Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02938585
Sponsor trial ID:	NN7008-4028
Official title of study:	Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A
Document date:	21-July-2017

Protocol

guardian™7

Trial ID: NN7008-4028

Efficacy and safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with haemophilia A

Final protocol version 1 (13 February 2014), Final protocol version 2 (10 May 2016), Final protocol version 3 (19-Aug-2016)

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

Protocol originator

[redacted], [redacted]

Biopharm Trial Ops 4

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List of abbreviations

AE	adverse event
$AUC_{0\text{-}inf}$	area under the curve
BU	Bethesda unit
BW	body weight
CL	clearance
C_{max}	highest measured FVIII activity in the profile
CRA	clinical research associate
CRF	case report form
CVAD	central venous access device
DFU	directions for use
DUN	dispensing unit number
eCRF	electronic case report form
ED	exposure day
EMA	European Medicines Agency
FAS	full analysis set
FVIII	Factor VIII
GCP	Good Clinical Practice
HLA	human leucocyte antigen
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	Institutional Review Board
IU	International units
i.v.	intravenous
IWRS	interactive web response system
Kg	Kilogram
LAR	legally acceptable representative
LPLV	last patient last visit
MESI	medical event of special interest

mL	millilitres
PK	pharmacokinetic
PRO	patient reported outcome
PTP	previously treated patients
rFVIII	recombinant factor VIII
SAE	serious adverse event
SIF	safety information form
SUSAR	suspected unexpected serious adverse reaction
T½	half life
TMM	trial materials manual
ULN	upper limit of normal
UTN	universal trial number

1 Summary

Objectives and endpoints:

Primary objective:

- To evaluate the clinical efficacy of turoctocog alfa in treatment of bleeding episodes in Chinese patients with severe haemophilia A (FVIII≤1%)

Key secondary objective:

- To assess the safety of turoctocog alfa in terms of immunogenicity
- To evaluate the clinical efficacy of turoctocog alfa during prophylaxis treatment
- To evaluate the consumption of turoctocog alfa during prophylaxis treatment and treatment of bleeding episodes

Primary endpoint:

Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months duration per patient)

Key secondary endpoint:

- Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the trial period of 24 months
- Incidence rate of inhibitory antibodies against FVIII (≥0.6 Bethesda unit (BU)) during both the main phase of 6 months and during the trial period of 24 months[I]
- Number of bleeds (total bleeds assessed as annual bleeding rate) per patient during both the main phase of 6 months and during the trial period of 24 months[II]
- Consumption of turoctocog alfa during both the main phase of 6 months and during the trial period of 24 months[III]
- Consumption of turoctocog alfa for bleeding treatment (average dose to treat a bleed, number of injections and IU/kg per bleed), during both the main phase of 6 months and during the trial period of 24 months[IV] Consumption of turoctocog alfa during prophylaxis treatment (average prophylaxis dose and IU/kg per month and per year) per patient, during both the main phase of 6 months and during the trial period of 24 months[V]

[I] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[II] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[III] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[IV] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[V] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov

- Total consumption of turoctocog alfa (IU/kg per month and per year) per patient, during both the main phase of 6 months and during the trial period of 24 months[I]

- Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during both the main phase of 6 months and during the trial period of 24 months[II]

Trial design:
This is a single-country, multi-centre, open-label and non-randomised trial. Both a prophylactic and on-demand regimen of turoctocog alfa will be provided. This trial has a main and extension phase.

Trial population:
65 previously treated patients (PTPs) with congenital severe haemophilia A (FVIII≤1%) with no history of inhibitors will be enrolled to allow for at least 60 patients to complete the main phase of the trial. All ages are eligible.

Key inclusion criteria:
- Male patients
- Age from 0 years
- With severe congenital haemophilia A (FVIII≤1%)
- History of exposure days (ED) to any FVIII products fulfilling the criteria of previously treated patients:
  - Patients of 12 years or above: 100 exposures days (ED) or more
  - Patients below 12 years: 50 exposure days (ED) or more

Key exclusion criteria:
- Inhibitors to factor VIII (≥0.6 BU) at screening as assessed by central laboratory
- Known history of FVIII inhibitors

Assessments:
- Evaluation of haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none)
- Presence of FVIII inhibitors will be tested throughout the trial
- Consumption of trial product IU/kg body weight (BW will be monitored throughout the trial

Furthermore physical examination, vital signs, laboratory tests and recording of adverse events and serious adverse events will be performed for safety assessments.

- Measurement of FVIII activity for pharmacokinetic (PK) evaluation for 12-18 selected patients during visit 2 and for patients who develop low titer inhibitors and continue in the trial.

[I] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[II] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov

Surgery:
Patients undergoing surgical procedures will receive trial product as surgery treatment before, during and after surgery according to standard of practice at the trial site. All surgery procedures (e.g. minor, major, elective and emergency) may be performed using turoctocog alfa at the investigators discretion.

Trial products:
The following trial products will be provided by Novo Nordisk, Denmark:

Table 1–1 Trial products

Trial product	Strength	Dosage form	Route of administration
Turoctocog alfa	500 IU/vial	Sterile, freeze-dried powder	Intravenous injection
Turoctocog alfa	2000 IU/vial	Sterile, freeze-dried powder	Intravenous injection
Sodium Chloride	0.9 % 4.3mL	Solution for injection in prefilled syringes	Solvent for solution for injection

2 Flow chart

Table 2–1 Visit flow chart – main and extension phase

Trial Periods	Screening	Treatment 1st dose	Assessment	Assessment	Assessment	Assessment	Assessment	Assessment and end of main trial	Dispensing (extension)	Dispensing (Extension)	Assessment (Extension)	End of trial	Unscheduled	Surgery	Follow-up
Visit number	1	2	3	4	5	6	7	8	9	10	11				
Timing of visit Days since previous visit	0	14	14	28	28	28	28	28	56	56	56				28[3]
Visit window Days	0	±4	±3	±3	±3	±3	±3	±3	±14	±14	±14				±14
PATIENT RELATED INFO/ASSESSMENTS															
Informed consent	X														
Informed assent	X[1,2]														
In/exclusion criteria	X[1,2]	X													
Genotyping consent, optional	X[1,4]														
Biospecimen consent	X[1]														
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X		X	X	
Haemophilia treatment and bleed history	X														
Concomitant illness	X														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Haemophilia details	X														
Medical history	X														
Demography	X														
Body measurements	X				X[5]			X[5]	X[5]	X[5]	X[5]		X[1]		
EFFICACY															
Bleeding episodes[6]															
Target joint assessment	X							X			X	X			
Surgical interventions														X	
Profiles (Pharmocokinetics)		X[1,7]											X[8]	X[1]	
PRO questionnaires		X						X			X[9]	X			
SAFETY															
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X							X			X	X			
Vital signs	X	X[10]			X			X			X	X			
LABORATORY															
Genotype		X[1,4]											X[1,4]		
Hepatitis	X[11]							X				X[11]	X[1]		
HIV	X[12]							X				X[12]	X[1]		
Immunology – blood, CD4+ T	X												X[1]		

Trial Periods	Screening	Treatment 1st dose	Assessment	Assessment	Assessment	Assessment	Assessment	Assessment and end of main trial	Dispensing (extension)	Dispensing (Extension)	Assessment (Extension)	End of trial	Unscheduled	Surgery	Follow-up
Visit number	1	2	3	4	5	6	7	8	9	10	11				
cells															
Antibodies	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13,14]	X[13,14]	X[13]	X[13]	X[1,13]	X[13]	X[13]
Biochemistry	X	X[15]			X			X			X	X	X[1,15]	X[15]	
Haematology	X				X			X			X	X	X[1]		
Coagulation parameters, FVIII activity	X[16]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17,18]	X[19]	X[19]	X[17]	X[17]	X[1]	X[17]	X[20]
Coagulation parameters, Lupus Anticoagulant		X											X[1,21]		
Biospecimen sample		X	X	X	X	X	X	X			X	X	X[1]		X
TRIAL MATERIAL															
Injection of trial product[6]		X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1,18]	X[1]	X[1]	X[1]		X[1]	X	
Hand out trial card	X														
Hand out diary/collect diary	X	X	X	X	X	X	X	X	X	X	X	X			
Dispensing trial product		X	X	X	X	X	X	X	X	X	X		X[1]	X	
REMINDERS															
Case book sign off								X[22]				X[22]			X[22]
End of trial form								X[23]				X			
IWRS session	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	
Drug accountability		X	X	X	X	X	X	X	X	X	X	X	X[1]	X	
Review diary		X	X	X	X	X	X	X	X	X	X	X			
Home treatment training		X													
Planned regimen and dose adjustment		X	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]	X[1]		

X[1] If applicable

X[2] Can be signed at any visit, see section 17.1

X[3] Patients with inhibitors can be followed up at 3 follow-up visits scheduled with a month apart, see section 8.1.9

X[4] Genotype consent is not mandatory at visit 2, but has to be collected before genotype is sampled, see section 8.5.3.4 , 8.5.3.5

X[5] Guidance on when to measure height and weight see Table 8–2 and Table 8–3

X[6] Bleeding and dosing information between visits and at visits are recorded in the diary

X[7] Must only be performed on PK patients. Washout period before PK is dependent on age, see Table 8–1

X[8] Determination of half-life if the patient has a low titer inhibitor (≥0.6 BU and ≤5 BU). Washout period before sampling for half-life see Table 8–1

X[9] Only annually

X[10] Performed before and after the first trial drug injection

X[11] Not mandatory at screening in case the patient is previously diagnosed with Hepatitis B or C or have previously been tested within 6 months. Mandatory at an unscheduled visit in case the patient during the course of the trial has been injected with a medication that may contain a risk of hepatitis infection see section 8.5.3.1

X[12] Not mandatory at screening if the patient previously has been diagnosed with HIV or has previously been tested within 6 months. Mandatory at an unscheduled visit in case the patient during the course of the trial has been injected with a medication that may contain a risk of HIV infection see section 8.5.3.2

X[13] A washout period of 48 hours since last dosing of any FVIII product is required before inhibitor testing

X[14] If the patient has a low titer inhibitor (≥0.6 BU and ≤5 BU)

X[15] CRP, only for pharmacokinetic (PK) patients sampled before dosing for PK

X[16] Baseline FVIII level, see section 8.5.2.3

X[17] Test for FVIII trough and recovery. Trough is mandatory for all patients on the prophylaxis regimen, except at visit 1 and at the dispensing visit (except if the patient has a low titer inhibitor) it is also mandatory when determining half-life for inhibitor patients at an unscheduled visit. Recovery is optional, except if the patient has a positive inhibitor test (≥0.6 BU (Bethesda unit)) or there is suspicion of inhibitors. or the patient has performed PK at visit 2 then recovery must be performed at visit 8 . or before surgery, except if a PK has been performed previously in the trial or when determining half-life for inhibitor patients in the unscheduled visit, see section 8.5.2.3

X[18] Injection of trial product and recovery at the end of trial visit will be reported in the extension trial

X[19] Trough and recovery if the patient has a low titer inhibitor (≥0.6 BU and ≤5 BU)

X[20] FVIII activity.

X[21] If a second confirmatory inhibitor test must be taken

X[22] If there is a follow-up visit after end of trial, the case book must be signed at the follow-up visit

X[23] Only to be performed if the patients withdraw from the trial during the main phase of the trial

Table 2–2 Pharmacokinetic flowchart

	Nominal time				
	hours	min	Sample window (min)	Visit 2 0-11 years	Visit 2 ≥12 years
Day1	-01	00	+55	X	X
	00[2]	00[2]		X[1]	X[1]
	00	15	±5		X
	00	30	±5	X	X
	01	00	±10		X
	04	00	±60	X	X
	08	00	±60		X
	12	00	±60		X
Day 2	24	00	±120	X	X
	30	00	±120		X
Day 3	48	00	±120		X

X[1] Patient must be dosed with 50 ±5 IU/kg body weight (BW) trial product

X[2] Time of dosing is equal to the stop time of injection

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) [1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[2]

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

3.1 Background information

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutation in the coagulation factor VIII (FVIII) gene on the long arm of the X-chromosome. Approximately 1 in 5,000 males is born with haemophilia A. Haemophilia is classified as "severe (<1%)", "moderate (1-5%)" or "mild (>5%)" according to the residual plasma activity of the affected clotting FVIII[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.

Recurrent bleeding episodes in the same location, most commonly a weight-bearing joint, lead to chronic arthropathy, muscular atrophy, and deformities. Treatment of bleeds as they manifest (on-demand treatment) may delay this process, but does not prevent it[4]. For this reason, in many developed countries prophylaxis with regular FVIII injections is a standard practice from early childhood to at least 18 years of age. The primary goals of haemophilia therapy are the prevention of bleeding episodes, rapid and definitive treatment of bleeds that do occur, and the provision of adequate haemostasis during surgery and other major challenges to haemostasis.

3.2 Novo Nordisk's recombinant FVIII, turoctocog alfa

3.2.1 Clinical data

Novo Nordisk A/S has developed turoctocog alfa, a B-domain truncated human recombinant FVIII for the treatment of patients with haemophilia A. For information on the medicinal aspects, non-clinical data and quality of turoctocog alfa, please refer to the Investigator's Brochure[5]. The clinical experience with turoctocog alfa is described below.

In accordance with the European Medicines Agency (EMA) guidelines on development of new FVIII products[6] the clinical development program for turoctocog alfa started with a first human dose trial (NN7008-3522) to document the essential PK characteristics of the product and to obtain initial safety information. The trial also included a comparison of the PK profiles of turoctocog alfa and Advate®, a marketed recombinant serum free product. Twenty three previously treated patients

with severe haemophilia A completed the trial. Overall, the PK profiles of turoctocog alfa and Advate® were comparable[7]. No safety concerns were observed in the trial.

Clinical experience further includes two completed phase 3 trials, i.e. the pivotal (NN7008-3543, guardian™1) and paediatric (NN7008-3545, guardian™3) trials. A total of 213 previously treated patients (PTPs) with severe haemophilia A (FVIII≤1 %) from 18 countries participated in these trials. In both trials, the primary objective was to assess safety, including the incidence rate of FVIII inhibitors (≥0.6 BU). Secondary endpoints included evaluation of efficacy during prophylaxis treatment and treatment of bleeding episodes, PK and patient-reported outcome parameters. Furthermore, safety and efficacy during surgical procedures were assessed.

An extension trial (NN7008-3568, guardian™2) will finalise during 2016. Table 3–1 provides an overview of phase 3 clinical trials including patient groups and treatment regimens.

Table 3–1 Overview of finalised turoctocog alfa phase 3 (guardian™) trials

Trial ID	Number of dosed patients	Treatment
NN7008-3543 (guardian™1)	**Total trial (including sub-trial):** 150 adolescent or adult patients with severe haemophilia A. **Surgery sub-trial:** 9 adolescent or adult patients with severe haemophilia A	**Prophylaxis** 20−50 IU/kg 3 times weekly or 20−40 IU/kg every second day **Treatment of acute bleeds** 20−200 IU/kg daily at the investigator's discretion **Surgery** 20−200 IU/kg daily from Day 1 to 7 aiming for a FVIII trough activity of >0.5 IU/mL and from Day 8, the doses should be according to local standard practice at the treatment centre
NN7008-3545 (guardian™3)	63 paediatric patients (below 12 years of age) with severe haemophilia A	**Prophylaxis** 25–60 IU/kg 3 times weekly or 25–50 every second day **Treatment of acute bleeds** Max 150 IU/kg daily at the investigator's discretion
NN7008-3568 (guardian™2)	55 paediatric, 23 adolescent and 109 adult patients with severe haemophilia A (up until the cut-off date 1 Sept 2012) Surgery sub-trial:5 adolescent or adult patients with severe haemophilia A (up until the cut-off date 1 Sept 2012)	**Prophylaxis** 20−60 IU/kg 3 times weekly or 20−50 IU/kg every second day **Treatment of acute bleeds** 20−200 IU/kg daily at the investigator's discretion ***Surgery*** 20−200 IU/kg daily from Day 1 to 7 aiming for a FVIII trough activity of >0.5 IU/mL and from Day 8, the doses should be according to local standard practice at the treatment centre

In summary, all three trials demonstrated excellent safety profile of turoctocog alfa with no development of FVIII inhibitors.[5]

3.2.2 Risks and benefits

FVIII products are used in the standard care of patients with haemophilia A. Although not identical in structure, the effect of turoctocog alfa is similar to other marketed FVIII products which are of either plasma derived or recombinant origin. Turoctocog alfa is a recombinant protein manufactured in a serum-free process, and the risk of transmission of infectious agents through this product is therefore extremely low.

