be reported as AEs if~~ evaluated as related to trial product or trial procedure by the Investigator. ~~Furthermore~~ However, fatal or life-threatening ~~SAEs~~ *bleeds* must be reported *as a SAE* regardless of relatedness. All bleeds and other symptoms related to the underlying disease will be captured in the eCRF *and diary.*

12.5.2 Rules for putting the enrolment on hold

There is one pre-planned safety interim analysis. At this interim all patients exposed at the pre-defined time points determined by number of patients exposed will be evaluated for inhibitor development.

- Safety interim: After the first 25 patients *either* have been to Visit 4 (20-25 exposure days) *or have developed inhibitors before visit 4*

……

The diagnosis of inhibitor is made if the patient has been tested positive for inhibitors (~~BU~~ ≥0.6 *BU*/~~mL~~) at two consecutive tests at central laboratory, sampled preferably within 2 weeks.

13.4 Analysis Results

……
Laboratory reports from the central laboratory will be provided to the Investigator *except the two-stage chromogenic assay.*

14 Monitoring Procedure

During the course of the trial, the Monitor will visit the trial site to ensure that the protocol has been adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. ~~The first~~ *A* monitoring visit *must* ~~will~~ be performed as soon as possible after *screening of a patient* ~~FPFV~~ and no later than 4 weeks after. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, and must not exceed 12 weeks. ~~after preventive treatment has been commenced. Prior to initiation of preventive treatment monitoring should be performed when a patient has been screened and after each treatment requiring bleed.~~

18.2.2 Primary Endpoint(s)

Incidence rate of inhibitors defined as inhibitor titres ≥ 0.6 B*U*~~ethesda units/mL~~ for the main phase of the trial

18.2.4 Supportive Secondary Endpoints

……..

Incidence rate of inhibitors defined as inhibitor titres ≥ 0.6 ~~Bethesda units~~ *BU*/~~mL~~ for the extension part of trial and the combined main and extension phases of the trial**.**

……

- Incidence rate of high-titre inhibitors defined as inhibitor titre ≥ 5 ~~Bethesda units~~ *BU*/~~mL~~

……

- Incidence rate of clinically relevant inhibitors defined as an inhibitor titre (≥ 0.6 BU~~/mL~~) combined with a decreased recovery (<66% of expected level)

The incidence rate of clinically relevant 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 Furthermore, the time to inhibitor development and clinically *relevant* inhibitor development will be presented by a Kaplan Meyer plot.

18.3 Sequential Safety Analysis/Safety Monitoring

- Safety interim: After the first 25 patients *either* have been to Visit 4 (20-25 exposure days) *or have developed inhibitors before visit 4*

18.4 Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

The data from genotyping and ~~immunogenicity~~ *non-neutralising antibody* assessment will be summarised using descriptive statistics.

19.1 Informed Consent Form for Trial Patients

……

~~FVIII~~ Genotype Testing

A collection of samples for genotype testing is offered to the patients participating in this trial. Prior to any trial-related activity, the Investigator must provide the patient and/or the patient's LAR the possibility to abstain from the genetic testing but still be able to participate in the trial.

Retention of blood samples

The patients parents are requested to give consent to retain the remaining blood samples after the primary analysis mentioned in this protocol for later exploratory analysis, see section 25.2 The Investigator must provide the patient and/or the patient's LAR the possibility to abstain from the retention of blood samples but still be able to participate in the trial.

24.1 Communication ~~and Publications~~ *of results*

No permission to publish shall be granted to any clinical research organisation involved in the trial.

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials 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.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

Novo Nordisk reserves the right to ~~not~~ *defer the* release *of* data until specified milestones *are reached,~~e.g.~~ for example*. when the clinical trial report is available. This includes the right ~~to~~ not *to* release *the results of* interim ~~results of clinical trials~~ *analyses*, because the release of such information ~~can invalidate~~ *may influence* the results of the entire trial.

At the end of the trial, one or more ~~manuscripts~~ *scientific* publications ~~will~~ *may* be prepared collaboratively ~~between~~ *by the* Investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for ~~less than~~ *up to* 60 days to protect intellectual property.

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

Where required by the journal, the principal investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish 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 Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

24.1.1Authorship

Authorship of publications should be in accordance with ~~guidelines from~~ *the Uniform Requirements of* ~~T~~the International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria)[27]

~~Notwithstanding anything to the contrary in this protocol. Novo Nordisk acknowledges the Investigators' right to publish the entire results of the trial. Any such scientific paper, presentation, communication or other information concerning the investigation described in this protocol, must be submitted in writing to the Novo Nordisk International Trial Manager prior to submission for~~

~~publication/presentation for comments. Comments will be given within four weeks from receipt of the manuscript.~~

~~24.1.2 Publications~~

~~The results of this trial will be subject to public disclosure at external web sites according to international regulations, which is reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.~~

~~In all cases, the trial results shall be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the trial. 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 Investigators' and Novo Nordisk's opinions shall be fairly and sufficiently represented in the publication.~~

~~In a multi-centre trial based on the collaboration of all trial sites, any publication of results must acknowledge all trial sites.~~

~~Novo Nordisk maintains the right to be informed of any Investigator 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 Trial Manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication~~

24.1.2 Site-Specific Publication(s) by Investigator(s)

For a multi-centre clinical trial, 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 trial.

Novo Nordisk reserves the right to prior review of such publications *Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy.*

Submission for publication of such primary policy will take place no later than 18 months after trial completion. ~~and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication~~.

