Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03449342
Sponsor trial ID:	NN7008-4304
Official title of study:	Safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India.
Document date:	26 August 2019

16.1.1 Protocol and protocol amendments

List of contents

Protocol version-2.0..... Link

Attachment I and II..... Link

Protocol

guardian™ 10

Trial ID: NN7008-4304

Safety of turoctocog alfa for prophylaxis and treatment of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India.

Trial phase: 4

Table of contents

Page

Table of contents **2**

Table of figures **6**

Table of tables **6**

List of abbreviations **7**

1 Summary **8**

2 Flow chart **10**

3 Background information and rationale for the trial **13**
3.1 Background information 13
3.1.1 Epidemiology of Haemophilia A in the Indian population 13
3.1.2 Current standard of care 13
3.1.3 Turoctocog alfa 14
3.2 Rationale for the trial 15

4 Objective(s) and endpoint(s) **16**
4.1 Objective(s) 16
4.2 Endpoint(s) 16
4.2.1 Primary endpoint 16
4.2.2 Secondary endpoints 16

5 Trial design **17**
5.1 Type of trial 17
5.2 Rationale for trial design 17
5.3 Treatment of patients 17
5.4 Treatment after discontinuation of trial product 19
5.5 Rationale for treatment 19

6 Trial population **20**
6.1 Number of patients 20
6.2 Inclusion criteria 20
6.3 Exclusion criteria 20
6.4 Withdrawal from trial 21
6.5 Criteria for premature discontinuation of trial product 21
6.6 Patient replacement 21
6.7 Rationale for trial population 21

7 Milestones **22**

8 Methods and assessments **23**
8.1 Visit procedures 23
8.1.1 Visit 0 - Information visit 24
8.1.2 Visit 1 - Screening 25
8.1.3 Visit 2 - Baseline 26
8.1.4 Visit 3 - Treatment 27

8.1.5 Visit 4 - End of trial visit 27
8.1.6 Follow up visit 28
8.1.7 Unscheduled visit 28
8.2 Patient related information/assessments 29
8.2.1 Demography 29
8.2.2 Concomitant illness and medical history other than haemophilia 29
8.2.3 Concomitant medication 29
8.2.4 Details of the haemophilia 30
8.2.5 Haemophilia treatment and bleed history 30
8.2.6 Body measurements 30
8.3 Efficacy assessments 31
8.3.1 Bleeding episodes 31
8.3.2 Injection of trial product 32
8.4 Safety assessments 33
8.4.1 Adverse events 33
8.4.1.1 Medication error 33
8.4.2 Antibodies 33
8.4.2.1 FVIII inhibitors 33
8.4.2.2 Antibody characterization 34
8.4.3 Physical examination 34
8.4.4 Vital signs 35
8.4.5 Surgery 36
8.5 Laboratory assessments 36
8.5.1 Blood sampling volume 37
8.5.2 Safety laboratory parameters 38
8.5.2.1 Haematology 38
8.5.2.2 Biochemistry 38
8.5.2.3 Coagulation parameter, FVIII activity 38
8.5.2.4 Hepatitis 38
8.5.2.5 HIV 39
8.5.3 Other laboratory parameters 39
8.5.3.1 Genotype 39
8.5.3.2 Samples for future research, biospecimen samples 39
8.5.3.3 Retention of blood samples 40
8.6 Trial material 40
8.6.1 Trial card 40
8.6.2 Diary 41
8.6.3 Dispensing of trial product 41
8.6.4 Home treatment training 42
8.7 Patient compliance 42

9 Trial supplies 43
9.1 Trial products 43
9.2 Labelling 43
9.3 Storage 44
9.4 Drug accountability and destruction 44
9.5 Auxiliary supplies 45

10 Interactive voice/web response system 45

11 Randomisation procedure and breaking of blinded codes....46

12 Adverse events and technical complaints....47
12.1 Definitions....47
12.1.1 Adverse event....47
12.1.2 Serious adverse event....48
12.1.3 Non-serious adverse event....50
12.1.4 Medication errors....50
12.1.5 Adverse events requiring additional data collection....50
12.1.6 Technical complaints....51
12.2 Reporting of adverse events....51
12.3 Follow-up of adverse events....54
12.4 Technical complaints and technical complaint samples....55
12.4.1 Reporting of technical complaints....55
12.4.2 Collection, storage and shipment of technical complaint samples....55
12.5 Precautions and/or overdose....56
12.6 Committees related to safety....56
12.6.1 Novo Nordisk safety committee....56