Potential risks are common to all recombinant FVIII (rFVIII) products and include allergic reaction and formation of antibodies to FVIII which may be neutralising (inhibitors). Although an allergic reaction to the trial product is possible in susceptible individuals, no severe reactions to turoctocog alfa have been observed so far. Inhibitor formation occurs in up to 30-35% of previously untreated patients with severe haemophilia A[8], but is a rare occurrence in patients with a history of treatment with FVIII products. This trial will enrol patients with a considerable previous exposure and no inhibitors in previously treated patients were detected in previous trials. Therefore the risk of antibody formation to turoctocog alfa in this trial is considered low, though it is known that de novo inhibitors may develop lifelong.[9]

The potential benefit to the patients treated with turoctocog alfa includes more treatment choices and expanded access to safe and effective treatment of haemophilia A. Furthermore the patients in the trial will have access to FVIII product that has been demonstrated to be effective in already conducted clinical trials.

For further information on risk and benefits and safety of turoctocog alfa please see the Investigator Brochure.[5]

3.3 Rationale for the trial

The rationale for this trial is to accumulate sufficient exposure to turoctocog alfa in order to obtain efficacy data and evaluate safety in terms of immunogenicity from treatment of bleeding episodes and with prophylaxis in Chinese patients with severe haemophilia A.

Globally there is still a vast unmet medical need for treatment of haemophilia A. Through 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 improving treatment in haemophilia A.

3.3.1 Clinical development program

The phase 3 clinical development program was presented in section 3.2 . The present trial NN7008-4028 (guardian™7) will support the program with clinical data on inhibitor development and will contribute to establish the overall efficacy and safety profile of turoctocog alfa.

In addition, Novo Nordisk is conducting a phase 3b (NN7008-3568 guardian™2) extension trial and a phase 3a (NN7008-3809, guardian™4) PUP trial to collect longer term efficacy and safety data.

Turoctocog alfa has obtained approval in Europe, North America and Japan by 01-Jan-2016 under the trade name of NovoEight® or Novoeight®.

4 Objectives and endpoints

4.1 Objectives

Primary objective:

- To evaluate the clinical efficacy of turoctocog alfa in treatment of bleeding episodes in Chinese patients with severe haemophilia A (FVIII≤1%)

Secondary objectives:

- To assess the safety of turoctocog alfa in terms of immunogenicity
- To evaluate the clinical efficacy of turoctocog alfa during prophylaxis treatment
- To evaluate the consumption of turoctocog alfa during prophylaxis treatment and treatment of bleeding episodes
- PK phase only: To investigate the pharmacokinetic (PK) characteristics of turoctocog alfa after single dose injection
- Surgery only: To evaluate the efficacy and safety of turoctocog alfa during surgical procedures
- To evaluate impact of turoctocog alfa treatment on patient's health related quality of life (HRQOL)

4.2 Endpoints

4.2.1 Primary endpoint

- Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months duration per patient).

4.2.2 Supportive secondary endpoints

- Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the trial period of 24 months
- Incidence rate of inhibitory antibodies against FVIII (≥0.6 BU) during both the main phase of 6 months and during the trial period of 24 months[I]
- Number of bleeds (total bleeds assessed as annual bleeding rate) per patient during both the main phase of 6 months and during the trial period of 24 month[II]
- Consumption of turoctocog alfa during both the main phase of 6 months and during the trial period of 24 months[III]:

[I] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[II] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov
[III] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov

- Consumption of turoctocog alfa for bleeding treatment (average dose to treat a bleed, number of injections and IU/kg per bleed) during both the main phase of 6 months and during the trial period of 24 months
- Consumption of turoctocog alfa during prophylaxis treatment (average prophylaxis dose and IU/kg per month and per year) per patient during both main phase of 6 months and during the trial period of 24 months
- Total consumption of turoctocog alfa (IU/kg per month and per year) per patient during both the main phase of 6 months and during the trial period of 24 months
- Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during both the main phase of 6 months and during the trial period of 24 months[I]

4.2.2.1 Pharmacokinetic endpoint

PK endpoints after a single dose of turoctocog alfa:

- Incremental recovery of FVIII
- Area under the curve ($AUC_{0\text{-}inf}$)
- Half-life ($t_{½}$)
- Clearance (CL)
- Highest measured FVIII activity in the profile (C_{max})

4.2.2.2 Surgery endpoints

The surgery endpoints will be evaluated both for the main phase of the trial (6 months duration per patient), and for the combined main and extension phase (total trial period of 24 months).

- Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon on the day of surgery (Day 1) and on the last day in the post-operative period the patient is at the trial/surgery site
- Loss of blood and requirements for transfusion on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site whatever comes first
- Adverse Events/Serious Adverse Events occurred on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site whatever comes first

4.2.2.3 Patient reported outcome endpoints

- Change in total scores for reported health-related quality of life during both the main phase of 6 months and during the trial period of 24 months.

[I] Key supportive secondary endpoint prospectively selected for posting on www.clinicaltrials.gov

5 Trial design

5.1 Type of trial

This is a single-country, multi-centre, open-label and non-randomised trial. 65 PTPs with haemophilia A will be given a prophylactic regimen or an on-demand regimen of turoctocog alfa. It is not possible to switch between these 2 treatments regimens in the main phase of the trial, but the dose and frequency of dosing can though be changed. (Please see 5.3.1 for exemption of patients with low titer inhibitor) At least 10 patients on the on-demand and 20 patients on the prophylaxis regimen will complete the main phase of the trial, which will last for approximately 6 months.

If a patient has not finalised the main phase at the time of cut off for the main CTR they will though be moved to the extension phase of the trial and thus will not complete the main phase and will not have 6 months in this phase of the trial. See Figure 16–1. They will though have the visit 8 safety assessments performed at the last main visit or at the next extension visit.

For an individual patient the main phase is defined as from visit 1 to visit 8. On trial level the main CTR will be written with at least 60 patients having completed the main phase of the trial.

An extension phase (from visit 8 until LPLV, see section 7) is added to assess long term safety and efficacy, see section 7, and either prophylaxis or on demand treatment can be chosen also in this phase, but it is possible to switch between these treatments regimens during the extension phase and also to change the dose and frequency of dosing.

Of the 65 dosed patients, a minimum of 12 and a maximum of 18 patients (see Table 6–1) will be enrolled in the PK session to characterise the PK profile of turoctocog alfa in a Chinese population with severe haemophilia A.

Enrolled patients who need to undergo surgical procedures will remain in the trial provided that turoctocog alfa is used for the prevention and treatment of the surgical bleeding. All surgeries procedures (e.g. minor, major, elective, and emergency) may be performed using turoctocog alfa at the investigators discretion.

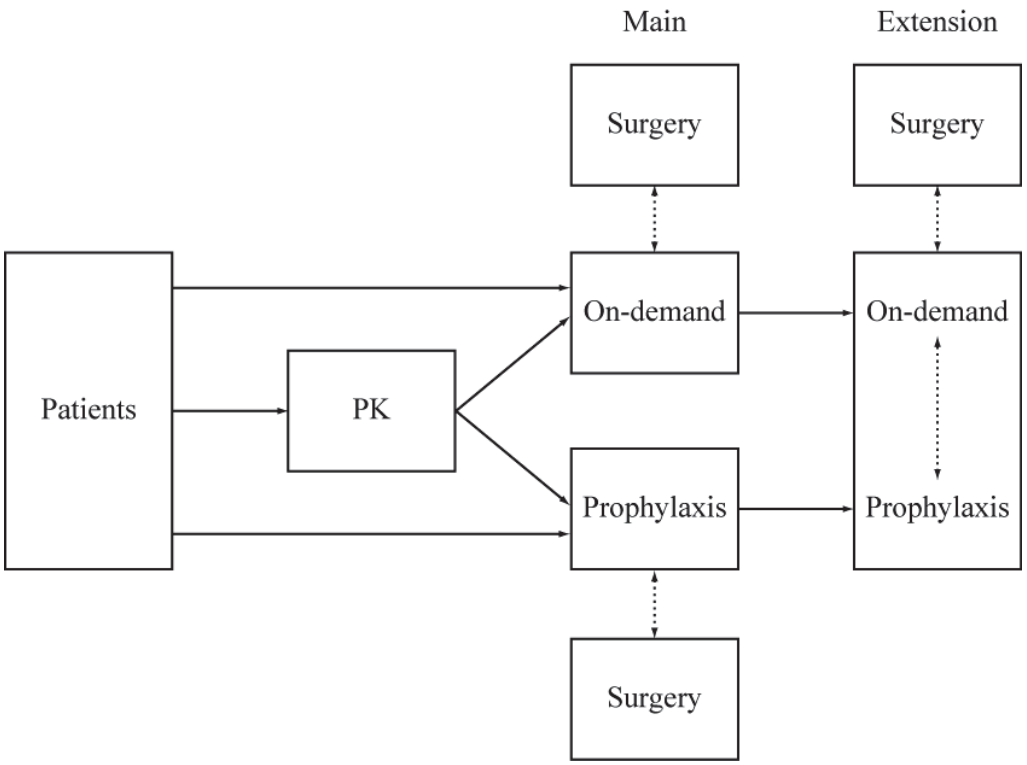

Figure 5–1 Overview of the trial design

5.2 Rationale for trial design

This is an uncontrolled, non-randomised trial and the design is common for trials with FVIII products in haemophilia A patients. In this trial, previously treated severe haemophilia A patients will receive routine prophylaxis treatment and treatment of bleeds, as well as prevention and treatment of bleeding episodes in surgery. This design is to a large extent similar to the pivotal NN7008-3543 (guardian™1) and NN7008-3568 (guardian™2) trial design. The patients will be treated for approximately 6 months in the main phase which will allow both patients on prophylaxis and on-demand treatment to accumulate sufficient exposures to turoctocog alfa in order to demonstrate efficacy and safety in treatment and prevention of bleeding episodes. If a patient has not finalised the main phase at the time of cut off for the main CTR they will be moved to the extension phase of the trial and thus will not have 6 months in the main phase of the trial. See Figure 16–1

This trial will also include a PK session at visit 2 to characterise the PK profile in Chinese population. This trial is conducted in a Chinese population and will be comparable to the pivotal trial in the guardian program.

5.3 Treatment of patients

Patients will receive prophylaxis treatment and/or treatment of bleeds, as well as surgery treatment and treatment of bleeding episodes during surgery and in the post-operative period.

The trial product is turoctocog alfa produced by Novo Nordisk. The trial product is a recombinant FVIII product and is a lyophilised powder in vials, which is reconstituted with solvent for injection. Trial product will be administered as intravenous injections (i.v.) at home by the patient or parent/caregiver, at the trial site or in exceptional cases in another clinic/hospital. To be able to train patients on home treatment of turoctocog alfa at least the first treatment should be at the trial site.

The investigator should together with the patient decide if the patient should receive the trial product as a prophylaxis treatment or as on-demand treatment.

Table 5–1 Treatment regimen overview of trial product

Treatment regimen	Age (Years)	Dose(IU/kg BW)	Dose frequency
Prophylaxis	<12	25-50	Once every second day
	≥12	20-40	
Prophylaxis	<12	25-60	3 times weekly
	≥12	20-50	
On-demand	All	Decided by investigator	When necessary
Surgery	All	Decided by investigator	When necessary

5.3.1 Switching between treatment regimens

It is possible to switch between prophylaxis and on-demand treatment in the extension phase of the trial. In the main phase, a switch from on-demand regimen to prophylaxis is only possible for a patient with confirmed low-titer inhibitor. A slow-start initiation phase may be used, but must be followed up with regular prophylaxis-treatment (ie. three times weekly or every second day) as soon as possible and no later than within 1 month.

5.3.2 Maximum dose

There is no maximum for the total daily dose of turoctocog alfa for the treatment of bleeds and surgery treatment. The maximum dose per injection must not exceed 100 IU/kg BW.

5.3.3 Prophylactic treatment

The frequency of dosing can be either every second day or 3 times weekly. The individual regimen is chosen by the investigator, taking into account the patient's wishes, clinical status and readiness to comply with frequent dosing. The investigator can start up the patient on prophylaxis regimen at his/her discretion, e.g. dosing once weekly. However, regular prophylaxis regimen in accordance with the protocol should be implemented as soon as possible and no later than within a month. See Table 5–1 for the allowed dose ranges in the trial. The starting dose should be defined by the investigator within the recommended range based on clinical status and results of the PK evaluation where available. Dose adjustments can be made based on the patient's clinical status (bleeding frequency).

In order to further optimise the prophylaxis treatment effect in this trial, a starting dose of 30 IU/kg for children below the age of 12 years and 25 IU/kg for age equal to or above 12 years is recommended in this trial.

5.3.4 Treatment of bleeding episodes

Bleeds occurring during both the on-demand and in the prophylaxis treatment regimen will be treated with one or more turoctocog alfa i.v. bolus injections. The individual dose is determined by the investigator, using the recommendations in the World Federation of Haemophilia (WFH) guidelines[10].

Dose (IU) = weight (kg) x desired factor level (IU/dl) x 0.5

Example: 50kg x 40IU/dl x 0.5 = 1000 IU of turoctocog alfa

In case of bleeding events, Table 5–2 as well as 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 5–2 Guide for trial product 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] NovoEight® approved summary of turoctocog alfa characteristics

This formula may be used to calculate resulting factor levels:

IU/dl (or % of normal) = [Total Dose (IU)/BW (kg)] x 2 [IU/dl]/[IU/kg]
Example: 2000 IU x ([2 IU/dl]/[IU/kg]) / 70 kg = 57 IU/dl
A dose of 2000 IU administered to a 70 kg patient should result in a post-injection FVIII level increase of 57 IU/dl, or 57%.

The patient will be withdrawn from the trial in case he is treated with another FVIII product than turoctocog alfa, see section 6.4

Bleeding treatment should start as soon as a bleed is identified. The investigator should provide the patient in advance the doses needed to treat the bleed of different severities.

In case the patient suspects the bleed is severe it must be reported to the trial site if possible immediately or within 24 hours. See Table 8–6 for a definition of severe bleeds. Furthermore, if there is no haemostatic improvement within 24 hours of the first trial product injection, the patient or parent/caregiver should immediately contact the investigator for advice.

The investigator must always be contacted in case of bleeds that require treatment in a hospital setting and should be consulted for determination of dose and treatment duration if possible.

Recording into the diary should be made preferably within 24 hours from onset of the bleed to ensure as correct information as possible. Any dose used for treatment of an active bleed must be recorded as a treatment of a bleed. When symptoms of active bleeding have stopped (e.g. pain is reduced and no increase in swelling/swelling diminishes), the patient or parent/caregiver can resume the prophylactic treatment regimen if on prophylaxis. The timing of the next dose should be

according to the prophylaxis dosing schedule. For patients on on-demand treatment, taking occasional prophylaxis doses it is allowed after bleeds to prevent re-bleeding, or before physical activity. The decision to allow these treatments should be made by the investigator. These doses should be recorded in the diary as treatment taken for "other" reasons, and not as trial scheduled prophylactic treatment. The decision to allow this treatment and the duration should be made by the investigator.

5.3.5 Treatment of patients with low titer inhibitors

Patients with low titer inhibitors (≥ 0.6 BU and ≤ 5 BU) in the trial can be treated within the recommended dosing range for prophylaxis and treatment of bleeds according to section 5.3.3 and 5.3.4. If the patients cannot respond well to treatment according to the protocol they must be withdrawn, see section 6.4.

Please see section 8.4.1 for the diagnosis of inhibitors.

5.3.6 Pharmacokinetic session

For PK sessions a dose of 50 ±5 IU/kg BW will be administered i.v. as a single bolus injection. The washout period before PK session will be dependent of the age, see Table 8–1.

5.3.7 Treatment during surgery

For dosing guidance in patients who need to undergo surgical procedures during the trial, investigators could refer to the below Table 5–3 and WFH guideline[10]. As the guidelines are recommendations non-compliance with them will not require any protocol deviations.