25 Retention of Clinical Trial Documentation *and Human Biospecimens*

25.1Retention of clinical trial documentation

……

Novo Nordisk will maintain Novo Nordisk's documentation pertaining to the trial as long as the product is on the market plus 20 years. The files from the Investigator site/institution will be retained 15 years after the completion of the trial, or longer if required by national regulations. *The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.* ~~For Japan, the files from the Investigator/institution must be retained longer in accordance with national regulations~~.

25.2 Retention of blood samples

Storage and disposition of blood samples analysed at local laboratories will be performed according to local laboratory procedures.

Remaining blood not used for the primary analysis mentioned in this protocol will be stored for future exploratory analysis until the trial has been evaluated by appropriate authorities or the project terminates or until the exploratory analysis has been performed, but no longer than 15 years from the end of the trial. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of turoctocog alfa may evolve during the conduct of the trial, the analyses of the stored blood samples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

Parents will be requested to consent to the long-time retention and exploratory analysis of blood samples, see section 19.1

The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral bio-repository with access to the samples. Samples might be transferred to other countries, if not prohibited by local regulations. The patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and bio-repository personnel (if applicable) will have access to the stored bio specimens.

In the event that the collected blood samples will be used in the future, the investigator will become directly informed by Novo Nordisk about the results if the findings are deemed clinically and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious genetically

hereditary diseases, other un-treatable diseases, or any other abnormal findings could be part of the observations. Subjects may at any time contact the investigator if they wish to be informed about results derived from stored blood samples obtained from their own body.

Subject information/Informed consent

1 Information about the trial and the trial product

The purpose of this trial is to collect information about a blood clotting factor (FVIII) medication called turoctocog alfa, hereafter also called trial medication. Turoctocog alfa is produced by Novo Nordisk A/S (using genetic recombinant methods without use of any animal products) for use in people with haemophilia A. The trial is focused on evaluating the safety of turoctocog alfa in young children *who have not been treated with FVIII products previously*. The effect of the trial medication for prevention and treatment of bleeds will also be assessed.

Treatment

In this trial, your child will receive preventive treatment with turoctocog alfa. It should be given once ~~weekly~~, *twice or* three times weekly or every second day, according to your child´s doctor's advice. The treatment could begin before your child suffers a bleed or alternatively after the first ~~one~~ or ~~two~~ *second* bleeds *that requires treatment with turoctocog alfa, whichever is* ~~according to~~ the usual practice at your *child's* treatment centre. However, the preventive treatment has to start once your child has reached the age of 2 years (24 months). The trial medication is administered by injection in a vein. Most of the injections will be performed at home by the parents, supported by the haemophilia centre. Your child´s doctor will instruct you how to manage the administration, and you and your child will receive a set of written instructions that you can take home.

Please be aware that you must ~~handle~~ *store* the trial medication according to the information on the label.

If your child experiences a bleed during this trial you should always call the trial hospital within 24 hours. All bleeding episodes can be treated at home but in case of a severe bleed, you might be advised by your child´s doctor to visit the trial hospital. Your child´s doctor will explain how you can tell which bleeds are considered mild, moderate and severe in this trial. ~~All treatment requiring bleeds during this trial will be treated with turoctocog alfa.~~

Your consent to allow the genotype information to be recorded, or to perform the genotype testing, will be done on a separate form, ~~the~~ addendum *1*.

The following will take place during visit 3 and 4
At these visits your child's weight will be measured and if ~~applicable~~ *necessary* the doctor will administer an injection of the trial ~~drug~~ *medication*.

The following will take place at Visit 5
Your child's weight will be measured and if ~~applicable~~ *necessary* the doctor will administer an injection of the trial ~~drug~~ *medication*.

Extension phase visits
In the extension phase six annual visits are planned and the interval between visits range from 8-10 weeks. Your child's weight will be measured and if ~~applicable~~ *necessary* the doctor will administer an injection of the trial *medication* ~~drug~~.

Unscheduled visits
Your child´s doctor or you might decide that your child needs to attend the haemophilia clinic for medical reasons for additional visits, which are not scheduled *in advance*

2 Risks and benefits

What are the possible risks if we participate in this trial?
The medicine that is being tested in this trial, turoctocog alfa, *a recombinant Factor VIII (rFVIII),* is an experimental *medication* ~~drug~~ *in this setting*. There may be potential side effects of the trial medication, and it is important that you consider all the options before you and your child decide to participate in this trial.

Based on data from more than 200 patients exposed to turoctocog alfa during completed clinical trials, approximately 9 % of the patients have reported adverse drug reactions. The most frequently reported adverse reactions were elevated hepatic enzymes and injection site reactions. Less frequent adverse reactions included insomnia, headache, dizziness, increased blood pressure, rash, stiffness and pain in muscles, pain in legs and arms, bruising, joint disease, swelling of legs and feet, fatigue, feeling hot, and fever.

2.1.1 Inhibitor development

There is a risk of development of antibodies against FVIII that could decrease the effectiveness of the treatment with turoctocog alfa and future treatments with products containing FVIII. In patients not previously treated with any FVIII product the risk for development of antibodies is approximately 30% while the risk is approximately 2% in patients previously treated with a FVIII product (>150 exposure days).

2.1.2 Allergic/hypersensitivity reactions

An allergic response to turoctocog alfa could develop. As turoctocog alfa is produced in a hamster ovary cell line patients with a known allergy to hamster protein should not be treated with turoctocog alfa. If you experience early signs of an allergic reaction such as hives, rashes, itching, tightness of chest, generalised urticaria (a pale red, itchy, raised skin rash on larger parts of the body), wheezing or sudden weakness please let your child's trial doctor know immediately.