13 Case report forms....57
13.1 Corrections to case report forms....57
13.1.1 Corrections to paper CRFs....57
13.1.2 Corrections to eCRFs....57
13.2 Case report form flow....58
13.3 Diary....58

14 Monitoring procedures....58

15 Data management....61

16 Computerised systems....61

17 Statistical considerations....61
17.1 Sample size calculation....61
17.2 Definition of analysis sets....61
17.3 Primary endpoint....62
17.4 Secondary endpoints....63
17.4.1.1 Efficacy endpoints....63
17.4.1.2 Safety endpoints....64
17.5 Interim analysis....64
17.6 Sequential safety analysis and safety monitoring....64
17.7 Explorative statistical analysis for pharmacogenetics and biomarkers....64
17.8 Pharmacokinetic and/or pharmacodynamic modelling....64
17.9 Health economics....65

18 Ethics....66
18.1 Benefit-risk assessment of the trial....66
18.2 Informed consent....66
18.3 Informed consent for genotyping....67
18.4 Informed consent for future research (biospecimen)....68
18.5 Data handling....68
18.6 Information to the patients during trial....68

18.7 Premature termination of the trial and/or trial site 68

19 Protocol compliance 69
19.1 Protocol deviations 69

20 Audits and inspections 70

21 Critical documents 70

22 Responsibilities 71

23 Reports and publications 72
23.1 Communication of results 72
23.1.1 Authorship 73
23.1.2 Site-specific publication(s) by investigator(s) 73
23.2 Investigator access to data and review of results 74

24 Retention of clinical trial documentation and human biosamples 75
24.1 Retention of clinical trial documentation 75
24.2 Retention of human biosamples 75

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities 77

26 Indemnity statement 78

27 References 79

Attachment I list of key staff and relevant departments and suppliers

Table of figures

Page

Figure 12–1 Reporting of AEs 53

Table of tables

Page

Table 1–1 Trial products 8
Table 2–1 Visit flow chart 10
Table 5–1 Guide for trial product dosing in bleeding episodes[1] 18
Table 8–1 Minimum requirements for washout periods 25
Table 8–2 Definition of stop of a bleeding episode 31
Table 8–3 Definition of haemostatic response 31
Table 8–4 Definition of bleeding episode severity 32
Table 8–5 Definition of bleeding episode categorisation 32
Table 8–6 Definition of surgery type 36
Table 8–7 Overview of samples for future research (biospecimen) 40
Table 9–1 Trial products 43
Table 9–2 Storage conditions 44

List of abbreviations

AE	adverse event
AR	adverse drug reaction
BU	Bethesda unit
BW	body weight
CL	clearance
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
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
mL	millilitres
PK	pharmacokinetic
PTP	previously treated patients
pdFVIII	plasma-derived factor VIII
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAR	Serious adverse reaction
SIF	safety information form
SUSAR	suspected unexpected serious adverse reaction
TMM	trial materials manual
WFH	World Federation of Haemophilia
UTN	universal trial number

1 Summary

Objective(s) and endpoint(s):

Primary objective:

- To assess safety of turoctocog alfa during treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India

Secondary objective:

- To assess efficacy outcomes with turoctocog alfa during treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India

Primary endpoint:

- Occurrence of confirmed FVIII inhibitor development (≥ 0.6 BU) during 8 weeks of treatment

Secondary endpoints:

- Frequency of adverse drug reactions (AR) and serious adverse reactions (SAR) reported until follow-up, 12 weeks after first treatment
- Successful haemostatic effect of turoctocog alfa in the treatment of bleeding episodes during 8 weeks of treatment
- Total annualised consumption of turoctocog alfa measured during the 8 weeks of treatment
- Frequency of allergic or infusion reactions related to the trial product reported until follow-up, 12 weeks after first treatment

Trial design:

This trial is a single-country, multicentre, open-label and non-randomised trial with turoctocog alfa treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe Haemophilia A for 8 weeks corresponding to at least 20 EDs.