Table 5–3 Guide for dosing in surgery

Type of surgical procedure	FVIII level required (%) (IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Minor surgery Including tooth extraction	30-60	Repeat every 24 hours if needed until healing is achieved
Major surgery	80-100 (pre-and postoperative)	Maintain factor VIII level by repeat injection every 8-24 hours until adequate wound healing, then adjust therapy for at least 7 more days to maintain a FVIII activity of 30% to 60% (IU/dl)

The specific treatment for each individual is decided by the investigator and the surgeon. Surgery can be done at the trial site, in another clinical department of the site, or at another hospital. If a surgery takes place at another location than at the trial site, the surgeon must be informed that the patient is participating in the trial, and the investigator should give instructions to the surgeon about the dosing treatment, the handling of the trial product and the efficacy and safety evaluation. The

trial and Novo Nordisk must ensure that there is enough available trial product for the whole surgery period including the post-operative period. . Please note the medication that is not permitted during the trial and surgery, see 8.2.2

5.4 Treatment after end of trial

When discontinuing trial product treatment, the patient should be switched to a suitable marketed product at the discretion of the investigator. In case the patient is withdrawn from the trial due to inhibitor development, NN will cover the cost of associated treatment in the event the inhibitor development is considered a trial related injury in accordance with Chinese law. Novo Nordisk will not provide any patient with trial medication after the end of the trial unless required in accordance with Chinese law or regulation.

5.5 Rationale for treatment

Dosing range and treatment regimens in this trial reflect the recommended dosing in prescribing information for turoctocog alfa approved by regulatory authorities worldwide.

See the Investigator's Brochure[5] and any updates hereof for further preclinical and clinical data.

6 Trial population

6.1 Number of patients – planned and required

- Number of patients planned to be screened: 70
- Number of patients planned to start on trial product: 65
- Number of patients planned to complete the main trial: 60
- Number of patients planned to complete the extension trial: 50

Completed patients in the main trial are defined as having completed visit 8. If a patient is withdrawn during the main part of the trial they are not counted as completers, except if they are withdrawn due to inhibitor development.

PK phase (Visit 2):
Assessment of a single dose PK profile at visit 2 is required in at least 12 patients and maximum 18 patients.

- At least 3 patients aged 0-5 years and maximum 6 patients
- At least 3 patients aged 6-11 years and maximum 6 patients
- At least 6 patients aged 12 and older and maximum 12 patients

Not all age groups can reach the maximum numbers of patients as the total number can only be 18 patients.

If a patient has started in the PK phase, but has not completed most of the blood samples he will not be counted as a PK patient, and a new PK patient must be enrolled into the PK part.

Main phase:
- At least 10 patients to complete the on-demand regimen
  - At least 12 patients planned to start on on-demand regimen
- At least 20 patients to complete the prophylaxis regimen
  - At least 22 patients planned to start on the prophylaxis regimen

Table 6–1 Patients planned to be dosed

<table>
<tr><th></th><th>PK phase</th><th>Main phase</th><th>Extension phase</th></tr>
<tr><td>Age (years)</td><td colspan="3">#patients</td></tr>
<tr><td>0-5</td><td>3-6</td><td rowspan="3">on-demand 12-43
prophylaxis 22-53</td><td rowspan="3">No requirement</td></tr>
<tr><td>6-11</td><td>3-6</td></tr>
<tr><td>≥12</td><td>6-12</td></tr>
<tr><td>All</td><td>12-18</td><td>65</td><td>No requirement</td></tr>
</table>

See above Table 6–1 for the minimum and maximum requirements of patients to start on trial product. The numbers in this table will be used to stop the screening of patients, see section 7. All patients already screened and who are eligible will be enrolled, which may cause the maximum numbers in Table 6–1 to be exceeded.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients
3. Age from 0 years
4. Severe congenital haemophilia A (FVIII≤1%)
5. History of exposure days (ED) to any FVIII concentrates fulfilling the criteria of previously treated patients:
   5a: Patients of 12 years or above: 100 exposures days (ED) or more
   5b: Patients below 12 years: 50 exposure days (ED) or more
6. Asian ethnicity and resident in China

6.3 Exclusion criteria

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

1. Inhibitors to FVIII (≥0.6 BU) at screening as assessed by central laboratory
2. Known history of FVIII inhibitors
3. Known or suspected hypersensitivity to trial product(s) or related products
4. Previous participation in this trial. Participation is defined as informed consent obtained
5. Receipt of any investigational medicinal product within 30 days of the first planned injection of the trial product
6. On-going treatment or planned treatment during the trial with chemotherapy, immunomodulatory agents (e.g. intravenous immunoglobulin (IVIG), routine systemic corticosteroids)
7. Significant hepatic or renal impairment (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >5 x upper limit of normal (ULN), serum creatinine >1.5 x ULN) as defined by central laboratory
8. Known congenital or acquired coagulation disorders other than haemophilia A
9. Use of Anticoagulants: Vitamin-K antagonists, direct factor Xa- inhibitors, direct thrombin inhibitors, heparin (except for flushing central venous access device (CVAD)) one week prior to first injection of trial product

10. Any disorder which, in the opinion of investigator, might jeopardise patient's safety or compliance with the protocol
11. Mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation
12. Immunocompromised patients due to HIV infection (defined as viral load ≥400.000 copies/mL and/or CD4+ T lymphocyte count ≤200/µL performed at screening or no older than 6 months)

6.4 Withdrawal criteria

The patient may withdraw at will at any time either by the patient or by the patient's parent or the patient's legally acceptable representative (LAR). The patient's request to discontinue must always be respected.

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

The patient must be withdrawn if the following applies:
1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. High titer FVIII inhibitor (>5 BU), confirmed by central laboratory
3. Patient with a low titer inhibitor (≥ 0.6 BU and ≤ 5 BU) and with a significantly reduced recovery who do not respond well to treatment according to protocol
4. Surgery required on a patient with a low titer inhibitor (≥0.6BU and ≤5BU)
5. Severe allergic or anaphylactic reaction to trial product
6. Use of prohibited medication mentioned in section 8.2.2
7. Persistent non-compliance with trial procedures

Patients who are withdrawn will not be replaced.

In case the patient is withdrawn due to criteria 2, 3 and 4 the patient should be followed up at follow-up visits, see section 8.1.9.

6.5 Rationale for trial population

Patients with severe haemophilia A and a history of exposure to FVIII products are selected as the most suitable group for evaluation of immunogenicity in previously treated patients, which is one of the objectives of this trial. The patient population in this trial is similar to that in NN7008-3543 (guardian™1). The main difference from the NN7008-3543 (guardian™1) trial is that this trial also includes paediatric population below 12 years, and the definition of PTP for patients equal to or above 12 years is 100 EDs and not 150 EDs. The reason for including paediatric population is to provide efficacy and safety data on Chinese PTPs covering paediatric, adolescent and adult population in order to support a New Drug Application (NDA) in China covering both children and adults. The reason for reducing 150 EDs to 100 EDs for PTPs aged ≥12 years is that, in China, most

haemophilia patients only receive on-demand treatment and many do not always receive treatment when bleeding. Consequently, only few younger patients may accumulate over 100 EDs. A recent survey conducted in big cities in China showed that only 1/3 of patients could get on demand treatment after every bleed, and very few patients could get prophylaxis treatment. The situation is expected to be worse in small cities.[11]

A history of inhibitors may be a risk factor for inhibitor development which could heighten the risk of inhibitor formation in the trial if not excluded. In order to avoid interference with immunogenicity assessment, only patients who are immunocompetent and currently without inhibitors to FVIII products are selected. These selection criteria are in accordance with the EMA guideline.[6] Haemophilia patients in China are not routinely tested for inhibitors and therefore it will not be possible to guarantee that patients with no previous inhibitor tests have no inhibitor history. To minimise the risk of inhibitor development, patients with a known history of inhibitors will be excluded and an inhibitor test will be done at screening. Furthermore, only patients with documented long-term exposure to FVIII products will be enrolled. A risk of inhibitor development after 100 EDs for patients equal or older than 12 years and 50 EDs for patients below 12 years is deemed minimal, though it is known that de novo inhibitors may develop lifelong.[9]

Patients that are withdrawn from the trial due to inhibitor development will be followed up at 3 follow-up visits scheduled with a month apart.

7 Milestones

Planned duration of recruitment period: First patient first visit until last patient first visit in the main trial (FPFV – LPFV in the main trial): 12 months

Planned FPFV: 15-Dec-2016

End of trial is defined as last patient last visit (LPLV):

- Planned LPLV for the main phase of the trial: 15-Jun-2018
- Planned LPLV for the extension phase of the trial: 15-Dec-2018

The total duration for a patient's participation in the trial is expected to be 6 months in the main phase of the trial and at most 18 months in the extension phase of the trial or until turoctocog alfa is commercially available or until the marketing authorisation application is rejected in China or until the trial, part of the trial or a trial site is terminated by Novo Nordisk or by a relevant authority for any reason. In any event, the LPLV for the trial will be no later than 18 months from FPLV in the main trial, which is planned to be the 15-Dec-2018 whether or not the product is commercially available in China**.**

If a patient has not finalised the main phase at the time of the cut off for the main CTR they will be moved to the extension phase of the trial and thus will not have 6 months in the main phase of the trial. See Figure 16–1

Recruitment:
The different age groups in the PK and main phase of the trial will be open for recruitment from the beginning of the trial. The extension phase will first open for a patient when he has finalised the main phase.

Trial registration:
Information of the trial will be disclosed at www.clinicaltrials.gov, www.chinadrugtrials.org.cn and www.novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE) [12], the Food and Drug Administration Amendment Act (FDAAA) [13], European Commission Regulation for EudraCT [14] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. The registry requires only full details concerning the principal investigator. For the participating sites only the name of the hospital/organisation and the province and the city must be entered.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the visit flow, the assessments and procedures are described in the flow chart, see section 2.

It is important to comply with the visit window mentioned in the flow chart, see section 2, to ensure correct timing of assessments and that the trial products do not expire while they are in the patient's possession.

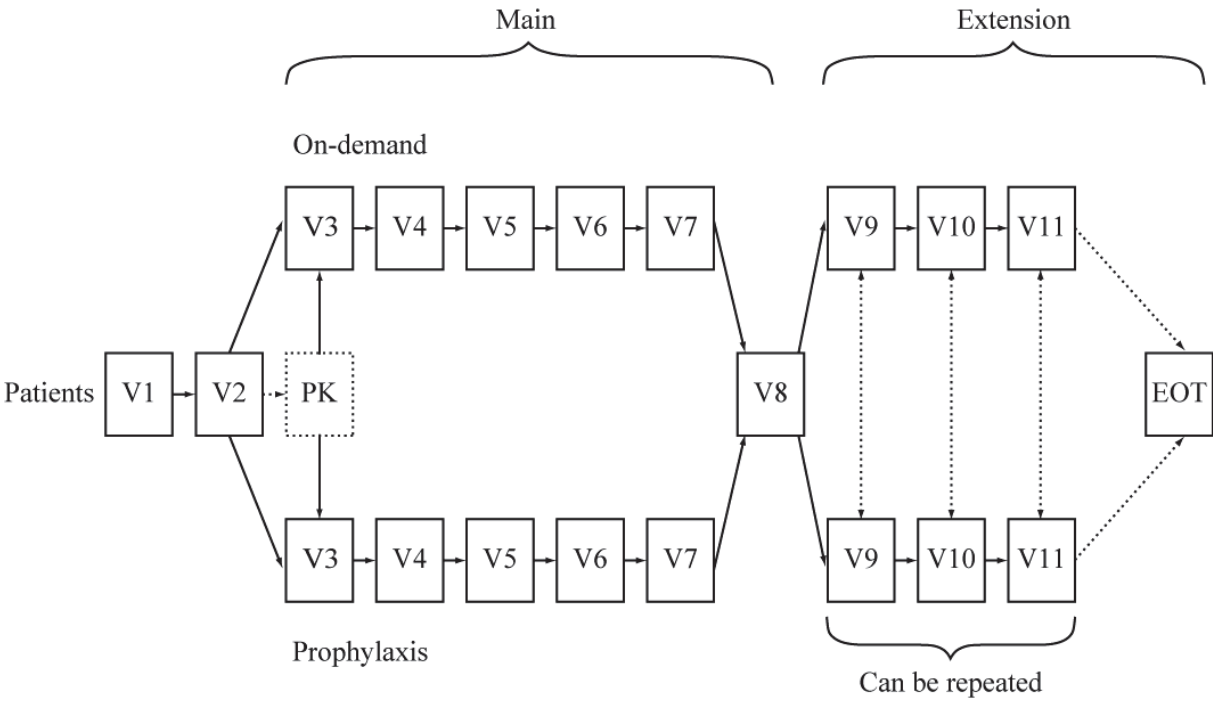

Figure 8–1 Overview of visit flow

PK is optional
Visit 9, visit 10 and visit 11 can be repeated both for on-demand and prophylaxis regimen
Surgery can be performed at any time during the trial, see section 8.1.6
The duration of the main phase of the trial is approximately 6 months before the cut off for the main CTR

Informed consent procedures
The patient or parent/LAR will be provided with full written and verbal information about the trial prior to conduct of any trial-related procedures/activities, in accordance with GCP[1] and local requirements, see section 17.1.

A child assent form may be provided to children. The child assent can be performed on a separate day. As this is a long term trial the investigator should check the progressing maturation of the child and his ability to assent throughout the trial.

Treatment in general
Trial product injection can be performed at all visits except at the screening visit. A trial product injection at visit 2 must be performed at the trial site to assess if the patient or parent/caregiver can handle the trial product injection both for patients on the on-demand and prophylaxis regimen. If assessed necessary, training sessions must be planned for and documented in the patient's medical records.

If injection of trial product is performed between scheduled visits at the trial site, this must be recorded at an unscheduled visit.

A washout period of trial product is necessary in order to ensure that there is no interference of the trial product with the assay, see Table 8–1.

Table 8–1 Minimum requirements for washout periods

Laboratory test	Washout period Below 12 years	Washout period 12 years and older
Screening – baseline FVIII level	48 hours	48 hours
Inhibitor sampling	48 hours	48 hours
PK	72 (- 6) hours	96 (- 12) hours
Determination of half-life	48 hours	48 hours

In case a patient does not fulfill the requirements of a washout period (e.g. the patient has received treatment for a bleed), the visit should be rescheduled.

Withdrawn patients
If a patient is withdrawn from the trial, the investigator must aim to undertake procedures similar to the end of trial visit as soon as possible. The end-of-trial form must be completed, and final drug accountability must be performed even if the patient is not able to come to the trial site. A withdrawal call must be performed in IWRS and the case book must be signed in the eCRF.

Although a patient is not obliged to give his reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Where the reasons are obtained, the primary reason for not completing the trial must be specified on the end-of-trial form in the eCRF.

Patients that are withdrawn from the trial due to inhibitor development will be followed up at 3 follow-up visits scheduled with a month apart, see section 8.1.9.

8.1.1 Visit 1

The patient or parent/LAR must give signed and dated informed consent prior to any trial-related activities. If the patient must withhold FVIII treatment before visit 1 that is not according to the patient's regimen the informed consent must be signed before this trial activity happens. All patients will be provided with a copy of the patient information and a copy of the signed and dated Informed Consent Form.

Informed consent for obtaining genotyping and biospecimen (blood sampling for future research) must also be collected, if the patient or parent/LAR agrees to this. The informed consent for genotyping can be obtained later in the main trial and at the latest before sampling for genotyping.

For all patients with a signed Informed Consent, the patient will be assigned a unique 6 digits patient number, which will follow the patient throughout the trial. It must be stated in the medical records that the patient is participating in the trial, including the patient number.

The investigator must keep a patient screening log, a patient identification code list and a patient enrolment log. The patient screening log and patient enrolment log may be combined in one list.

At this visit the patient's medical history must be recorded using the patient's current medical journal and the patient's current medical status will also be evaluated. Furthermore the patient will be preliminary evaluated for enrolment by examining the inclusion and exclusion criteria against the above information. The final evaluation for enrolment will be performed at the next visit, visit 2 using the laboratory results taken at this visit. Furthermore an inhibitor test and FVIII baseline level will be performed so the patient must withhold FVIII treatment for 48 hours prior to this visit to ensure there is no interference of a FVIII product with the assay.

At screening, the patient or parent/LAR will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Patients should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

The diary must be handed out to the patient or parent/caregiver and training must be done. The investigator should train in how to record and change information in the diary and that the patient or parent/caregiver should record in the diary preferably within 24 hours after a bleed has occurred or after the treatment has been injected (after visit 2) to ensure as accurate information as possible.

The assessments to be performed at this visit are listed in section 2.

Screening failures
For screening failures the screening failure form must be completed with the reason for not continuing in the trial. Follow-up of SAEs must be carried out according to section 11.