2.1.3 Other inconveniences

In order to take blood samples, your child's trial doctor will need to draw blood from your child's vessels. You may feel a little discomfort, bruising, bleeding or swelling at the place of the needle. There is also a slight risk of infection at the place where the needle goes into your child's vein.

In the trial a maximum of 40 mL blood will be taken for laboratory testing. If your child develops inhibitors then the trial doctor will decide how often you should visit the clinic. In this event, the amount of trial related blood samplings will increase but the total volume of blood collected will not exceed 65 mL

Your child's trial doctor will monitor you closely regarding possible side effects. Please inform him/her about all unexpected medical events and about any indispositions, even though you think that there is no causal relation with the trial medication. As with all medications, unforeseen risks may occur. You should not hesitate to report any side effects or health-related problems you may experience or report any questions you may have.

If information becomes available which might affect your willingness to participate you will be informed about this by your child's trial doctor.

~~The blood samples taken during the trial may cause a little discomfort, bruising, bleeding or swelling at the sampling site. There is also a slight risk of infection. Since this trial involves children the volume of blood drawn during the trial follow the European regulatory guidelines (Directive 2001/20/EC) or the local guideline in your country. The blood volume collected from your child for all tests in the trial will not exceed 40 mL if your child follows the regular visit schedule. If your child develops inhibitors then the doctor decide how often you should visit the clinic. In this event, the amount of trial related blood samplings will increase but the total volume of blood collected should not exceed 65 mL.~~

~~Your child´s doctor will monitor your child closely regarding possible adverse events. Please inform him/her about all unexpected signs and symptoms, even if you think that there is no connection with the trial medication.~~

~~The most frequently reported adverse events are expected to include headache, nasopharyngitis, upper respiratory tract infection, arthralgia and fever. Less frequent adverse events may include cough, abdominal pain, oropharyngeal pain, inhibitor development and allergic reactions.~~

~~As mentioned above, there is a risk of developing inhibitors (neutralising antibodies) against FVIII that could decrease the effectiveness of future treatments with medications containing FVIII. However, this risk is not expected to be greater than with other FVIII medications.~~

~~Allergic response to turoctocog alfa could develop as rFVIII is produced in a hamster ovary cell line. Patients with a known allergy to hamster protein should not receive turoctocog alfa. If your child experience early signs of an allergic reaction such as hives, rashes, itching, tightness of chest, generalised urticaria, wheezing or sudden weakness please let your doctor know immediately.~~

~~It is also possible that turoctocog alfa may not prevent your child's tendency to bleed or effectively stop the bleeding. This risk is also not expected to be greater than with other FVIII medications.~~

~~As required by the regulatory authorities, experimental studies with turoctocog alfa in animals have been completed and did not indicate any unexpected risks for humans.~~

~~Two previous trials with turoctocog alfa involving more than 200 haemophilia A patients, whereof about 30 children under the age of 6 years, have been completed without any safety concerns and without any inhibitor formation. If information becomes available which might affect your willingness to participate you will be informed about this by your trial doctor.~~

……

If your child develops inhibitors during the course of the trial, payment for medical care related to the inhibitors will be limited to continued treatment with the trial medication for *a maximum* of 24 months

3 Data privacy

Will our participation in this trial be kept confidential?

……

At novonordisk-trials.com you will be able to find an anonymised version of the clinical trial report, where you can find descriptions of all main results and conclusions of the trial. This report will be available 6 months after the last patient has attended the last visit in the trial.

Any information transferred electronically will be coded to protect your child's confidentiality. ~~Laboratory samples will be destroyed after analysis/trial completion~~. *The remaining of your child's*

laboratory samples may be stored for a longer periode for future analyses not currenlty defined. A request for your consent to perform this will be requested in addedum 2. If you do not consent to this it will not have any consequences for your child's future involvement in the trial. The reason for these future analysis is that they may benefit the understanding of haemophilia, and thereby in the future may benefit treatments for the disease

Trial documentation will be kept and securely archived for at least 15 years.

If you consent to participate in this trial in an EU country, please note that coded information from this trial may be archived or transferred outside of the EU for data processing and analysis purposes.

~~You and your child will be informed of any plans for new analyses on retained identifiable material that were not foreseen at time of consent and that a new consent will be asked for. You will have the right to refuse further analyses.~~

4 The consent procedure

……

- Have the time and willingness to attend the clinic according to the visit schedule plus any *additional visits if necessary* ~~visits required on-demand~~ (unscheduled visits)

……

- Visit the clinic in case of severe bleeds if the trial doctor evaluates *this as* ~~it is~~ necessary

How do I agree to participate in this trial?

……

~~You do not have to participate in this trial to obtain treatment for your child's condition.~~

6 Signature Page

……

Subject, *if applicable*

……

Subject's Legally Acceptable Representative, ~~if applicable~~

Addendum *1* – Genotyping

. . . . . .

Your child's data will be kept confidential and nobody besides the trial doctor, ~~and~~ clinic staff *and Novo Nordisk staff quality checking the data* will know his identity *and* ~~or~~ have access to the result of the genotyping test.

Addendum 2: Future blood analysis and long term storage of blood samples

In addition to this trial we would like to ask you to consider if we may perform future analysis not currently defined on your child's remaining blood after the primary analysis mentioned in this informed consent and if we may store these samples up to 15 years after this trial is finalised.

Your child will not have additional blood samples performed due to this consent.