Trial population:

60 previously treated patients (PTPs, ≥150 EDs with any FVIII containing product), 12 years or older, with congenital moderate or severe haemophilia A (FVIII ≤ 5%) with no history of inhibitors of FVIII, will be enrolled to allow for at least 50 patients to complete the trial.

Assessments:

- Presence of FVIII inhibitors will be tested at visit 1 (screening) and visit 4 (end of trial)

Trial products:

Table 1–1 Trial products

The following trial products will be provided by Novo Nordisk:

Trial product	Strength	Dosage form	Route of administration
Turoctocog alfa	2000 IU/vial	Powder for solution for injection	Intravenous injection
Sodium Chloride	0.9%	Solvent for solution for injection	Intravenous injection

2 Flow chart

Table 2–1 Visit flow chart

Trial Periods		Information visit	Screening	Baseline	Treatment	End of trial	Follow-up	Unscheduled Visit
Visit number		0	1	2	3	4	5	
Timing of visit	Weeks from baseline	-4	-3	0	4	8	12[a]	
Visit window	Days	0	±2	±7	±3	±3	±3	
SUBJECT RELATED INFO/ASSESSMENTS								
In/exclusion criteria			X	X				
Withdrawal criteria				X	X			X
Criteria for premature discontinuation of trial product				X	X			X
Concomitant illness			X					
Concomitant medication			X	X	X	X		X
Haemophilia treatment and bleed history			X					
Medical history			X					
Details of Haemophilia			X					
Informed consent		X	X					
Informed assent		X[b]	X[b]					
Genotyping consent, optional			X[c]					
Biospecimen consent			X[b]					
Demography			X					
Body measurements			X					
Height			X					
Body weight			X	X	X			X[b]
EFFICACY								
Bleeding episodes				X[d]	X[d]	X[d]		

Trial Periods		Information visit	Screening	Baseline	Treatment	End of trial	Follow-up	Unscheduled Visit
Visit number		0	1	2	3	4	5	
Timing of visit	Weeks from baseline	-4	-3	0	4	8	12[a]	
Visit window	Days	0	±2	±7	±3	±3	±3	
SAFETY								
Adverse events			X	X	X	X	X	X
Medication Error				X	X	X		X
Physical examination			X			X		
Vital signs			X			X		
Hypersensitivity reaction				X[e]	X[e]	X[e]		X[e]
Technical complaints				X[e]	X[e]	X[e]		X[e]
Surgical interventions				X[f]	X[f]	X[f]		X[f]
LABORATORY								
Biochemistry			X			X		
Coagulation parameters			X[g]					
Haematology			X			X		
Hepatitis			X[h]					
HIV			X[h]					
Genotyping			X[c]					
FVIII inhibitors			X[i]			X[i]		X[b]
TRIAL MATERIAL								
Administration of trial product				X[j]				X[j]
Dispensing trial product				X	X			
IWRS session			X	X	X	X		X[b]
Drug accountability				X	X	X		
REMINDERS								
Review diary					X	X		
Home treatment training				X	X[b]			X[b]
Hand out trial card			X					
Hand out diary/collect diary				X	X	X		

[a] If patient has withdrawn the follow-up-visit must be performed 4 weeks after end of trial visit

[b] If applicable

[c] Genotype consent is not mandatory at visit 1, but has to be collected before genotype is sampled, see section 8.5.3.1

[d] Bleeding episodes and dosing information are recorded in the diary

[e] If hypersensitivity reaction or technical complaints are identified, please ensure to complete the relevant form, see sections 12.1.5 and 12.1.6

[f] If patient had any surgical interventions (minor surgery), please ensure to complete the surgery form, see section 8.4.5

[g] Baseline FVIII level, a washout period of 72 hours since last dosing of any FVIII concentrate is required before FVIII activity test, see section 8.5.2.3

[h] Not mandatory at visit 1 if the patient previously has been tested within 6 month and it is documented in the medical journal

[i] A washout period of 48 hours since last dosing of any FVIII concentrate is required before inhibitor testing