A screening failure call must be made in the IWRS and the case book must be signed in the eCRF.

Re-sampling or re-screening is not allowed if the patient has failed to meet one of the inclusion or exclusion criteria related to laboratory parameters.

Key reminders:
- Informed consent must be obtained before any trial related activities starts
- Ask for any concomitant medications
- Trial card must be dispensed
- Screening session in IWRS must be performed
  - In case of a screening failure a screening failure session in IWRS must be performed and the case book must be signed off
- Check for 48 hours washout of FVIII products before inhibitor and FVIII level test
- Ask if the patient has experienced any AEs during this visit
- Hand out the bleed diary and train in how to use the diary
- Next visit should be scheduled

8.1.2 Visit 2

The visit must be scheduled 14 days after the screening visit with a window of 4 days. This is to allow sufficient time for the arrival of the laboratory reports as all results necessary for evaluation of the inclusion and exclusion criteria must be available before determining whether or not the patient can continue in the trial.

The main purpose of visit 2 is to inject the trial product the first time after the final evaluation of the inclusion and exclusion criteria and to assess the patient's medical status after the first dose of turoctocog alfa. This is also applicable for patients on the on-demand regimen and will need to record this dose as another dose. The investigator must also hand out the diary and train how to use it. Furthermore the visit can also be attended for PK assessments, see section 8.1.2.1.

It is not possible to change between the prophylactic and on-demand regimen during the main phase. (Please see 5.3.1 for exemption of patients with low titer inhibitor) It is possible to switch between the 2 different prophylactic dosing frequencies at a visit to the trial site in the main phase. However, if the patient changes regimen from three times weekly to every second day the site should contact the monitor at least seven days before the next scheduled visit so as to ensure there is sufficient trial product at site.

The investigator must judge if the patient or parent/caregiver capability of handling the trial product injection and plan for home training at unscheduled visits if necessary.

Trial product for home treatment must be dispensed to the patient or parent/caregiver if necessary until next visit.

In case the patient will have a PK session the first dose at visit 2 is administered for PK, see section 8.1.2.1.

The assessments to be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Training for home injection
- Dispensing session for the first dose and dispensing trial product until next visit must be performed in the IWRS
  - In case the patient will perform PK the first dose must be a PK session, see section 8.1.2.1
- Drug accountability must be performed in the IWRS for the first dose
- Hand out diary
- Check for 48 hours washout of FVIII products before inhibitor test
- Trial product must be dispensed
- Next visit should be scheduled

8.1.2.1 PK at visit 2

Blood sampling for PK will be performed during a period of 48 hours for patients who are 12 years and older and 24 hours for children below the age of 12 years, see Table 2–2 for the specific sampling time points. It is not required that the patient stay overnight.

PK sampling must start after the assessments performed at visit 2. See section 8.3.4 for more information in regards to the PK sampling.

Patients must not be dosed with FVIII or other products containing FVIII before the PK session, see Table 8–1 for the required washout periods as this is dependent of the age.

Key reminders:

- Check for adequate washout periods of FVIII products before the trial product injection, see Table 8–1 and for other rescheduling criteria, see section 8.3.4
- PK dose is 50 ±5 IU/kg BW

8.1.3 Visit 3-8

These visits must be scheduled 28 days after the previous visit with a visit window of 3 days, except visit 3 that must be scheduled 14 days after visit 2. The main reasons for these visits are to assess the patient's medical status after a longer use of the trial product.

At visit 5 some extra safety assessment will be performed, see the flow chart in section 2.

The assessments to be performed at these visits are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Dispensing session for trial product until next visit must be performed in the IWRS
- Drug accountability of trial product must be recorded in the IWRS
- Collect and review of the diary
  - Evaluate together with the patient the correctness of the haemostatic efficacy for treatment of bleeds
- Check for 48 hours washout of trial product before the inhibitor test
- Trial product must be dispensed
- Next visit should be scheduled

8.1.4 Visit 9 and visit 10 (Dispensing visits) – extension phase

The dispensing visits in the extension phase must be scheduled 56 days (approximately 2 months) after the previous visit with a window of 2 weeks. The main reason for these visits is to dispense trial product to the patient or parent/caregiver. In case the patient has a positive inhibitor (≥0.6 BU) some laboratory test must also be performed, see section 2.

Visit 9 and 10 will be repeated every six months until LPLV with a consecutive visit number see section 7.

The assessments to be performed at these visits are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Dispensing session for trial product until next visit must be performed in the IWRS
- Drug accountability of trial product must be recorded in the IWRS
- Review of the diary
  - Evaluate together with the patient the correctness of the haemostatic efficacy for treatment of bleeds

- Trial product must be dispensed
- Next visit should be scheduled

8.1.5 Visit 11 (Assessment visits) extension phase

The assessment visits in the extension phase must be scheduled 56 days (approximately2 months) after the previous dispensing visit with a window of 2 weeks. The main reasons for these visits are to assess the patient's medical status after a longer use of the trial product.

Visit 11 will be repeated every six months until LPLV with a consecutive visit number see section 7.

The assessments to be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Dispensing session for trial product until next visit must be performed in the IWRS
- Drug accountability of trial product must be recorded in the IWRS
- Collect and review of the diary
  - Evaluate together with the patient the correctness of the haemostatic efficacy for treatment of bleeds
- Check for 48 hours washout of trial product before the inhibitor test
- Trial product must be dispensed
- Next visit should be scheduled

8.1.6 Surgery visits - main and extension phase

Patients undergoing surgery will continue the regular visit schedule and will not need to reschedule visits during the surgery period, except if the surgery treatments do not allow for the necessary washout period of 48 hours, then the visit must be re-scheduled.

The surgery and the injection of trial product during the surgery and in the post-operative period will be recorded in the eCRF, except if the injection is performed at home or at another site as these doses will be recorded in the diary and then later transferred into the eCRF by the trial site. For more information regarding surgery see section 8.3.5. The post-operative period is defined as the period the patient is not following his ordinary planned treatment regimen after the surgery has been performed.

The assessments to be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Dispensing session for trial product during surgery must be performed in the IWRS
- Before the surgery day the patient must have a negative inhibitor test and a satisfactory recovery test from central laboratory, except for emergency surgery, see section 8.3.5
- Evaluate if a PK is necessary especially before a major surgery.

8.1.7 Unscheduled visits - main and extension phase

An unscheduled visit can be performed after the screening visit has been performed. Unscheduled visits can also be performed at the surgery day and during the post-operative surgery period. The date and time of the unscheduled visits must be recorded in the eCRF.

The main reason for the unscheduled visits is to record information that is important for this trial that do not occur during the scheduled visits. This information can be laboratory tests, dosing adjustments, a dose injection or for determination of half-life in case the patient has a low titer inhibitor (≥ 0.6 BU and ≤ 5 BU), lab samples to confirm a positive inhibitor test or a PK before surgery. Please note that AEs, withdrawal criteria and concomitant medication must be assessed at every unscheduled visit. Phone calls should not be recorded as an unscheduled visit as the patient have not visited the trial site, but information regarding the call must be recorded in the medical records.

Unscheduled visits can be performed to dispense additional trial product during the day of surgery and the post-operative period.

The assessments that can be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Check for 48 hours washout of trial product before a possible inhibitor test

8.1.8 End of trial visit - main and extension phase

For patients who withdraw from the trial, an end of trial visit must be performed as soon as possible. For the main phase, visit 8 is the end of trial visit. If the patient will not continue into the extension phase then visit 8 will be the last visit and the end of trial form must be filled in at this visit.

The assessments to be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Check for 48 hours washout of trial product before the inhibitor test
- Completion or withdrawal session must be performed in the IWRS

8.1.9 Follow up visit

Patients withdrawn due to inhibitors must attend a follow up visit 3 times with a month apart for a follow up of the patient's inhibitor status. The first follow up visit should be 28 days after the end of trial visit with a visit window of 2 weeks and the next follow up visits should likewise be after 28 days with a window of 2 weeks.

The lab tests to be performed at this visit are listed in section 2.

Key reminders:

- Ask if the patient has experienced any AEs since last visit
- Check for 48 hours washout of FVIII products before the inhibitor test

8.2 Patient related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit, screening visit).

Medical history is a medical event that the patient has experienced in the past. Historical bleeding episodes should not be recorded in medical history as this will be collected in another eCRF form called "Haemophilia treatment and bleeding history".

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuing, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the trial products, which is taken during the trial, including the screening period.
Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuing.

If a change is due to an AE, then this must be reported according to section 11. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

The following concomitant medications are not allowed from visit 2 and during the course of this trial:

- Vitamin K antagonists
- Direct thrombin inhibitors
- Direct factor Xa inhibitors
- FVIII concentrates (other than turoctocog alfa)
- Coagulation factor containing products including PCC, aPCC, whole blood, plasma or cryoprecipitate are allowed in emergency situations for a maximum of 5 administrations. Unrestricted uses of factor containing products is allowed during surgery. See Table 8–1 for washout periods and section 8.5.3.1 and 8.5.3.2 for necessary laboratory tests
- Use of heparin for a period exceeding 1 month, except for flushing of CVAD

8.2.3 Haemophilia treatment and bleed history

Historical information regarding the patient’s previous haemophilia A treatment and bleeding pattern must be recorded at visit 1.

Going back 1 year. In case a child is younger than 1 year then until date of birth.

- Type of treatment regimen (on-demand, prophylaxis, treatment of bleed)
- Start date of regimen
- Stop date of regimen
- Number of bleeds during regimen period (per year)
- Type of product during regimen period
- Dose
- Dosing frequency

From birth:.

- Total number of previous exposure days (≥50 ED, ≥100 ED or exact number of ED).

The “total number of previous exposure days” must be assessed to ensure that an inclusion criteria is met, see section 6.2. The previous exposure days must be documented in medical records, which may be calculated based on known treatment regimen(s).

8.2.4 Haemophilia details

Historical information regarding the patient's haemophilia A status must be recorded at visit 1.

- Date of diagnosis of haemophilia A
- Inhibitor tests taken (yes/no)
- Cut off value for positive inhibitor result

8.2.5 Body measurements

Body weight can be measured at visit 1, visit 5 and visit 8 in the main part of the trial. In the extension part it can be measured at every assessment and dispensing visit. See Table 8–2 and Table 8–3 for when it is mandatory.

If necessary height and weight can also be measured at an unscheduled visit.

- Body weight (kg) [xxx.x]
- Height (cm) [xxx.x]

Table 8–2 Body measurements – main trial

Age	Weight AND height	Weight OR height
0-5 years	Visit 1, 5 and 8	
>5 < 18 years	Visit 1 and 8	Visit 5 (only height)
18 years plus	Visit 1	Visit 8 (only weight)

Table 8–3 Body measurements – extension part

Age	Weight and height	Only weight
0-5 years	Visit 11, 14, 17 and 20	Visit 9, 10, 12, 13, 15, 16, 18 and 19
>5 < 18 years	Visit 11, 14, 17 and 20	
18 years plus		Visit 11, 14, 17 and 20

8.2.6 Demography

Following information will be collected at visit 1.

- Date of birth
- Sex
- Race

The patient's "Sex" and "Race" must be used for the assessment of inclusion criteria, see section 6.2

8.3 Assessments for efficacy

To ensure standardisation of methods across the trial sites, definitions for evaluation of bleeding episodes, such as the haemostatic evaluation, are provided in this protocol.

All assessments used in this trial are widely used and are standard assessments used for care of haemophilia A patients.

8.3.1 Bleeding episodes

During the entire trial period all bleeding episodes treated with turoctocog alfa or another haemostatic medication must be entered in the diary, see section 8.6.2. Bleeding episodes which do not require treatment can also be entered in the diary

The following will be recorded in the diary for bleeding episodes:

- Date and time of start of bleed
- Date and time of stop of bleed, see Table 8–4
- Anatomical location of the bleeding episode (Joint, muscle, skin, stomach (gastrointestinal bleeding), mucosal (mouth, gums, nose), urinary system, central nervous system, other)
  - If joint is chosen: knee, ankle, wrist, fingers, elbow, shoulder, hip, toes, jaw
  - If muscle or skin is chosen: arm, leg, hand, buttocks, head/neck, chest, back, stomach, foot
- Anatomical position of body part (left, right)
- Classification of bleed (spontaneous, traumatic, surgical)
- Severity category (mild/moderate or severe), see Table 8–6 Only evaluated by site
- Haemostatic treatment (turoctocog alfa or other treatment to achieve haemostasis)
- Non-medical therapy used
- Clinical evaluation of the haemostasis (Excellent, Good, Moderate or None) – only for bleeds treated with turoctocog alfa, see Table 8–5

Table 8–4 Definition of stop of bleed

Stop time is: When the patient/parent or LAR experiences/observes signs of cessation of the active bleed such as; pain relief, no increase in swelling/limitation of motion and improvement in other objective signs of the bleeding episode Stop time is not: When pain and objective signs of the bleeding episode are completely resolved

Table 8–5 Definition of haemostatic response

Category	Definition
Excellent	abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection
Good	definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection for complete resolution
Moderate	probable or slight beneficial effect within approximately 8 hours after the first injection; usually requiring more than one injection
None	no improvement, or worsening of symptoms within approximately 8 hours after the first injection; usually requiring more than one injection

The patient or parent/caregiver must in the diary assess the haemostatic efficacy for treatment of bleeds, but the investigator must together with the patient during the diary review evaluate the correctness of the evaluation.

Table 8–6 Definition of bleeding episode severity

Category	Definition	Comment
Mild/Moderate	Minor bleeds which are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal or subcutaneous bleeds	
Severe	Major bleeds that require hospitalisation; intracranial, retroperitoneal, iliopsoas and internal neck bleeds; muscle bleeds with compartment syndrome; bleeds associated with a significant decrease in the haemoglobin level (>3g/dl). Traumatic bleeds at other locations than described above can always be considered severe at the investigators discretion.	These bleeding episodes must be treated immediately at home or at the local emergency room, and the trial site must be contacted..

Table 8–7 Definition of bleeding episode categorisation

Category	Comment
Spontaneous	Not linked to a specific event
Traumatic	Caused by a specific, known action or event (e.g. injury or exercise)
Surgical bleed	Bleeds after surgery from the surgical wound. Bleeding episodes during surgery does not fall under this category and will be evaluated in the surgical haemostatic evaluation
Re-bleed	Classification will be done by Novo Nordisk as part of the statistical analysis based on bleeding information: 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 (or subset of the same) anatomical location. If a bleed occurs in the same location 72 hours after stopping, the treatment is defined as a new bleeding episode

8.3.2 Injection of trial product

The following information will be recorded regarding the injection of trial product:

Actual dose:

- Dose (volume and vial strength)
- Start date and time of injection
- Stop date and time of injection (only for PK)
- Reason for dosing (prophylactic, treatment of bleeding episode , surgery, PK or other)
- Injection method (butterfly or other)

Planned regimen and dosing:

- Planned regimen (prophylaxis, on-demand)
- If the regimen is prophylaxis:
  - Dosing frequency
  - Planned dose (mL, IU/kg and vial strength)

  Did you use butterfly (without flushing) for injection (yes/no)

See section 5.3 for an overview of the requirements and guidelines for dosing and dose frequency.

8.3.3 Target joint assessments

A target joint is defined as 3 or more bleeds in the same joint within 6 months. When there has been no bleed in the same joint for 12 months, such a joint is no longer considered a target joint.

The following will be recorded in the eCRF:

- Anatomical location of target joint (knee, ankle, wrist, fingers, elbow, shoulder, hip, toes, jaw)
- Anatomical position of target joint (left, right)
- Number of bleeds in target joint within the last 12 months (only at visit 1)

Target joint assessment will be performed at visit 1 and visit 8 in the main phase of the trial and at the assessment and end of trial visit in the extension part of the trial.

8.3.4 Pharmacokinetics

PK at visit 2 will take 48 hours for patients who are 12 years and older and will take 24 hours for children below the age of 12 years, see Table 2–2 for the specific sampling time points. Only the pre-dose sample can be taken with other samples if they have to be performed before dosing. This PK can also be performed for surgery patients. The patients that perform a PK at visit 2 must also perform a recovery test at visit 8 (see 8.5.2.3) with the same dose as at visit 2.

A determination of the half-life by sampling at different time points will be performed at an unscheduled visit for patients that have a low titer inhibitor (≥ 0.6 BU and ≤ 5 BU) see section 8.4.2.1.

CRP must be sampled before dosing for PK, see section 8.5.2.2, to ensure accurate interpretation of PK results (e.g. in case measurements are affected by inflammation or infection).