What is the procedure?

These blood samples will be used to explore any additional test that may be of interest that we currently cannot foresee.

Your child's data will be kept confidential and nobody besides the trial doctor and clinic staff will know your child's identity or have access to the result of these future tests.

Your child's trial doctor will only receive these results if they show any new information in regards to your child's illness or any other new illness and Novo Nordisk can come into contact with your child's trial doctor. It may though take up to several years before these tests are performed and your child's trial doctor receives any results.

In the event that these long term stored blood samples will be used in the future, the trial doctor will become directly informed by Novo Nordisk about the results if the findings are evaluated to be correct. Potentially, any other abnormal findings could be part of the observations. You may at any time contact your child's trial doctor if you wish to be informed about these results.

Can I say no to this?

Yes, this is entirely voluntary and it is up to you to decide if this is something you would like to have done or not. If you decide not to have this performed, your child can continue in the trial as planned and the laboratory samples will be destroyed at trial completion.

Is there anything else I need to know?

Should you regret this consent, you just need to say this to the trial doctor and he/she will ensure that the samples are destroyed after the trial is finalised, unless the tests already have been performed.

All information regarding conditions for participating in a clinical trial explained to you in the patient information sheet for this trial are also valid for this part.

Informed Consent – Signature page for future analysis and long term storage of blood samples

Title of trial: Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A.

I hereby confirm that I have been given oral and written information about the above mentioned long term storage and future analysis of my child's remaining blood samples and that I have received a copy of this information. I have had enough time to consider my participation in this part of the trial. I have had the possibility to ask all questions I have about the long term retention of my child's blood samples and analysis of these, and they have been answered to my satisfaction. I know the long term retention of my child's blood samples and future analysis of these is completely voluntary and I can at any time withdraw my consent without it having any consequence for my child's future treatment or participation in the trial.

I know that the above mentioned data are collected and kept confidential, and my data may be transferred securely to other countries for analyses. Representatives from Novo Nordisk A/S and the IEC/IRB and international regulatory authorities will have access to my data to oversee the trial conduct.

I will receive a copy of this information signed and dated

Person who conducted the information discussion:
(If the information discussion about the trial was conducted by a person other than the trial doctor then this signature/date is required)

Date: _____ *Time:* _____ *(hh:mm)* *Signature:* _____

Name (print): _____

Subject, if applicable:

Date: _____ *Time:* _____ *(hh:mm)* *Signature:* _____

Name (print): _____

Trial doctor or appropriately medically qualified designee seeking the informed consent:

(If the information discussion about the trial was conducted by the trial doctor or an appropriately medically qualified person delegated by the trial doctor ONLY this signature/date is required)

Date: _____ *Time:* _____ *(hh:mm)* *Signature:* _____

Name (print): _____

Subject's Legally Acceptable Representative:

Date: _____ *Time:* _____ *(hh:mm)* *Signature:* _____

Name (print): _____

Relationship to Subject: _____

Impartial Witness, if applicable:

Date: _____ *Time:* _____ *(hh:mm)* *Signature:* _____

Name (print): _____

Protocol Amendment

no 10
to Protocol, final version 6.0
dated 12 June 2014

Trial ID: NN7008-3809

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to all countries

Amendment originator:

[redacted]

Haemophilia, Clinical Operations 1

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

The main reason for amending the protocol is to update the trial timelines to reflect an extension in the recruitment period. In addition other changes have also been applied with the purpose of clarifying the protocol and correcting minor inconsistencies, ambiguities and typographical errors. The list of changes and the related rationales is provided in section 1.1 and 1.2.

1.1 Overview of changes

1. Deleted appendix A (Table of contents)

2. Added items in list of abbreviations. (List of abbreviations)

3. Deleted sentence in the Summary stating that initial infusions of trial product should be done at investigational site. (Summary)

4. Clarified and corrected footnotes in visit flow charts. (Section 2)

5. Clarified in the visit flow chart for the extension trial phase that genotype can be tested at unscheduled visits. (Section 2)

6. Added visit flow chart table describing which assessments to be done at the unscheduled visit for inhibitor confirmation, and at the inhibitor unscheduled visit(s). (Section 2)

7. Clarified that eligible patients <u>can</u> receive first dose at Visit 2. (Section 5.1)

8. Changed the maximum duration of treatment of a patient from first to last turoctocog alfa administration.(Section 5.3)

9. Clarified how patients can be treated with turoctocog alfa. (Sections 5.3 and 9.5)

10. Clarified in section 5.3.2 that all treatments administered in relation to bleeds must be recorded as ‘treatment of bleeds’.

11. Updated trial timelines. (Section 7)

12. Clarified that the main purpose of Visit 2 is to enrol eligible patients, to dispense the trial product and to administer turoctocog alfa for the first time, if applicable. (Section 8.1.3)

13. Added that patients with inhibitors must attend inhibitor unscheduled visit at least every third month. (Section 8.1.5.2)

14. Clarified in the list of assessments to be performed at inhibitor unscheduled visit, that Lupus anticoagulant and FVIII Non-neutralising antibodies should be performed. (Section 8.1.5.2)

15. Clarified that the minimum 48 hours washout period of turoctocog alfa does not apply for inhibitor patients on ITI treatment. (Section 8.2.2.1)

16. Added that 'used' vials should be recorded in the IV/WRS Drug Accountability module. (Section 9.4)

17. Added that treatment with blood and blood component products containing FVIII, e.g. cryoprecipitate and plasma except during surgery should be avoided during the course of the trial. (Section 11)

18. Deleted MESI reporting timelines in section 12.1.2 Medical Event of Special Interest and other events for expedited reporting. (Section 12.1.2)

19. Changed minor inconsistencies, ambiguities and typographical errors.

Subject information/Informed consent:

No changes to the Subject information/Informed consent.