[j] Injection of trial product at site

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH 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

3.1.1 Epidemiology of Haemophilia A in the Indian population

Haemophilia A is an X-linked recessive disorder that is characterised by bleeding episodes. It results from the deficiency of factor VIII (FVIII). The severity of bleeding in Haemophilia A is generally correlated to FVIII level in the plasma. Haemophilia A is considered severe when plasma FVIII level <1%, moderate when plasma FVIII level is 1-5% and mild when plasma FVIII level is 5 – 40%. The mainstay of management of Haemophilia A is replacement of deficient FVIII. Main goals of therapy include not only treating bleeding episodes but also help patients lead a normal life with little compromise on quality of life (QoL) due to haemophilia. This is possible when clotting factors are administered for prophylactic use on a regular basis (to prevent the occurrence of a bleeding episode) instead of on-demand treatment (i.e. administered after each bleeding episode).[3]

The estimated number of haemophilia patients in India is over 70 000.[4] However less than a quarter of these patients are diagnosed and registered in India. The registered number of haemophilia patients in India is 17,470 which include 14,450 patients with Haemophilia A and 2281 patients with Haemophilia B. It is reported that among 14,450 patients, 30% belong to ≤ 18 years of age and 33% belong to age group of 19 – 44 years. The main modality of management of haemophilia in India is on-demand regimen (i.e. administration of clotting factor after each bleeding episode). Patients visit their respective treatment centres for management of each individual bleeding episode. Less than 1% of Haemophilia A patients under age of 18 years receives prophylactic replacement in selected centres.[5]

3.1.2 Current standard of care

Among FVIII concentrates used in India in 2014, 98% consumption was plasma derived FVIII (pd-FVIII) and the remaining 2% was recombinant FVIII (rFVIII).[5] This partly explains the inadequate supply and delay in supply of FVIII as pd-FVIII alone is not able to meet the patients' requirements as elsewhere in the world.[6] Hence a significant proportion of Haemophilia A patients in India are still treated with blood or blood derived products, namely fresh frozen plasma and cryoprecipitate. The prevalence of HIV, Hepatitis B and Hepatitis C burden among patients with haemophilia due to use of blood products is approximately 1 %, 6 % and 30 % respectively.[7, 8]

The risk of infections in patients with Haemophilia A due to prions and small non-enveloped viruses like parvovirus B19 exists as these are neither removed nor inactivated in any of the currently available pd-FVIII in India.[5, 9, 10] The currently available first generation rFVIII uses albumin and other human/animal serum or proteins in various stages of production process which lowers their final purity.[5, 9] Concentrates of lower purity may give rise to allergic reactions.[3] In addition it does not undergo any standard recommended purification technique namely solvent detergent method or nanofiltration as per World Federation of Haemophilia (WFH).[9, 10] Hence availability of recombinant FVIII concentrates is considered as an unmet need for management of patients of Haemophilia A in India.

3.1.3 Turoctocog alfa

Turoctocog alfa (NovoEight®), a third generation recombinant human coagulation factor VIII intended for prophylaxis and treatment of bleeding episodes in haemophilia A patients, was recently approved in India with a waiver for conducting a phase III clinical trial in Indian patients.[11]

Turoctocog alfa is a recombinant factor VIII (rFVIII) with a truncated B-domain made from the sequence coding for 10 amino acids from the N-terminus and 11 amino acids from the C-terminus of the naturally occurring B-domain. The truncated B-domain was selected to achieve a well-defined product when produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. When turoctocog alfa is activated by thrombin, the truncated B-domain is cleaved, leaving an active FVIII molecule that is similar to endogenous FVIII in its activated form. It is a third generation factor VIII product prepared without the addition of any human or animal derived protein in the cell culture process, purification or final formulation. Turoctocog alfa is isolated from the culture media using an optimized five-step purification process: i) detergent inactivation and concentration; ii) immunoaffinity chromatography using a recombinant monoclonal antibody; iii) anion exchange chromatography; iv) nanofiltration with a 20 nm pore size filter; and v) a final gel filtration (size exclusion chromatography) step. Inactivation of enveloped viruses like HIV, HBV and HCV is ensured by detergent treatment (included in the initial purification step) and removal of prions and non-enveloped viruses like Parvovirus B19 is ensured by a 20-nm filtration step prior to the size exclusion step.[12, 13]