The vein used for injection of trial product must not be used for blood sampling until more than 30 minutes after the injection, i.e., cannot be used for the 30 minutes post-dose sample.

The PK sampling should be rescheduled if any of the following applies:

- Major surgery performed 1 month prior to PK
- Use of FVIII product prior to PK, see Table 8–1 for the age dependent washout periods
- Illness or fever 48 hours prior to PK
- In a bleeding state that requires treatment with haemostatic agent

If a treatment-requiring bleeding episode interferes with PK sampling and assessments, rescheduling of PK sessions can be done at the discretion of the investigator taking the patient's safety and the bleeding episode severity into account.

The PK dose is 50 ±5 IU/kg BW of trial product and the lines/tubes must be flushed immediately, with 2-5ml sodium chloride, after administration of the trial product.

The injection stop time of the PK dose is time 0.

FVIII activity will be analysed by using a chromogenic and a one stage FVIII clotting assay and both assays are validated.

The remainder of the PK sample will, after the initial analysis, be used for further research. A separate informed consent will be requested for this. See further information in section 8.5.3.6 and 8.5.3.7 for handling of the stored samples

A final draft bio-analytical report from the laboratory for PK analyses must be available at database lock to Novo Nordisk.

The parameters that will be calculated using the PK sampling at visit 2 is shown in Table 8–8.

Table 8–8 Definition of PK parameters

Parameter	Description	Calculation
$t_{½}$ (hours)	Terminal half-life	$t_{½} = \ln(2) / \lambda_z$, where λ_z is the terminal elimination rate. The terminal elimination rate will be estimated using linear regression on the terminal part of the time vs. log(concentration) curve
AUC_{last} ((IU*h)/mL)	Area under the plasma concentration vs. time curve from time zero to the last measurable concentration	AUC_{last} is calculated using the linear trapezoidal method from time 0 to the time for the last measurable concentration. The concentration at time 0 will be estimated by log-linear extrapolation of the two initial post-administration concentrations (see below) and used in the calculation of AUC_{last}.
Incremental Recovery ((IU/mL)/(IU/kg))	Peak level recorded 30 min. after end of infusion, adjusted for pre-administration concentration ([IU/mL]/[IU/kg])	The incremental recovery is calculated as (FVIII:C activity measured in plasma 30 min after dosing - FVIII:C activity measured in plasma immediately before dosing) / (dose injected at time 0 min), where the dose is expressed as IU FVIII product per kg BW.
$AUC_{0\text{-inf}}$	Area under the concentration vs. time from time curve zero to infinity	$AUC_{0\text{-inf}} = AUC_{last} + (C_{(t)} / \lambda_z)$, where $C_{(t)}$ is the last measurable concentration.
AUC%Extrap	The extrapolated part of $AUC_{0\text{-inf}}$	$100 \cdot (C_{(t)} / \lambda_z) / AUC_{0\text{-inf}}$. . This is not a PK parameter. It is only a description of the extent of extrapolation in the AUC calculation.
C_{max} (IU/mL)	The maximal concentration	The maximal observed concentration. Note that this will likely be obtained at the first measurement and will be sensitive to deviations from the scheduled sampling time. This limits the value of this parameter, especially when comparing to other studies.
CL (mL/h/kg)	Total plasma clearance of drug after intravenous administration	CL= Dose / $AUC_{0\text{-inf}}$

Parameter	Description	Calculation
MRT (hours)	Mean Residence Time	MRT = AUMC/$AUC_{0\text{-inf}}$, where AUMC is the area under the first moment curve, i.e. the area under the curve t·C(t) , calculated with the same method as AUC (linear trapezoidal method + extrapolated area).
V_{ss}	Apparent volume of distribution at equilibrium	$V_{ss} = CL \cdot MRT$
V_z	Apparent volume of distribution based on the terminal phase	$V_z = CL/\lambda_z$
$C_{(0)}$	The estimated concentration at time 0 (end of infusion), given that the dose was given as an instantaneous bolus.	$C_{(0)}$ will be calculated by log-linear extrapolation of the two initial post-administration concentrations. If the second value is not lower than the first value, $C_{(0)}$ will be defined as the highest of these two.

8.3.5 Surgery

For patients who require surgery during the trial, relevant treatment and assessment will be performed and recorded. The treatment regimen will be given by the investigator or surgeon (guided by the investigator), see Table 5–3.

The following data must be recorded for surgery, see Table 8–9. Minor and emergency surgery requires less information to be recorded:

Table 8–9 Surgical intervention

Surgery information	Planned Major	Planned Minor	Emergency Minor/Major surgery
Surgery type , see Table 8–10	X	X	X
Surgical indication	X	X	X
Surgical procedure	X	X	X
Surgery location	X	X	X
Start date and time of surgery	X	X	X
Stop date and time of surgery	X	X	X[1]
Haemostatic response after surgery, see Table 8–12	X	X	X[1]
Haemostatic response during surgery, see Table 8–11	X	X	X[1]
Actual blood loss during surgery, see Table 8–13	X		X[1]
Estimated blood loss during surgery, see Table 8–13	X		X[1]
Blood and blood products transfusion quantity	X		X[1]
Blood and blood products transfusion type	X		X[1]

X[1] If possible

Emergency surgery is allowed in this trial if adequate supply of trial product is available. . The investigator can decide which trial assessments can be made in an emergency situation, except for the above information mentioned in the “Emergency minor/major surgery” column.

The patient must be withdrawn from the trial in case he is treated with another FVIII concentrates than turoctocog alfa during the surgery, please see the allowed products during surgery in section 8.2.1. Also patients with a low titer inhibitor (≥0.6BU and≤5BU) must be withdrawn from the trial if they need surgery.

The patient may have a PK (see 8.3.4) performed before the surgery at an unscheduled visit at the discretion of the investigator.

A negative inhibitor test result and a satisfactory recovery test from central laboratory must be performed prior to the surgery day. It is expected that 2 weeks is the approximate time for laboratory results to be analysed and reported from central laboratory. If this cannot be achieved with a scheduled visit, then the patient must be called in for an unscheduled visit. An exception from this is emergency surgery.

Only 10 planned major surgeries in total may be performed during the main phase of the trial, after this all planned surgeries must be performed in the extension phase of the trial.

Table 8–10 Definition of surgery type

Surgery type	Definition
Major surgery	is any invasive operative procedure where any one or more of the following occur • A body cavity is entered. • A mesenchymal barrier (e.g. pleura, peritoneum or dura) is crossed. • A fascial plane is opened. • An organ is removed. • Normal anatomy is operatively altered These procedures may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation or with a combination of these modalities
Minor surgery	is any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated. Examples of minor surgery include vascular cutdown for catheter/fistula placement, implanting pumps or CVAD in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire. Dental surgery will be classified as minor or major based on above definitions

Table 8–11 Haemostatic response during surgery

Category	Definition
Excellent	blood loss less than expected
Good	blood loss as expected
Moderate	blood loss more than expected
None	uncontrolled bleeding

This evaluation must be performed by the surgeon

.

Table 8–12 Haemostatic response after surgery

Category	Definition
Excellent	Better than expected in this type of patient and procedure
Good	As expected in this type of patient and procedure
Moderate	Less than optimal for the type of procedure, maintained without change of treatment regimen
None	Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required

This evaluation will most likely be assessed by the investigator, but could also be the surgeon.

The haemostatic response after surgery is only measured once at the last day of the post-operative period the patient is at the trial/surgery site.

Table 8–13 Definition of blood loss

Blood loss	Definition
Actual blood loss (mL)	during the procedure as recorded in surgical procedure report (or chart) by the surgery team (surgeon and anaesthesiologist)
Estimated blood loss (mL)	blood loss for similar procedures in non-haemophilia and haemophilia (if available for this type of procedure) patients undergoing the same type and extent of surgical procedure stated before the procedure by the surgery team (surgeon and anaesthesiologist)

8.3.6 Patient reported outcomes

Disease and age specific health related quality of life (HRQOL) will be collected through use of the patient reported outcome (PRO) instruments HAEM-A-QOL (for adults) and HAEMO-QOL (for children/adolescents and their parents) at visit 2 and 8 in the main phase of the trial and in the assessment visit, though only annually and at the end of trial visit in the extension phase of the trial.

Table 8–14 Patient reported outcome questionnaires by age group

Name	Age group (years) (patient age in years at baseline)	Comment
HAEM-A-QOL	17 and older	To adults
HAEMO-QOL	13-16	To adolescents and parents
HAEMO-QOL	8-12	To children and parents
HAEMO-QOL	4-7	To parents
	0-3	No PRO questionnaire

The patient's age at the time when he or his parent/LAR signs the informed consent, determines which age group he belongs to and consequently which PRO questionnaire that should be used throughout the trial. The same PRO questionnaire should be used during the whole trial including in the extension phase and even if the patient grows into another age group during the conduct of the trial. If parents/caregiver stop accompanying a patient to visits they do not have to fill in the HAEMO-QOL parent version.

The questionnaires were originally developed in UK in English and have been translated and linguistically validated into simplified Chinese. The questionnaire must be filled in at visits 2 and end of trial in the main phase. In the extension phase it must be filled in annually and at the end of trial visit, preferably before any other trial-related procedures.

When PROs are filled in by the patient, these must be reviewed by the investigator to ensure that AEs, including any overall change in health and concomitant medication, are reported, see section 11. This review must be documented in the patient's medical record.

If clarification of entries or discrepancies in the PROs is needed, the patient must be questioned and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

The completed PRO questionnaires (top page) must be sent to data management in India by the monitor for data entry into the clinical database. The copy (bottom page) must be retained by the site.

8.4 Assessments for safety

To ensure standardisation of safety assessment across trial sites a centralised laboratory is used for most laboratory assays, except for trough and recovery values analysed at the local laboratory to ensure fast laboratory results. Trough and recovery values will also be analysed at the central laboratory.

All the safety assessments are standard assessments widely used for haemophilia care.

The evaluations must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (Yes/No)

8.4.1 Adverse Events

Monitoring of AEs will be performed from the first trial-related activity after signing of the informed consent according to procedures described in section 11.

8.4.2 Antibodies

8.4.2.1 FVIII inhibitors

FVIII inhibitors will be measured at every scheduled visit in the main phase. In the extension phase of the trial, inhibitors will be measured at every assessment visit, i.e. at least twice annually. If there is any suspicion of FVIII inhibitor development FVIII inhibitors must be measured at an unscheduled visit. At visit 1 the inhibitor test will be taken for baseline characteristics and must be used for the assessment of exclusion criteria, see section 6.3.

Analysis for FVIII inhibitors will be carried out at a central laboratory using the Nijmegen modified Bethesda assay. A positive inhibitor test is defined as ≥ 0.6 Bethesda Unit (BU).

If FVIII inhibitor development is suspected by increased number of bleeding episodes, bleeding episodes difficult to treat and/or peak and trough levels below expected values, a Nijmegen modified Bethesda test must be performed. In addition, a recovery test must also be performed, because the decrease of recovery may indicate an early signal of inhibitor development. If the result of the modified Bethesda test is positive, another sample must be collected for a confirmatory Nijmegen modified Bethesda assay at an unscheduled visit preferably within 2 weeks and not later than 4 weeks of the first positive test result from central lab. The diagnosis of inhibitor is made if the patient has been tested positive for inhibitors (≥0.6 BU) at two consecutive tests at central lab.

If the first FVIII inhibitor test is positive, a lupus anticoagulant (see section 8.5.3.5) must be sampled with the second sampling for a confirmatory FVIII inhibitor test at an unscheduled visit. These samples should preferably be sampled prior to any change of treatment. The dose taken at the confirmatory visit is preferable the same as a prophylaxis dose or at the discretion of the investigator.

Blood sampling for FVIII inhibitor test must be performed after a 48 hours washout period since last dosing with trial product.

If the second confirmatory test is positive (≥ 0.6 BU), but below or equal to 5 BU the patient has a low titer inhibitor, but can continue in the trial. This may only occur if the investigator evaluates that the patient can be treated with turoctocog alfa within the recommended dosing range for prophylaxis and treatment of bleeds according to section 5.3. A trough and recovery test and a FVIII activity tests at 60 and 240 min after dosing (see Table 8–15 and section 8.3.4) must be performed at an unscheduled visit as soon as possible and at every scheduled visit hereafter a FVIII trough and recovery test must be taken in the main phase. In the extension phase a patient with a low titer inhibitor must take an inhibitor, trough and recovery test at the assessment, dispensing and at an unscheduled visits every month.

Table 8–15 Sampling times after a positive confirmatory low titer inhibitor test

Time (Min)	Sample window	Remark
-60	(+55)	FVIII trough
00		Dosing
30	(±5)	FVIII recovery
60	(±10)	FVIII activity
240	(±60)	FVIII activity

A confirmed positive inhibitor is considered to have disappeared if the inhibitor is <0.6 BU on 2 consecutive inhibitor tests (performed at 2 consecutive visits) and the FVIII recovery is ≥66% of expected values.

If the second confirmatory test or any test subsequent to this is above 5 BU then the patients must be withdrawn from the trial, see section 6.4, and the inhibitor must be followed up every month for 3 months at the follow-up visits, see section 8.1.9.

See Figure 8–2 for an inhibitor decision tree.

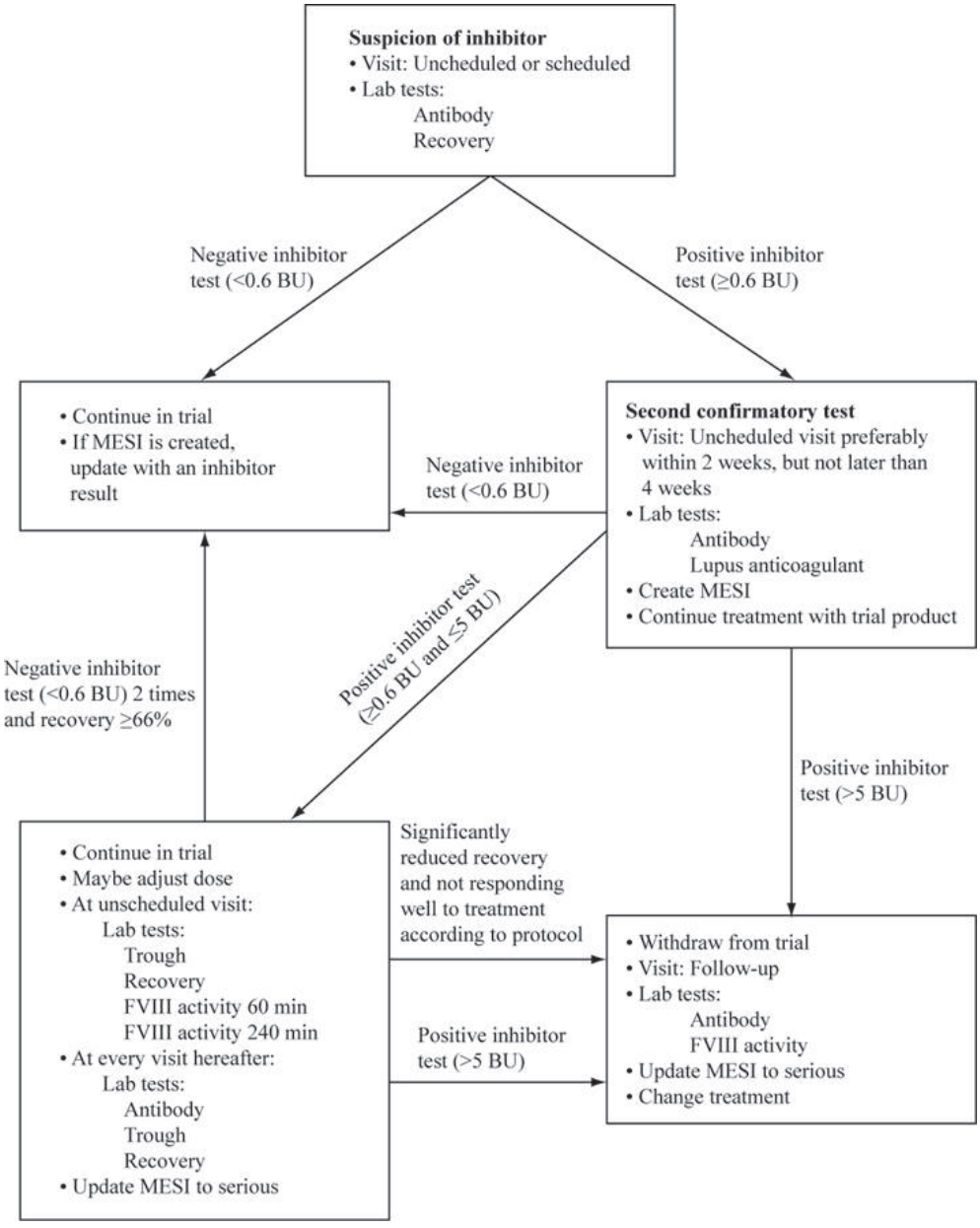

Figure 8–2 Inhibitor decision tree

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.