1.2 Rational for changes

1. Appendix is not required to be included in the protocol and has therefore been deleted.

2. Description of two abbreviations were missing.

3. The sentence was inserted in error and the deletion is in accordance with the Protocol.

4. To ensure alignment with the Methods and Assessments section of the Protocol.

5. To ensure alignment with the Methods and Assessments section of the Protocol.

6. To make it clear how to conduct Unscheduled Visit with inhibitor confirmation and Inhibitor Unscheduled Visit.

7. To make it clear that patients will not necessarily be administered the first dose at Visit 2. The first dose may be administered at a later time point.

8. To reflect the expected maximum treatment duration.

9. To clarify that patients can be treated at non-investigational site in addition to treatment at investigational site and at home. Furthermore the section describing that investigator needs

to instruct patients/parents/caregivers/support persons in how to handle administration of turoctocog alfa has been moved from Section 9.5 Trial Product Administration to Section 5.3 Treatment of Patients.

10. To ensure that all treatments of turoctocog alfa administered in relation to bleeds are reported as 'treatment of bleeds'. This ensures consistent reporting of the treatment of bleeds.

11. Timelines have been revised to reflect an extension of the recruitment period.

12. To detail that the main purpose of Visit 2 is to enrol eligible patients and to dispense trial product in addition to administer trial product for the first time, if applicable.

13. To ensure that patients with inhibitors attends inhibitor unscheduled visits with a frequency that allows close follow up on safety and efficacy status and on the inhibitor status.

14. To clarify that Lupus anticoagulant and FVIII non-neutralising antibodies should be performed at inhibitor unscheduled visit. This is in accordance with the visit flow chart and with the description of the two assessments Lupus anticoagulant and FVIII non-neutralising antibodies.

15. The 48 hours washout period is not applicable for patients on ITI treatment, where the treatment regimen require daily administration of turoctocog alfa.

16. All vials; used, unused and lost should be recorded in the IV/WRS Drug Accountability module. The word 'used' was by error deleted in the former version of the protocol.

17. To avoid the use of blood and blood component products containing FVIII as these treatments may confound the effects of the investigational product.

18. MESI reporting timelines were not correctly defined in section 12.1.2. The correct MESI reporting timelines are defined in section 12.2 Collection, Recording and Reporting of Adverse Events.

19. To enhance the quality of the Protocol.

Subject information/Informed consent:

Not applicable.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

Table of Contents

…

~~**Appendix A**~~	~~**Agreement on Final Protocol**~~
Appendix B	**Whole Blood Volume Rules in the Paediatric Population,** ***Version 6.0 dated 12 June 2014***
Appendix C	**Anaphylaxis,** ***Version 6.0 dated 12 June 2014***
Appendix E	**Patient Reported Outcome Questionnaire,** ***Version 6.0 dated 12 June 2014***

…

List of abbreviations

…

NB	*nota bene (take notice)*
PUP	*previously untreated patients*

1 Summary

…

Trial Product

…

~~The initial infusions will be administered at the investigational site, but after adequate instruction and practice the goal is to implement home treatment with intravenous (i.v.) injections given by the parent or a support person.~~ Turoctocog alfa will be supplied as freeze dried powder to be reconstituted with a sterile sodium chloride solution for injection.

2 Flow Chart

Table 2-1 Visit Flow Chart main trial phase

Visit number	Screen. Visit 1	Visit 2[#]	Visit 3	Visit 4	Visit 5	Unscheduled Visit
Visit window	NA	≤ 21 d post V1	10th -15thED	20th -25th ED	50th -55th ED	
PATIENT RELATED INFO / ASSESSMENTS						
Informed consent	●					
Inclusion/Exclusion Criteria	●	●				
Consent for genotype test	●b					
Biospecimen consent	●b					
Withdrawal Criteria		●	●	●	●	●b
Haemophilia treatment history	●					
Concomitant illnesses / Medical history	●					
Concomitant medication	●	●	●	●	●	●b
Demography	●					
Body measurements	●	●d	●d	●d	●	●~~b~~*a*,d
Genotype test [‡]			●b, *f*	●b, *f*		●b, *f*
Details of haemophilia	●					
EFFICACY						
Bleed(s)		●	●	●	●	●b
SAFETY						
Adverse events	●	●	●	●	●	●b
Physical examination	●	●	●	●	●	●~~b~~*a*
Vital signs	●				●	
FVIII activity	●~~a~~*c*					
Antibodies - FVIII inhibitors - FVIII non-neutralising antibodies	●~~a~~*c*		●~~a~~*c*	●~~a~~*c*	●~~a~~*c*	●a, *c*~~, b~~
Lupus Anticoagulant						●b
FVIII trough level			●*a*~~b~~	●*a*~~b~~	●*a*~~b~~	●*a*~~b~~
FVIII recovery		●*a*~~b~~	●*a*~~b~~	●*a*~~b~~	●*a*~~b~~	●*a* ~~b, c~~
Biochemistry	●				●	●*a*
Haematology	●				●	●*a*
OTHER ASSESSMENTS						
PRO questionnaire			●		●	
HE assessment		●*b*	●*b*	●*b*	●*b*	●b
Viral antibody test	●i					●*a*~~b~~