8.4.2.2 Binding antibodies

Binding antibodies against turoctocog alfa will be analysed in order to characterise the underlying immunogenicity towards FVIII (e.g. isotyping, binding properties). The analysis will be carried out by validated antibody assays.

The remainder of the antibody samples will after the initial FVIII inhibitor test be frozen and stored and used for analysing the binding antibodies.

The binding antibodies will be analysed:

- At visit 1 (screening)
- At visit 3
- At visit 8
- At end of trial (extension)

Exception, patients with a confirmed inhibitor test, will have binding antibodies analysed at all visits

The investigator will not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV. If needed, the sites/investigators may contact Novo Nordisk for information.

8.4.2.3 Antibody characterization

By request from authorities antibody characterization (future research) can also be performed on the frozen and stored antibody sample, see further information in section 8.5.3.6 and 8.5.3.7 for handling of the stored samples.

8.4.3 Physical examination

Physical examination must be performed at visit 1 and at visit 8 in the main phase of the trial. In the extension phase of the trial physical examination must be performed at every assessment visit and at the end of trial visit. Physical examination should be performed according to the practice at the site and include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Lymph node palpation
- Abdomen
- Skin
- Respiratory system

- Musculoskeletal system
- Central and peripheral nervous system

If the patient experiences any changes during the visits which fulfil the criteria of an AE it must be recorded as such, please refer to section 11.

8.4.4 Vital signs

Vital signs must be assessed at visit 1, visit 2, visit 5 and visit 8 in the main phase. At visit 2 vital signs should be taken before and after injecting trial product. In the extension phase vital signs must be assessed at every assessment visit and at the end of trial visit.

- Systolic blood pressure, sitting (mmHg)
- Diastolic blood pressure, sitting (mmHg)
- Pulse, sitting (beats per minute (BPM))
- Body temperature (Degrees Celsius)

Vital signs can be measured using the normal practice at the trial site.

If the patient experiences any changes during the visits which fulfil the criteria of an AE it must be recorded as such, please refer to section 11.

If any of the above assessments are measured using electronic devices and is printed, this document must be signed and dated to verify that the data has been reviewed and that any AEs have been reported.

8.5 Laboratory assessments

The collection of all blood samples for the laboratory tests will be performed before injection of the trial product, except the recovery samples and PK samples which must be collected after.

Laboratory results being out of normal range must be categorised as “out of normal range and not clinically significant” or “out of normal range and clinically significant”. A laboratory result evaluated as “out of normal range and clinically significant” must be recorded as an AE, or if present at visit 1 it should be recorded as concomitant illness. See section 11.1 how a laboratory results is evaluated as clinical significant.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values must be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

All laboratory assessments will be analysed at a central laboratory. The FVIII trough and recovery test will though both be analysed at the central and local laboratory, except at the follow-up visits, were it only will be analysed at the central laboratory. Normal ranges from the local laboratory will not be collected, as FVIII results will not be evaluated against the normal ranges. All FVIII activity analysed centrally will be analysed using the one-stage FVIII clotting activity assay and a two-stage chromogenic, but only the one-stage clothing activity assay result will be reported to the investigator.

Laboratory results are considered as source data and must be signed and dated by the investigator to verify that the data has been reviewed and that any AEs have been reported.

Storage handling and disposition of samples analysed at local laboratories will be performed according to local laboratory procedures. Laboratory data from the central laboratory will be reported to Novo Nordisk electronically, and in a manner that anonymity of patients will be maintained. 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 description of procedures for obtaining samples and for storage, handling and disposition of specimens, see the laboratory manual.

The local trough and recovery results will not be listed in the clinical trial report (CTR), except in possible narratives/text. Furthermore the results of the future research (Biospecimen), the antibody characterisation and possibly the non-neutralising antibodies will not be reported in the CTR as they will be available after the trial is final and therefore reported in separate reports and appended to the CTR later.

8.5.1 Blood sampling volume

The blood sampling volume for the patient must not exceed 1% of the total blood volume at one occasion or 3% within in 28 days. This is in accordance with European regulatory guidelines (Directive 2001/20/EC)[15]. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 1% is 0.8 ml blood per kg body weight. [15]

The total volume of blood to be collected for each patient per visit will not exceed 20 mL, of which 4 mL is for genotyping and 8 mL for the exploratory sample. For the adults performing PK an extra 30 mL over 3 days will be sampled.

For the smallest children the total volume of blood to be collected for each patient per visit will not exceed 10 mL, of which 3 mL is for genotyping. For the smallest children performing PK an extra 6 mL over 2 days will be sampled. If this is exceeding 1% of the child's blood volume then the blood volume must be decreased.

Detailed instructions will be provided to the trial sites regarding blood sampling volumes depending on age and prioritisation of the samples which must be used for infants and children. If trial sites as part of routine assessments perform additional blood draws, they must ensure that the blood sampling volume will not exceed the above requirements. As an example the investigator can decide to postpone the CD4+ blood sampling at the screening visit until after the HIV test result has arrived. It will be necessary however, to call the patient in for an extra blood sampling visit in case the chid is HIV positive.

It is recommended not to attempt venepuncture more than 3 times for the purpose of obtaining sufficient blood sampling for children 12 years and younger. Documentation of this must be available in medical records.

CVADs should preferably not be used for blood sampling due to risk of contamination and dilution. However, if it is used the CVAD must be locked with saline between blood sampling for PK sessions or pre- and post-dose samples. The following guideline must be adhered to:

When locked with saline:
- Flush the CVAD with 5 ml saline
- Discard as minimum 5 ml blood (2 x dead space)
- Take the blood sample

When locked with heparin:
- Flush the CVAD with 5 ml saline
- Discard as a minimum 15 ml blood (6 x dead space)
- Take the blood sample and/or Lock with saline in preparation for blood sample

The discard blood sampled must not be re-infused to the patient due to the risk of clots and other side effects.

8.5.2 Safety laboratory parameters

The below listed parameters will be sampled for safety reasons:

- Antibodies, FVIII inhibitors, see section 8.4.2
- Haematology
- Biochemistry
- Coagulation parameters, FVIII activity

8.5.2.1 Haematology

The assessment will be performed at visit 1, visit 5 and visit 8 in the main phase and at all assessment visits in the extension phase, at the end of trial visit and optionally at the unscheduled

visits. Analysis of Haematology is performed according to the normal practice of the central laboratory and includes:

- Haemoglobin (g/L)
- Haematocrit (Packed cell volume, PCV) (%)
- Leucocytes (White blood cell count) ($x10^9$/L)
- Thrombocytes (Platelet count) ($x10^9$/L)

8.5.2.2 Biochemistry

The assessment will be performed at visit 1, visit 5 and at visit 8 in the main phase and at all assessment visits in the extension phase, at the end of trial visit and optionally at an unscheduled visit. For PK patients C-reactive protein (CRP) will be sampled at visit 2 and at an unscheduled visit before dosing for PK.

Biochemistry analysis is performed according to practice of the central laboratory and includes:

- Creatinine (micromole/L)
- Aspartate aminotransferase (AST) (IU/L)
- Alanine aminotransferase (ALT) (IU/L)
- C-reactive protein (CRP) (mg/L)

At visit 1 alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine must be used for the assessment of an exclusion criteria, see section 6.3.

8.5.2.3 Coagulation parameters, FVIII activity

FVIII trough and recovery at the central laboratory will be analysed by using a chromogenic and one stage FVIII clotting assay. Blood samples for the chromogenic assay will be shipped out of China. The analysis method for local assessment of FVIII activity for trough and recovery will be recorded in the eCRF at visit 1.

FVIII baseline level:
In order to establish the severity of haemophilia A, a baseline FVIII level must be taken at visit 1. The result of this laboratory test must be used for the assessment of an inclusion criterion, please refer to section 6.2.

Any anti-haemophilic treatment with blood components should not be administered for at least 48 hours prior to blood sampling to ensure there is no interference of the trial product with the assay.

- FVIII activity (IU/mL)

FVIII recovery

At all scheduled visits it is optional to take a FVIII recovery test, except

- if the patient has a low titer inhibitor
- together with a confirmative inhibitor test, if there is suspicion of an inhibitor
- at visit 8 if a PK has been performed at visit 2
- before surgery if a PK test has not been taken
- when determining half-life at an unscheduled visit in case the patient has a low inhibitor titer

The dosing for recovery at visit 8 for PK patients must be 50 (±5 IU/kg BW) and all other dosing for recovery is at the discretion of the investigator.

FVIII recovery is the FVIII plasma level 30 ± 5 minutes after trial product has been injected. The blood sample must not be taken from the same vein as used for injection of trial product.

- FVIII activity (IU/mL)

The incremental recovery, which is the FVIII activity 30 minutes post dosing divided by the dose injected, will be calculated by Novo Nordisk. To ensure this is possible the volume injected and the vial strength during dose injection for recovery will be recorded in the eCRF to calculate the incremental recovery, see section 8.3.2.

- Incremental recovery ((IU/mL)/(IU/kg))

FVIII trough
At all scheduled visits a FVIII trough level must be taken for all patients on the prophylaxis regimen, except

- at visit 1
- at the dispensing visits in the extension phase, except if the patient has a low titer inhibitor

Furthermore FVIII trough must be taken

- when determining half-life at an unscheduled visit in case the patient has a low inhibitor titer

The FVIII trough level is defined as the lowest level of FVIII measured immediately prior to dosing.

- FVIII activity (IU/mL)

FVIII activity test
At a follow-up visit a FVIII activity sample will be drawn.

- FVIII activity (IU/mL)

8.5.3 Other laboratory parameters

8.5.3.1 Hepatitis

- Blood samples for Hepatitis B and C are sampled at visit 1, visit 8, end of trial visit and if applicable at an unscheduled visit.
- Hepatitis B
- Hepatitis C
  - RNA viral load

In case Hepatitis C is positive a RNA viral load will be performed to evaluate whether a chronic Hepatitis C disease is present.

If the patient has a previous positive Hepatitis B or C test or a Hepatitis B and C test that has been performed within 6 months, the result can be transcribed into the eCRF and the above test do not need to be performed.

If the patient has during the trial been injected with a product that may contain any risk of hepatitis infection a test for hepatitis must be performed at the next injection of trial product. If a local test for hepatitis has been performed before injection of the product this must be recorded in the eCRF.

8.5.3.2 HIV

Blood samples for HIV testing is sampled at visit 1, visit 8, end of trial visit and if applicable at an unscheduled visit.

- HIV 1
- HIV 2
- HIV viral load

If the patient has a previous positive HIV result or a HIV test that has been performed within 6 months, the result can be transcribed into the eCRF and the above test do not need to be performed.

In case the patient is HIV positive, the result of the viral load must be used for the assessment of an exclusion criterion, see section 6.3.

If the patient has during the trial been injected with a product that may contain any risk of HIV infection a test for HIV must be performed before the next injection of trial product. If a local test for hepatitis has been performed before injection of the product this must be recorded in the eCRF.

8.5.3.3 Immunology (CD4+ T Cells)

A blood sample for counting CD4+ T cells are sampled at visit 1 and if applicable at an unscheduled visit.

- CD4+ T Cells

In case the patient is HIV positive the result of this laboratory test must be used for the assessment of an exclusion criterion, see section 6.3.

8.5.3.4 Genotype

Genotype tests is optional in this trial and can only be performed after a separate informed consent has been signed, see section 17.2. The blood sample for the test can be taken at any visits in the main phase, but it is recommended to sample for genotype at visit 2. Note that the test can only be analysed once.

- FVIII genotyping
- HLA genotyping

Some HLA genotypes have been reported to have a promoting and others a preventive effect on the development of inhibitors in haemophilia A, so the HLA genotype test will further characterize genetic factors which determine the patient's immune response to the FVIII treatment.[16] [17] [18] [19]

The FVIII and HLA genotype test will only characterise the genes in relation to haemophilia A and those related to immune response in haemophilia.

All test results are kept strictly confidential and the patient, investigator or parent/LAR has the right to refuse genotyping. This will not prevent the patient to continue participation in the trial.

8.5.3.5 Coagulation parameters, Lupus Anticoagulant

Lupus anticoagulant is tested at visit 2 and at an unscheduled visit with the second confirmatory FVIII inhibitor test in case the patient has a first positive FVIII inhibitor test to assure that a possible positive inhibitor result is correct and not a false positive.

- Lupus Anticoagulant

8.5.3.6 Biospecimen sample

In order to explore immunogenicity (section 8.4.2.2 and 8.5.3.4), and perform further PK analysis of turoctocog alfa the remaining part of the blood sample for antibodies and PK will be stored for a longer period. Furthermore an additional blood sample will be drawn to perform future research (marked in the flow chart in section 2 as biospecimen sample), as new biomarkers or analytic methods may evolve during the conduct of the trial or after the trial, the analyses of the stored human bio-specimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

As the above mentioned future research may be performed on the biospecimen samples after completion of the trial, the results will be reported in separate reports and appended to the CTR.

The biospecimen for future research can only be sampled if a separate informed consent form has been signed, see section 17.2

Table 8–16 Overview of biospecimen samples

Test	Remaining sample of	Sampled when
Antibody characterisation	Antibody sample	All assessment visit
PK analysis	PK sample	Visit 2
Extra blood sample	NA as this is a separate blood sample	All assessment visit

Furthermore the investigator may not be able to review the results in relation to potential AEs for this trial, but in the event that the collected blood will be used in the future, the investigator will be directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of patient 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. Patients may at any time contact the investigator if they wish to be informed about these results.

8.5.3.7 Retention of blood samples

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

Biospecimen samples (see section 8.5.3.6) will be collected and stored at a Novo Nordisk appointed referral bio-repository. All biospecimens will be shipped out of China except the extra sample marked as biospecimen in the flowchart, please see Table 2–1. The patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification will be stored together with the samples, so the patient's identity will remain confidential and the analyses will not have any medical consequences for the patient or their relatives.

The samples will be stored for up to 15 years from end of the trial, where after all samples will be destroyed according to standard operating procedures at the bio-repository.

8.6 Trial material

8.6.1 Trial card

At visit 1 the patient or parent/LAR will receive a trial card stating that the patient is participating in a clinical trial. Telephone numbers and contact persons at the trial site will be listed.

8.6.2 Diary

The patient or parent/LAR will be provided with a diary for recording of bleeding episodes and the home treatment hereof. All the treatments, including treatment of bleeds and any surgery treatment administered at home must also be recorded in the diary see section 8.3.1. All bleeding episodes including the bleeding episodes that are experienced while at site must be recorded in the diary. At visit 1, the patient or parent/caregiver will receive the first diary and they will be trained in the use by the investigator.

The diary is split into a bleed and treatment diary. The patient will only receive one bleed diary for the whole trial but will receive many treatment diaries during the trial. The treatment diary must be returned at every scheduled visit and a new treatment diary will be handed out to the patient or parent/caregiver. Only the filled in pages in the bleed diary needs to be returned to the site at each scheduled visit. During trial site visits, the diary must be reviewed together with the patient or parent/LAR and evaluate together with the patient the correctness of the haemostatic efficacy for treatment of bleeds. The severity rating of the bleeding episode and the treatment type must be entered by the trial site staff, if necessary into the diary. Afterwards the diary data must be recorded in the eCRF by the investigator

Patient diaries must be reviewed by the investigator at every scheduled visit to ensure that AEs, including any change in health and concomitant medication, are reported. Furthermore the diary must also be reviewed for accuracy, completeness and consistency with the requirements defined in this protocol, see section 8.7. This review must be documented in the patient's medical record.

Only the patient or parent/LAR is allowed to change entries in the diary except for the severity rating and treatment type if they are entered into the diary by the site. If corrections are made, a straight line must be drawn through the incorrect data and the correct entry must be written next to the data that was crossed out with the patient number, dated and explained (if necessary). The date format must be DD-MM-YY (e.g. 01-O1-13)

If clarification of entries or discrepancies in the diary that are entered by the patient is needed, the patient must be questioned and a conclusion made in the patient's medical record. Care must be taken not to bias the patient. A correction is done by both changing the entry in the paper diary and the entry in the eCRF.

8.6.3 Dispensing of trial product

At all visits, after visit 1, trial product will/can be handed out to the patient or parent/LAR which will cover the patient's need for trial product until the next visit. Trial product can though not be handed out at the end of the trial and at follow-up visits.

A dispensing session must be performed in the IWRS, see section 10. See section 9 for how the trial product must be stored.

8.6.4 Home treatment training

Home treatment training with injection of turoctocog alfa can start after injections of the first dose at the trial site, and should continue until the patient or parent/LAR is comfortable with the reconstitution and injection process. The training must be documented in the medical records.

A home treatment guide for the reconstitution and injection process must be handed-out to the patient or parent/LAR at every dispensing visit.

If the patient does not follow the planned dosing schedule, the investigator must retrain the patient or parent/LAR if they are performing home treatment.

8.7 Patient compliance

Throughout the trial the investigator will remind the patients to follow the trial procedures and requirements to ensure patient compliance. If a patient is found to be non-compliant, the investigator will remind the patient of the importance of following the instructions given including taking the trial products as prescribed. Full compliance with protocol procedures is expected in this trial. If the investigator concludes that the bleeds a patient experiences are due to exceeded time between doses, the investigator must retrain the patient or caregiver.

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

The investigator must check the patient's compliance by reviewing the diary data to check if the home treatment is administered in the frequency prescribed by the investigator and also if the questions are understood, accurate and complete. Furthermore the investigator must during drug accountability compare the drug consumption in the diary with the number of used vials.

9 Trial product and auxiliaries supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual (TMM).

NCC 0155-0000-0004, N8, NovoEight® and turoctocog alfa are all synonyms of the same trial product. The names are used for different purposes during the development program. NovoEight® is the registered trade mark for turoctocog alfa.

Trial products must not be dispensed to any person not included in the trial.

Turoctocog alfa is a formulation for single use and to be reconstituted with 4.3 mL of 0.9% sodium Chloride delivered in prefilled syringes.

After reconstitution the solution appears as a clear or slightly opalescent solution and the solution must not be used if it appears different. In case this happens a technical complaint must be filled in.

9.1 Trial products

The following trial products will be provided by Novo Nordisk, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration
Turoctocog alfa	500 IU/vial	Sterile, freeze-dried powder	Intravenous injection
Turoctocog alfa	2000 IU/vial	Sterile, freeze-dried powder	Intravenous injection
Sodium Chloride	0.9 %, 4.3 mL	Solution for injection in prefilled syringes	Solvent for solution for injection

All sites will be supplied with sufficient trial product on an on-going basis controlled by the IWRS. DUNs will be distributed to the sites according to screening information.

9.1.1 Sodium Chloride (NaCl) for injection

After reconstitution with 4.3 mL Sodium Chloride 0.9%, each vial contains 125 IU/mL of turoctocog alfa (500 IU/vial) or 500 IU/mL (2000 IU/vial). The reconstituted solution must not be further diluted and it is recommended to use turoctocog alfa immediately after reconstitution.

9.2 Labelling and direction for use

Labelling of the trial product will be in accordance with Annex 13[20], local regulations and trial requirements.

Detailed instructions regarding reconstitution of turoctocog alfa is described in the TMM and the direction for use (DFU). A DFU which contains details on how to perform the reconstitution of turoctocog alfa must be handed-out to the patient or parent/caregiver at every dispensing visit. The site will be provided with the TMM.

The investigator must document that DFU is given to the patient orally and/or in writing at each dispensing visit.

9.3 Storage

Trial product	Storage conditions[2] (not-in-use)	In-use conditions	In-use time[1]
Turoctocog alfa	2-8°C	2-8°C	24 hours
		9-30°C	4 hours
	Below 30°C	N/A	As soon as possible
Sodium Chloride	2-30°C	NA	NA

1"in-use time" starts from reconstitution is finalised

2 Expiry date will be stated on the trial product

At the trial site turoctocog alfa must be stored at 2-8°C, and the patient is requested to store the turoctocog alfa refrigerated. If necessary, the patient may also store the turoctocog alfa up to 30°C, but not longer than 6 months. Please ensure the patient record the date when turoctocog alfa starts to be stored at room temperature on the carton. Do not store turoctocog alfa in the refrigerator again after it has been stored at room temperature.

The investigator must ensure the availability of proper storage conditions, record and evaluate the temperature. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator. The investigator or delegated person will perform drug accountability in the IWRS Drug Accountability module.

The IWRS will allocate all trial products DUN (dispensing unit number) to the patient at each dispensing visit. The correct DUNs according to the dispensing session in IWRS must be dispensed to the patient and recorded in the Drug Accountability module by the investigator or delegated person after they have been handed out to the patient.

Unused trial product must be stored separately from used trial product.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product. All returned and lost DUNs (except Sodium Chloride) must be recorded in the Drug Accountability module by the investigator or delegated person.

It will not be possible for sites to perform drug accountability for the solvent syringes, thus no drug accountability will be performed for Sodium Chloride.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented using the IWRS, with the exception of Sodium Chloride.

9.5 Auxiliary supplies

All auxiliaries used in this trial will be provided by Novo Nordisk such as syringes, butterflies and vial adapters etc.

10 Interactive voice/web response system

A trial-specific interactive voice/web response system (IWRS) will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Trial product arrival
- Dispensing including dispensing for PK
- Dispensing of additional trial products (including surgery)
- Withdrawal
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Adverse events and technical complaints

11.1 Definitions

Adverse event
An AE is any untoward medical occurrence in a patient administered a 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 product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:
- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- 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.

- Disease related bleeds and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection to bleeds that is evaluated by the investigator as part of the underlying disease should not be reported as AEs or SAEs unless evaluated by the investigator as related to trial product. In case of fatal/life-threatening outcome, the bleeding episode must be reported as a SAE. All bleeds and other symptoms related to the underlying disease will be captured in the medical records or diary.

The following three definitions are used when assessing an AE:

- **Severity assessment**
  - **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.

- **Causality assessment**

The following terms are used when assessing the relationship between an AE and the relevant trial product(s):

- **Probable** - Good reason 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.

If the patient has been exposed to both vial strengths then causality needs to be rated against both vial strengths.

- **Final outcome of an AE**
  - **Recovered/resolved** - The patient has 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 is only applicable if the patient has completed the trial or has died from another AE.
  - **Recovered/resolved with sequela** - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an 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 patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequela" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the patient is lost to follow-up.

Serious adverse event

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

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life-threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

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 was more severe.
b. The term "hospitalisation" is used when a patient:
   - Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
   - 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 not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
c. A substantial disruption of a patient's ability to conduct normal life functions (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).
d. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:

- suspicion of transmission of infectious agents via the trial product
- risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).
- inhibitor development confirmed by two consecutive FVIII positive inhibitor tests (≥0.6 BU)

Non-serious adverse event
A non-serious AE is any AE which does not fulfil the definition of an SAE.

Medical event of special interest
A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:

- Injection of wrong drug or use of wrong device
- Wrong route of injection, such as intramuscular instead of intravenous
- Injection of an overdose with the intention to cause harm (e.g. suicide attempt)
- Accidental injection of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although not necessarily did happen

2. Inhibitor formation against FVIII
   - If an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, it must be reported as a MESI
   - Blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk and if the first test is positive (≥0.6 BU) a MESI must be reported by the investigator
   - A second consecutive FVIII inhibitor test must be performed if the first test is positive – sampled preferably within 2 weeks. The results of the second confirmatory inhibitor test must be reported as follow up to the MESI already reported regardless of the resultIn case the patient stays in the trial with a positive inhibitor test, but <5 BU all subsequent inhibitor test must be reported as follow-up to the SAE
   - In case the patient is withdrawn, and continues with follow-up visits, all the inhibitor tests at these visits must be reported as follow-up to the SAE

3. Allergic reaction including anaphylaxis reaction as defined in Table 11–1.
   - Allergic reactions included but not limited to any acute immunoglubulin E (IgE) medicated reaction or delayed type hypersensitivity (clinical signs may include various types of skin rashes) that do not meet the definition of anaphylaxis as described in Table 11–1 All hypersensitivity reactions reported as MESI will be followed up with a hypersensitivity questionnaire

Table 11–1 Definition as per the reference by Sampson et al 2006[21]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following: – Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) – Reduced BP or associated symptoms of end-organ dysfunction (eg, 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) – Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) – Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) – Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): – Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* – Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline Peak expiratory flow (PRG); blood pressure (BP). *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.

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- All packaging material including labelling

11.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until the end of the post-treatment follow-up period (last follow-up visit). The events must be recorded in the applicable eCRF or CRF (case report forms) in a timely manner, see timelines below and Figure 11–1.

During each contact with the trial site staff, the patient must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?"

The patient or parent/LAR should though only be asked about technical complaints if they inject the trial product at home.

All AEs, observed either by the investigator or by the patient, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference document: Current version of Investigator's Brochure[5] and any updates thereto.

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form (by ticking of the MESI criterion) and the safety information form.

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 complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs**: The AE form in the eCRF **within 24 hours** and the paper safety information form (SIF) **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 in the eCRF and the paper SIF **within 14 calendar days** of the investigator's first knowledge of the event
- **Hypersensitivity questionnaire**: **Within 14 calendar days** of the investigator's first knowledge of the event

The paper SIF must be forwarded to Novo Nordisk either by fax, email or courier.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must re-enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigators trial file.

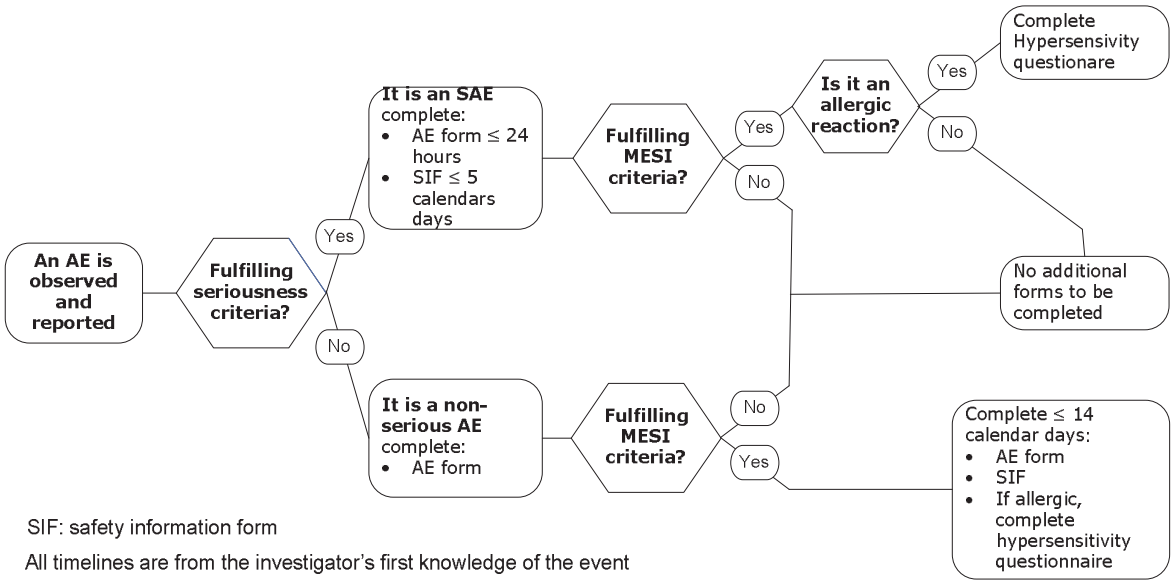

Figure 11–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by the sponsor:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP.[1] In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

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 investigator of trial product-related SUSARs and the investigator inform the IRBs (Institutional Review Board)/IECs (independent ethics committee) in accordance with local requirement and GCP.[1]

If an AE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

11.3 Follow-up of adverse events

The investigator must record follow-up information by 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 must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequela" 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) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the 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 and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs
- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequela" 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, cancer or AEs on-going at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover
- **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 ensure that the worst case severity and seriousness of an event is kept 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.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a subject after the subject has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

11.4 Technical complaints and technical complaint samples

11.4.1 Reporting of technical complaints

All technical complaints on any of the products:

- Turoctocog alfa 500 IU/vial, powder for reconstitution
- Turoctocog alfa 2000 IU/vial, powder for reconstitution
- Sodium Chloride 0.9 % pre-filled syringes
- Novo Nordisk Trial Injection kit

which occur from the time of first usage of the product until the time of the last usage of the trial product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE within 24 hours
- All other technical complaints within 5 calendar days

If the eCRF is unavailable or when reporting a technical complaint that is not patient related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above.

Contact details (fax, e-mail and address) are provided in attachment I to the protocol.

11.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the DUN number, if available.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

11.5 Precautions and/or overdose

As with any protein injected i.v., severe allergic or 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 the patient should receive treatment as appropriate according to the hospital practice. The investigator should consider whether further injections should be stopped.

No symptoms have been seen in connection with an overdose of turoctocog alfa.

11.6 Committees related to safety

11.6.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal turoctocog alfa safety committee to perform ongoing safety surveillance. The safety committee works according to a written guideline and will meet regularly to discuss and evaluate the overall safety for turoctocog alfa for this trial and all other turoctocog alfa 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 turoctocog alfa.

12 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be supplied by a vendor.

Ensure that all relevant questions are answered in the eCRF, and that no empty data field exists. If a test or an 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 following eCRFs will also be provided as paper CRFs:

- AE forms
- Technical complaint forms

These must be used when access to the eCRF is revoked or is not accessible.

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, (e.g. discovered at trial site before allocation) the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated in section 11.4.1.

Safety information form (SIF) will only be provided as paper CRF.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.

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

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

12.1 Corrections to case report forms

12.1.1 Corrections to eCRFs

Corrections to the eCRF data may be made by the investigator or the investigator's authorised staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, 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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

12.1.2 Corrections to the paper CRFs

Corrections to the data in the paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that was crossed out. Each correction must be initialled, dated and explained (if necessary). The date format must be DD-MMM-YY (e.g. 01-Jan-13) If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the case book in eCRF, it must be signed and dated again by the investigator.

Corrections necessary after the paper CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor -initiated discrepancy form (MIDF).

12.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 working days of the visits. This also includes the patient diary data. The top page of the PRO questionnaires is sent by the monitor to data management in India for data entry. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

The paper CRFs/hypersensitivity forms will be supplied as paper-set including two different coloured copies, except for the PRO forms that only have one copy. The CRA (clinical research associate) will collect the original (top page) during the monitoring visits after source data verification (SDV) has been performed and send it to Novo Nordisk Global Development-Global Service Centre (GD-GSC) in India where data entry into oracle clinical (OC) will be performed. One copy (bottom page) of the CRF/hypersensitivity form will be retained at the site. The CRA will keep the middle copy of the CRFs, except for the PRO as there is no copy for the CRA.

Central laboratory results will be transferred electronically to Novo Nordisk and will also be provided to the investigator.

13 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, and 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 at the specific site and no later than 4 weeks after. The monitoring 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[1], but will not exceed 12 weeks. This is though not a requirement after LPLV at the specific site.

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. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation, except for the data in the diary and PROs.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

The investigator must make a reasonable effort to obtain the following medical history from external sources e.g. primary physician and other hospitals/departments if not accessible in the medical records. The effort to obtain this information must be documented in the medical records:

- Any positive inhibitor history
- Known or suspected hypersensitivity to trial product(s) or other FVIII products
- Congenital or acquired coagulation disorders other than haemophilia A
- Use of Anticoagulants: Heparin, vitamin-K antagonists, and direct thrombin inhibitors one week prior to first injection of trial product
- Any disorder which, in the opinion of investigator, might jeopardise patient's safety or compliance with the protocol
- Mental incapacity
- Haemophilia treatment and bleed history

All the above elements in the patient's medical history are required for evaluating different exclusion criteria in this trial; see section 6.3, except the last point which is not an exclusion criterion.

The following medical history the trial site do not need to require from other external sources e.g. primary physician and other hospitals/departments if not accessible in the medical records as these can be tested in this trial:

- Diagnose of FVIII severity
- HIV, CD4+ T cell status and viral load
- Hepatitis B and C

All the above elements in the patient's medical history are required for evaluating different inclusion and exclusion criteria, see section 6, except the hepatitis B and C test.