Visit number	Screen. Visit 1	Visit 2#	Visit 3	Visit 4	Visit 5	Unsche duled Visit
Visit window	NA	≤ 21 d post V1	10th -15thED	20th -25th ED	50th -55th ED	
T cells subset: CD4+	●*b,* h	●*b,* h				●b, h
TRIAL MATERIAL						
turoctocog alfa administration		●*a*~~b~~	●*a*~~b~~	●*a*~~b~~	●*a*~~b~~	●*a*~~b~~
Home treatment training		●				
Diary ~~and~~ *or* Trial card dispensing and/or collection~~e~~	●*e*	●*e*	●*e*	●*e*	●*e*	●b, *e*
Review of patient diary and entry of data in eCRF			●	●	●	●b
Enrolment session in IV/WRS	●					
Drug dispensing and accountability		●g	●	●	●	●b
Diary training		●				

- Visit 2 can be performed at the same day as Visit 1

~~a – minimum 48 hours washout period of turoctocog alfa (or blood component products at Visit 1).~~

a – optional, at discretion of Investigator

b – if applicable~~ or optional~~

~~c – mandatory to confirm clinical relevant inhibitorscd~~

c – Minimum 48 hours washout period of turoctocog alfa (or blood component products at Visit 1). Not a requirement for patients on ITI treatment.

d – weight only

e – Visit 1 trial card only, Visit 2-5 diary only

f – if previous tests are not available, if allowed by local law and after consent

g – Visit 2 dispensing only

h – if HIV positive, last value of CD4+ T-cells (if available), or new cell count

i - if HIV, HBsAg and/or HCV status unknown

Table 2-2 presents the rolling visit schedule in the extension phase over the period of one year. It comes to effect after Visit 5 or after inhibitor treatment.

Table 2-2 Visit Flow Chart trial extension phase

Visit type	Dispensing		Assessment & Dispensing	Dispensing		Assessment & Dispensing	End of Trial	Unsch Visit
Visit number[#]	6	7	8	9	10	11		
Previous visit time(w)	-8	-8	-10	-8	-8	-10	< 8	
Visit window	± 1w	± 1w	± 1w	± 1w	± 1w	± 1w	NA	NA
ASSESSMENTS								
Withdrawal Criteria	●	●	●	●	●	●		●b
Concomitant medication	●	●	●	●	●	●	●	●b
Body measurements			●c			●c	●	●a, *c*
Genotype								●*b*
EFFICACY								
Bleed(s)	●b	●b	●b	●b	●b	●b	●b	●b
SAFETY								
Adverse events	●	●	●	●	●	●	●	●b
Physical examination			●a			●a	●	
Vital signs			●a			●a	●	
Antibodies[f] - FVIII inhibitors - FVIII non-neutralising antibodies	●a, *f*	●a, *f*	●, *f*	●a, *f*	●a, *f*	●, *f*	●, *f*	●a, *f*
Lupus Anticoagulant								●b
FVIII trough level	●a	●a	●a	●a	●a	●a		●a
FVIII recovery	●a	●a	●a	●a	●a	●a		●a
Biochemistry			●			●	●	●a
Haematology			●			●	●	●a
OTHER ASSESSMENTS								
PRO questionnaire						●	●	
HE assessment	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●*b*	●b
Viral antibody test							●	●a
T cells subset: CD4+							●	●b
TRIAL MATERIAL								
turoctocog alfa administration	●a	●a	●a	●a	●a	●a		●a
Diary dispensing and/or collection	●	●	●	●	●	●	●d	●b
Review of patient diary and entry of data in eCRF	●	●	●	●	●	●	●	●b
Completion session in IV/WRS							●	
Drug dispensing and accountability	●	●	●	●	●	●	●e	●b
EoT form							●	

- Presented numbers are for the first 12 months. Visit numbers for future years will be in consecutive order

a – optional, at discretion of investigator

b – if applicable
c – weight only
d – collection only
e – accountability only
f - Minimum 48 hours washout period of turoctocog alfa. Not a requirement for patients on ITI treatment.

Table 2-3 presents the assessments to be made at unscheduled visit with inhibitor confirmation and at inhibitor unscheduled visit.

Table 2-3 Visit Flow Chart inhibitor related visits

Visit type	*Inhibitor confirmation at Unscheduled Visit*	*Inhibitor Unscheduled Visit*
PATIENT RELATED INFO / ASSESSMENTS		
Withdrawal Criteria	*Assessments according to normal Unscheduled Visit*	●*b*
Concomitant medication		●*b*
Body measurements		●*a, c*
EFFICACY		
Bleed(s)		●*b*
SAFETY		
Adverse events		●
Physical examination		●*b*
Antibodies *- FVIII inhibitors* *- FVIII non-neutralising antibodies*	●*e*	●*a, e*
Lupus Anticoagulant	●	●*d*
FVIII trough level	●*a*	●*a*
FVIII recovery	●	●*a*
OTHER ASSESSMENTS		
HE assessment	*Assessments according to normal Unscheduled Visit*	●*b*
TRIAL MATERIAL		
turoctocog alfa administration		●*a*
Diary dispensing and/or collection		●*b*
Review of patient diary and entry of data in eCRF		●*b*
Drug dispensing and accountability		●*b*

a – optional at discretion of investigator
b – if applicable
c – weight only

d – In the event that a patient has both a positive Lupus Anticoagulant and a positive confirmatory inhibitor test, Lupus Anticoagulant must be taken at every subsequent inhibitor test thereafter until the inhibitor test is negative (<0.6 BU).
e – Minimum 48 hours washout period of turoctocog alfa. Not a requirement for patients on ITI treatment.