It must be evaluated carefully what data is source data. The earliest practically retainable record should be considered as the location of the source data and therefore the source document, for instance if any electronic instruments are used for measuring vital signs the printout from these instruments should be considered as the source. The laboratory reports sent to the site should also be considered the source. The data entered directly into the diary and PRO questionnaires are also considered as source.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original PRO and paper CRF/hypersensitivity form must not be removed from the trial site. Each copy of the PRO and paper CRF/hypersensitivity form are considered to be source and this allows that the top page of the PRO or paper CRF/hypersensitivity form to be removed from the trial site and sent to data management. Data is entered directly into the diary and thus the diary is considered to be the source.

The monitor will check that the eCRFs, paper CRFs, PROs and the diary are completed and that paper CRFs are collected.

The monitor will check eCRF pages and other trial-related forms containing data from screening failures. Only the informed consent, AEs and screening failure reason should be monitored and/ or source data verified.

Monitors must review the patient's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit addressing any action to be taken.

See section 9.4 how drug accountability must be performed.

14 Data management

Data management is the responsibility of Novo Nordisk.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of patient data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically from the laboratory performing the analyses. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

Both the central and local laboratory will provide all laboratory reports to the investigator for storage at the trial site.

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

15 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk 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.

16 Statistical considerations

Evaluation of data will be based mainly upon descriptive statistics, i.e. summary tables, listings, and figures. Categorical data will be summarised by frequency tables while continuous data will be summarised by mean, standard deviation, minimum and maximum value.

All efficacy endpoints will be reported only for patients without inhibitors (<0.6 BU) and using bleeds with turoctocog alfa treatment. Base on the full analysis set (FAS), but if a patient develops an inhibitor only the time before the positive inhibitor test will be used to evaluate the efficacy endpoints.The following sensitivity analyses will be performed:

- The annualised bleeding rate will be calculated for both treatment-requiring bleeds and non-treatment requiring bleeds
- The annualised bleeding rate will be calculated excluding data from low titer periods
- Treatment success will be summarised excluding data from low titer periods

The main CTR will be written when at least 60 patients have completed the main phase of the trial (completed visit 8 and data is available, including PK data).The patients that have not completed the main phase at the cut off time for the main CTR will also be reported as part of the main phase. These patients will be included with data until their last visit prior to the cut-off date. The extension phase data at this time will also be included in the main CTR. The main CTR will present data separately (when relevant) for the above mentioned main and extension phase and this data will also be presented combined. The primary conclusion will be based on the main CTR and only on the above mentioned main phase data. An updated CTR will be conducted when all patients have completed the extension phase of the trial. The updated CTR will present data separately (when relevant) for the main and extension phase and the combined main and extension phase data. The definition of the main phase will be the same in the main and updated reports. See Figure 16–1.

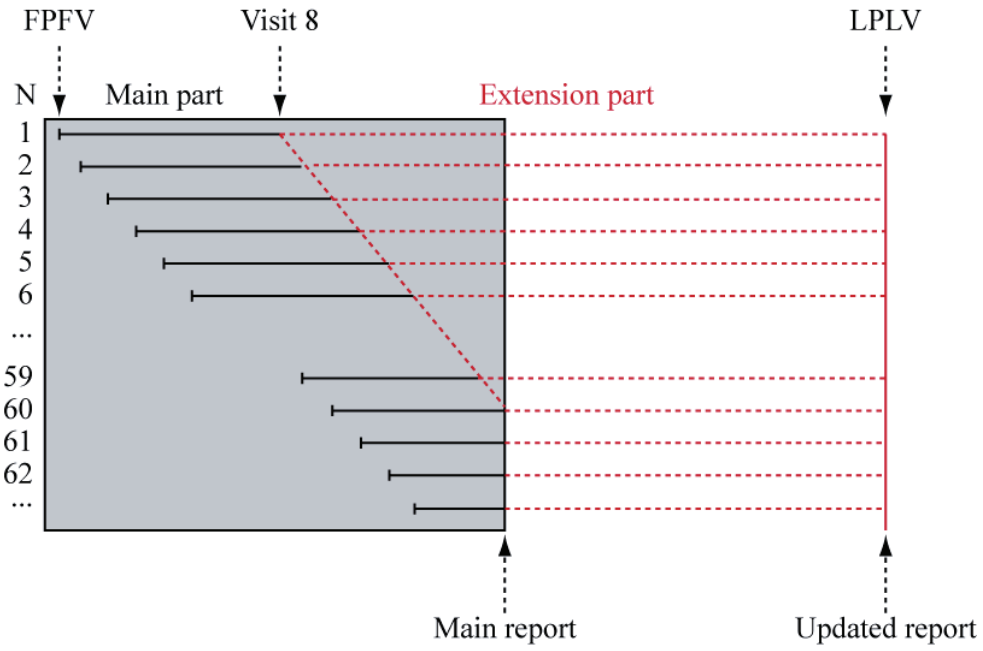

Figure 16–1 CTR reporting

16.1 Sample size calculation

No formal sample size calculations have been performed. A sample size of 60 patients is considered a sufficient number of patients to evaluate safety and efficacy of turoctocog alfa. The results of this study will supplement results from a corresponding study in non-Chinese patients.

16.2 Definition of analysis sets

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

The ABR 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)

16.2.1 Handling of exceptional pharmacokinetic outlier data

Exceptional outlier PK profiles and/or individual plasma concentrations may be excluded when analysing PK endpoints based on the FAS. If exceptional outlier data are identified, a sensitivity analysis including the outlier data will be conducted.

Unless otherwise stated, analysis results obtained from FAS excluding exceptional outliers will be presented with reference to the "full analysis set excluding outliers". The results of the sensitivity analysis including the exceptional outliers will refer to "full analysis set incl. all data".

16.2.2 Documentation of analysis sets

The decision to exclude data points from analysis of PK endpoints based on the FAS will be made from a review prior to database lock. It will be the joint responsibility of the clinical pharmacology scientist and the trial statistician.

The profiles or observations to be excluded from the FAS and the reason for their exclusion will be documented and signed by the clinical pharmacology scientist and the trial statistician as part of the database lock minutes. The documentation will be stored together with the remaining trial documentation. This will also be described in the CTR.

16.3 Primary endpoint

- Haemostatic effect of turoctocog alfa when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) during the main phase (6 months duration per patient).

In addition treatment success will be summarised by counting haemostatic responses rated as good or excellent as success and responses rated as moderate and none as failure. If the haemostatic response is missing, the response will be counted as failure in the primary analysis, but a sensitivity analysis will be performed excluding bleeding episodes with missing response. Treatment success will also be summarised excluding data from low titer periods as a sensitivity analysis to the primary analysis.

The haemostatic effect of turoctocog alfa 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)

Analyses and presentations will be made by age groups, type of regimen, trial phase and total.

16.4 Supportive secondary endpoints

All the following endpoints will be analysed for the main and extension phase and the combined main and extension phase data.

16.4.1 Efficacy endpoints

The primary endpoint will be repeated for the extension phase and the combined main and extension phase (total trial period of 24 months). The analysis is similar to the primary analysis

Number of bleeds (total bleeds assessed as annual bleeding rate) per patient during both the main phase of 6 months and the trial period of 24 months. This endpoint will only be presented for patients on prophylaxis regimen and will be reported using only treatment requiring bleeds.-The following sensitivity analyses will be performed:

- The annualised bleeding rate will be calculated for both treatment-requiring bleeds and non-treatment requiring bleeds
- The annualised bleeding rate will be calculated excluding data from low titer periods

The annualised bleeding rate will be analysed by a negative binomial model and estimated annualised bleeding rate with confidence interval will be presented by trial phase and treatment regimen. As a sensitivity analysis, a Poisson model with over-dispersion will also be applied. Analyses and presentations will be made for the preventative regimen by age groups, trial phase and total.

When turoctocog alfa is administered via a butterfly, the dead space is subtracted from the total volume of the dose to account for the compound left in the butterfly device after injection.

- Consumption of turoctocog alfa for bleeding treatment (average dose to treat a bleed, number of injections and IU/kg per bleed) during both the main phase of 6 months and the trial period of 24 months

This endpoint will be summarised and listed. The presentations will be made by age groups, type of regimen, trial phase and total.

- Consumption of turoctocog alfa during prophylaxis treatment (average prophylaxis dose, number of injections and IU/kg per month and per year) per patient during both the main of 6 months and the trial period of 24 months

This endpoint will be summarised and listed. The presentation will be made for the preventative regimen by trial phase, age groups and total.

- Total consumption of turoctocog alfa (IU/kg per month and per year) per patient during both the main phase of 6 months and the trial period of 24 months. This endpoint will be summarised and listed. The presentation will be made by type of regimen, trial phase, age groups and total
- Surgery-related endpoints where applicable:

- Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon at the day of surgery (Day 1) and on the last day in the post-operative period the patient is at the trial/surgery site
- Loss of blood and requirements for transfusion on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site whatever comes first

Surgery-related endpoints will be summarised by trial phase and listed.

16.4.2 Safety endpoints

- Incidence rate of inhibitory antibodies against factor VIII (≥0.6 BU) during both the main phase of 6 months and the trial period of 24 months

The incidence rate of inhibitors (≥0.6 BU) represented as the percentage of patients developing inhibitors will be calculated and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the incidence rate the numerator will include all patients with inhibitors while the denominator will include all patients in the trial exposed to turoctocog alfa.

FVIII activity (trough) at baseline will be compared graphically between patients with and without inhibitors. HLA genotype will be cross tabulated against the presence of inhibitors

- Frequency of Adverse Events (AEs) and serious adverse events (SAEs) reported during both the main phase of 6 months and the trial period of 24 months. AEs and SAEs reported during the study will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity will also be made. The summary tables will be made by patient with and without inhibitors (<0.6 BU), trial phase, age groups, type of regimen and total.

Furthermore, listings will be provided displaying all AEs and SAEs reported during the study including pertinent clinical information. For patients exposed to both vial strengths the strongest causality will be used in summary tables. In listings both causalities will be displayed for relevant events in these patients.

- Adverse Events/Serious Adverse Events occurred on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site whatever comes first

AEs and SAEs at the day of surgery (Day 1) and during the post-operative period Days 2-7 will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity will also be made.

16.4.3 Pharmacokinetic endpoints

- PK endpoints after a single dose of turoctocog alfa:
  - Incremental recovery of FVIII
  - Area under the curve ($AUC_{0\text{-}inf}$)
  - Half-life (t½)
  - Clearance (CL)
  - Highest measured FVIII activity in the profile (C_{max})

The PK endpoints will be presented by the mean, standard deviation, minimum and maximum value, the geometric mean and 95% confidence interval for the geometric mean.

16.5 Interim reporting

The main CTR will be conducted when at least 60 patients have completed the main phase of the trial (visit 8) and this data is available, including the PK data. The report will also include the full PK evaluation. An updated CTR will be written when all patients have completed the extension phase of the trial. The updated CTR will present separately the main and extension phase data and also the combined main and extension phase of the trial.

16.6 Patient reported outcomes

The main PRO endpoints will be total scores from each type of the questionnaires. Changes to scores over time of the main endpoints will be explored and presented graphically from:

- Baseline at visit 2 in the main phase until end of trial in the main phase (visit 8)
- Visit 11 until end of trial in the extension trial

Evaluation of PRO data will be done alone based on descriptive statistics, i.e. summary tables, listings and figures.

17 Ethics

17.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki.[2]

Before any trial-related activity, the investigator must give the patient and/or the patients' parents/legally acceptable representative (LAR) verbal and written information about the trial and the procedures involved in a form that the patient or the parent/LAR can read and understand. This includes the use of an impartial witness where required.

The patient or the parents/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 and/or parent/LAR ample time to come to a decision whether or not to participate in the trial.

The requirement for using 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. Patients incapable of giving informed consent can be children or illiterates who cannot read and/or understanding the patient information document.

A voluntary, signed and personally dated informed consent must be obtained from the patient and/or the patient's parents/LAR before any trial-related activity. If the patient is a child below the age of 18 years the LAR must be the parent(s) or a legal representative, as defined in the Chinese national laws, who consent on behalf of the child. . If a patient is deemed legally incompetent, such as a child or is not capable of giving informed consent for other reasons, but is able to give assent to decisions about participating in the trial and forming an opinion, the investigator must offer the possibility for the child to give assent in addition to the LARs consent by either co-signing the informed consent or signing a separate assent form.

The responsibility for seeking informed consent or assent must remain with the investigator, but the task may be delegated by the investigator to a medically qualified person, in accordance with local requirements. The written informed consent and assent form must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may influence the patient's willingness to continue participation in the trial, the investigator must inform the patient and/or the patient's parents/LAR in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

17.2 Informed consent for genotype testing and

Genotype testing is offered to patients participating in this trial. Before blood sampling for any potential genotyping is performed the patient or parents/LAR must sign a separate informed consent

Included in this information is that they can abstain from the genetic testing, but can still participate in the trial.

17.3 Informed consent for future research

An additional blood sample for future research (biospecimen) is offered to patients in this trial, but before any trial related activity starts the patient or parent/LAR must be informed about and consent on a separate information and consent form to this collection and storage for up to 15 years from end of the trial and testing. Included in this information is that they can abstain from the additional blood sample but can still participate in the trial. Furthermore, this informed consent also request to store other blood samples for future research, see section 8.5.3.4

17.4 Data handling

If the patient is withdrawn from the trial or lost to follow up, then the patient's data will be handled as follows:

- Data already collected and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

17.5 Information to the patient during the trial

The site will be offered a communication package to the patient during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the patients. The letters will be translated and adjusted to local requirements and distributed to the patient by discretion of the investigator. The patient may receive a "welcome to the trial letter" and a "thank for your participation letter" at the end of the trial. Further the patient may receive trial letters during the trial period.

All information to the patients will be submitted to the health authorities and IECs/IRBs for approval according to local regulations.

17.6 Premature termination of the trial and/or trial site

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

If a trial is suspended or prematurely terminated, the investigator must inform the patients promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the IRBs/IECs and provide a detailed written explanation. The relevant regulatory authorities must be informed.

If, after the termination of the trial, the risk/benefit analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

18 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, impact and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database. The investigator will be informed if any deviation in this trial is covered by the above.

Documentation on protocol deviations must be kept in the investigator's trial file and Novo Nordisk trial master file.

19 Audits and inspections

Any aspect of the clinical trial may be patient to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

20 Critical documents

An Investigator Portal, Global Haemophilia Network (GHN), will be used as primary media for exchange and handling of investigator trial file documents between Novo Nordisk and the site and for electronic storage of these documents during trial conduct.

Before a trial site is allowed to start screening patients, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure[5]
- Signed and dated agreement on the final protocol
- Signed and dated agreement on protocol amendment, if applicable
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all trial sites together.

For the local laboratory:

- The analysing method of FVIII activity (chromogenic or one stage FVIII clotting assay)
- Laboratory certification/QA scheme/other documentation
- Laboratory methods

By signing the protocol, each investigator agrees to comply fully with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki.[2]

By signing the protocol, each investigator also agrees to allow Novo Nordisk making investigator's name and information about site name and address publically available if this is required by national or international regulations.

21 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients.

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

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The patient identification code list must be kept securely and separate from the personal 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. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

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

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

22 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may 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.

One principal investigator will be appointed to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[22]

22.1 Communication of results

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 disclosure by other means.

The results of this trial will be patient 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 defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for 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.

22.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[22] (ICMJE) (sometimes referred to as the Vancouver Criteria).

Authorship for associated publications will be designated from the investigator list, as appropriate for each individual publication. Selection criteria may include: involvement in the design of the clinical trial, patient recruitment into the trial, interpretation and analysis of the trial data, and clinical expertise. The criteria and author selection will be agreed upon in collaboration with relevant members of the clinical project, including the publication planning group. In addition, all invited authors should meet the ICMJE authorship criteria.

22.1.2 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 a Novo Nordisk 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.

A full CTR will be made public according to Novo Nordisk's new disclosure code of conduct no later than 12 months after trial completion.

22.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research patient's data.

23 Retention of clinical trial documentation

23.1 Retention of clinical trial documentation

Patient's medical records 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, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other patient 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 and electronic devices 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the investigator site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or 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 Investigator's Brochure[5], unexpected SAEs where a causal relationship cannot be ruled out, 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. The investigator must ensure submission of the Clinical Trial Report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, 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 must be filed in the investigator's trial file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

25 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in China, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with Chinese law and guidelines.

26 References

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