…

5 Trial Design

5.1 Type of Trial

…

The trial consists of two phases i.e. main and extension, respectively. In the main phase the patients will attend a screening visit (Visit 1) in order to assess their eligibility. At Visit 2 eligible patient*s* ~~will~~ *can* receive their first dose, if applicable.

…

5.3 Treatment of Patients

…

Patients will enter a bleeding preventive regimen as described below, see Section 5.3.1.
For prevention one single bolus dose of turoctocog alfa is administered intravenously (i.v.) at each administration day. Turoctocog alfa should preferably be administered in the morning. The maximum duration of treatment of a patient from first to last turoctocog alfa administration is approximately *5* ~~4~~ years.

…

~~In most cases, treatment will be given at home with i.v. self-injection by the parent/caregiver/support person. However, on days when the patient is attending a trial visit, if applicable the dose may be administered at the clinic by a health care professional.~~*Initially treatment with turoctocog alfa will typically be carried out by the staff at the clinic. Treatment can also be given at home with i.v. injection by the parent/caregiver/support person and/or at a non-investigational site. All patients and/or parents/caregivers/support persons will be instructed by Investigator how to handle administration of turoctocog alfa before first dose is administered at home or at non-investigational site.*

…

5.3.2 Treatment of Bleeds

~~During preventive treatment, break-through bleeds may occur and require extra doses of turoctocog alfa.~~ Treatment *of bleeds* should be started as soon as a bleed is identified. All bleeds, mild/moderate and severe, can be treated at home. For severe bleeds (see Section 8.3.1.1) the Investigator should evaluate if the patient should be seen at the clinic. All bleeds must be reported to the clinic within 24 hours from onset of the bleed.

The dose for treatment of bleeds should aim at providing a post injection level of FVIII *according to Table 5-1*~~of at least 0.50 IU/mL or 50 IU/dL~~.

…

Each administered dose (mL given, vial strength and time of day) as well as efficacy in treatment of bleeds will be registered in the diary and in the eCRF. *All treatments (excluding ITI treatment) administered in relation to bleeds must be recorded as 'treatment of bleeds', e.g. scheduled preventive treatment administered between start and stop time of a bleed must be registered as 'treatment of bleed'.*

…

5.3.4 Treatment of Patients with Inhibitors

…

Treatment of bleeds with by-passing agents *e.g.*~~i.e.~~ FVIIa or activated prothrombin complex concentrate (APCC) according to local label, is allowed for patients who develop inhibitors. Bypassing agents are not considered trial medication.

…

7 Trial Schedule

Planned duration of recruitment period (FPFV-LPFV): ~~39~~*45* months

Planned date for FPFV:	December 2011
Planned date for LPFV:	~~31 December 2015~~*Q2 2016*
Planned date for LPLV:	~~30 June~~ *Q2* 2018

The duration of turoctocog alfa treatment in this trial is a minimum total 100 EDs for a particular patient. Once a patient has achieved 100 EDs, they may be offered the option to continue in the trial

until either turoctocog alfa is commercially available in the relevant country or until the marketing authorisation application for turoctocog alfa is rejected in the relevant country unless the trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the Last Patient Last Visit for the trial will be no later than 30 June 2018 whether or not the product is commercially available in the relevant country.

The following exceptions will be made:

- patients will be allowed to achieve at least 100 ED with trial product
- patients with inhibitor will be allowed to receive inhibitor treatment for up to 24 months.

The end of the clinical trial is defined as last visit of the last patient.

Planned completion of main clinical trial report (CTR): ~~Q1 2016~~*Q3 2017*

Planned completion of updated clinical trial report: Q4 2018

…

8 Methods and Assessments

8.1 Visit Procedures

8.1.1 Overall Procedures, Assessments and Methods

Specific procedures, assessments and methods for the scheduled visits are described in the Sections below, and the list of assessments for each visit is presented in the flow chart, see Table 2-1,~~and~~ Table 2-2 *and Table 2-3*.

…

8.1.3 Visit 2

…

The main purpose of Visit 2 is to *enrol eligible patients, to dispense the trial product and to* administer turoctocog alfa for the first time, if applicable~~, or alternatively dispense the trial product to eligible patients~~.

…

8.1.5.2 Inhibitor ~~Treatment~~ *Unscheduled* Visit

All patients, who develop inhibitors and continue treatment with turoctocog alfa, will follow an alternative visit schedule prescribed by the Investigator according to local standard of practice, ~~Monthly visits are recommended, at least initially, for patients who develop inhibitors.~~ *These patients must attend inhibitor unscheduled visits at least every 3rd month. However, initially monthly visits are recommended.*

These visits will be recorded as *inhibitor* unscheduled visits and the following assessments should be performed. *Please see also Table 2-3.*

- Assessment of withdrawal criteria
- Concomitant Medication
- Body measurements (weight)
- Bleeds including classification and site of bleeds
- Adverse Events
- Physical examination
- Collect and review diary
- Diary dispensing
- Dispensing of trial product
- Drug accountability
- Administration of turoctocog alfa, if applicable
- FVIII inhibitor test
- *FVIII Non-neutralising antibodies*
- *Lupus Anticoagulant*
- Performing drug accountability

…

8.2 Assessments for Safety

8.2.2 FVIII antibodies

8.2.2.1 FVIII Inhibitors

Blood sampling for FVIII inhibitor test should be performed at a trough level, i.e. with a minimum of 48 hours turoctocog alfa treatment washout period. *The 48 hours washout period does not apply for patients on ITI treatment.*

…

8.2.6 Lupus Anticoagulant

Lupus Anticoagulant will be sampled together with the confirmatory inhibitor test at an unscheduled visit.

In the event that a patient has both a positive Lupus Anticoagulant and a positive confirmatory inhibitor test Lupus Anticoagulant must be taken at every ~~consecutive~~ *subsequent* inhibitor test thereafter until the inhibitor test is negative (<0.6 BU).

…

9 Trial Supplies

…

9.4 Dispensing and Drug Accountability of Trial Products

Drug accountability is the responsibility of the investigator.

The IV/WRS will allocate a trial product DUN to the patient at each dispensing visit. The correct DUN must be dispensed to the patient.

- No trial product(s) should be dispensed to any person not enrolled in the trial (excluding parents/LAR).
- Unused trial product must be stored separately from used trial product.
- Once a patient is dosed, the vials (*used,* unused and lost) must be recorded in the IV/WRS Drug Accountability module.

…

9.5 Trial Product Administration

The IV/WRS will report the dosing volume of turoctocog alfa to be injected based on the patient's weight and dose IU/kg.

The trial product should be administered as a slow bolus i.v. injection over approximately 2 min. (from start to completion of injection) for all trial product administrations.

~~These administrations will primarily be performed at home. All patients and/or parents/caregivers will be instructed by Investigator how to handle home administration before first dose.~~

…

11 Concomitant Illnesses and Concomitant Medication

…

The following concomitant medications are not permitted during the course of this trial:

- Treatment with FVIII concentrates other than the trial product, see Section 6.4.

Treatment with blood and blood component products containing FVIII, e.g. cryoprecipitate and plasma, except during surgery, should be avoided.

~~In case these medications are used during the trial, the patient must be withdrawn.~~*The use of these medications during the course of the trial may lead to patient withdrawal as described in Section 6.4.*

…

12 Adverse Events

12.1 Definitions

…

Serious Adverse Event (SAE):
A SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience [a)]
- In-patient hospitalisation or prolongation of existing hospitalisation [b)]
- A persistent or significant disability/incapacity [c)]
- A congenital anomaly/birth defectImportant medical events that may not result in death, be life-threatening [a)] or require hospitalisation[b)] may be considered a SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of SAE[d)]. Suspicion of transmission of infectious agents via trial product and*/or* formation of inhibitory antibodies must always be considered an SAE

…

12.1.2 Medical Event of Special Interest and other events for expedited reporting

A medical event of special interest (MESI) is an event in which, in the evaluation of safety, has special focus.

~~A MESI should be reported following the same reporting requirements and timelines as for SAEs, irrespective of the MESI fulfils a seriousness criterion.~~

…

18 Statistical Considerations

…

18.6 Health Economics and Patient Reported Outcomes

Health economic data will be collected in the eCRF in connection with ~~severe~~ bleeds. Patient reported outcomes will be collected using questionnaires at visits 3 and 5 in the main phase, and annually during the extension phase. The health economic and PRO data will be summarised using descriptive statistics.

…

19 Ethics

19.1 Informed Consent Form for Trial Patients

…

Retention of blood samples

The patients parents *and/or the patient's LAR* are requested to give consent to retain the remaining blood samples after the primary analysis mentioned in this protocol for later exploratory analysis, see Section 25.2. The Investigator must provide the patient and/or the patient's LAR the possibility to abstain from the retention of blood samples but still be able to participate in the trial.

…

25 Retention of Clinical Trial Documentation and Human Biospecimens

…

25.2 Retention of blood samples

…

Parents *and/or LAR* will be requested to consent to the long-time retention and exploratory analysis of blood samples, see Section 19.1.

Protocol Amendment

No 11_AT
to Protocol, final version 6.0
dated 12 June 2014

Trial ID: NN7008-3809

Safety and Efficacy of turoctocog alfa in Prevention and Treatment of Bleeds in Paediatric Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to Austria

Amendment originator:

Name: [redacted]

Department: [redacted]

Table of contents

Page

1 Introduction including rationale for the protocol amendment

A new principal investigator at trial site [redacted] will start to work due to retirement of the previous PI. At site [redacted] a new principal investigator will start to work due to relocation of the previous PI. Substantial Protocol Amendment No. 11_AT will be forwarded to Health Authority and the Ethics Committees for approval prior to implementation.

2 Changes

At site [redacted] (Prof. Dr. [redacted]) the principal investigator will change due to retirement.

~~Principal Investigator: Title: Prof. Dr.~~

~~Name:~~ [redacted]

~~Address:~~ [redacted]~~,~~

[redacted]

[redacted]

~~Tel:~~ [redacted]

~~Fax:~~ [redacted]

~~Email:~~ [redacted]

Principal Investigator: Title: Dr.

Name: [redacted]

Address: [redacted]

[redacted]

[redacted]

Tel: [redacted]

Fax: [redacted]

Email: [redacted]

At site [redacted] (OA Dr. [redacted]) the principal investigator will change due to relocation.

~~Principal Investigator: Title: Dr.~~

~~Name:~~ [redacted]

~~Address:~~ [redacted]

[redacted]

[redacted]

~~Tel:~~ [redacted]

~~Fax:~~ [redacted]

~~Email:~~ [redacted]

Principal Investigator: Title: Dr.

Name: [redacted]

Address: [redacted]

[redacted]

[redacted]

Tel: [redacted]

Fax: [redacted]

Email: [redacted]