The First Human Dose and PK trial (NN7008-3522) results from 23 patients showed mean PK profiles of turoctocog alfa comparable to Advate® within the defined limits of comparability. In guardian™ 1 phase III trial, 150 previously treated (≥150EDs with other FVIII) adolescents/adults (≥12 year) with severe haemophilia A (and no history of inhibitors) received turoctocog alfa for 75 EDs.[13] In guardian™ 3 phase III trial 63 previously treated (≥ 50EDs with other FVIII) children (<12 year) with severe haemophilia A (and no history of inhibitors) received turoctocog alfa for 50 EDs, 188 of these patients continued into guardian™ 2 extension trial.[14] In the three trials, patients have received prophylaxis with turoctocog alfa three times weekly or every second day, or for treatment of breakthrough bleeding episodes. No safety concerns have arisen in any of the phase III trials, and no patients have developed confirmed inhibitors.[15, 16] Efficacy in bleeding prevention was

demonstrated by a bleeding frequency within the range expected during prophylaxis treatment in haemophilia A (mean annualised bleeding rate of 6.5 bleeds/year in guardian™ 1 trial and 2.4 bleeds/year in guardian™2 trial). Breakthrough bleeding episodes during prophylaxis were treated with turoctocog alfa and using a predefined four-point scale (Excellent, Good, Moderate or None), the haemostatic effect of turoctocog alfa was rated as excellent or good in 81 % of all bleeding episodes in guardian™ 1 trial and 91 % of all bleeding episodes in guardian™ 2 trial. For more information on safety and efficacy please refer to the Investigators brochure.[17]

For an assessment of benefits and risks of the trial, see Section 18.1.

3.2 Rationale for the trial

This trial is a post-approval commitment. Novo Nordisk has been mandated by the Indian Health Authorities to conduct a phase 4 study with at least 50 patients with Haemophilia A. This trial will provide documentation on the safety and efficacy of turoctocog alfa in patients in India as no study has previously been conducted with turoctocog alfa in India. Novo Nordisk A/S has been required to provide NovoEight® for the participants and to include mandatory inhibitor tests. Therefore this commitment must be done as an interventional trial.

Inhibitor development in previously treated Haemophilia A patients have been shown to be an extremely rare event, with a frequency rate of 1-3 per 1000 patient years[18]. It is thought to occur at random, without a clear association with a precipitating event such as switching to a new FVIII product[19]. No difference between inhibitor incidence in PTPs treated with pdFVIII and rFVIII has been demonstrated in a large prospective registry based study[20].

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective:

- To assess safety of turoctocog alfa during treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India

Secondary objectives:

- To assess efficacy outcomes with turoctocog alfa during treatment and prophylaxis of bleeding episodes in previously treated patients with moderate or severe Haemophilia A in India

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Occurrence of confirmed FVIII inhibitor development (≥ 0.6 BU) during 8 weeks of treatment

4.2.2 Secondary endpoints

- Frequency of adverse drug reactions (AR) and serious adverse reactions (SAR) reported until follow-up, 12 weeks after first treatment
- Successful haemostatic effect of turoctocog alfa in the treatment of bleeding episodes during 8 weeks of treatment
- Total annualised consumption of turoctocog alfa measured during the 8 weeks of treatment
- Frequency of allergic or infusion reactions related to the trial product reported until follow-up, 12 weeks after first treatment

5 Trial design

5.1 Type of trial

This is a single-country, multi-centre, open-label and non-randomised trial with a single treatment arm. 60 PTPs (≥150 EDs with any FVIII containing product) with moderate or severe haemophilia A will receive a prophylactic regimen with turoctocog alfa for a period of 8 weeks, which corresponds to at least 20 EDs on standard prophylaxis.

5.2 Rationale for trial design

This is a non-randomised trial and the design is common for trials with FVIII products in haemophilia A patients. In this trial, previously treated moderate or severe haemophilia A patients will receive routine prophylaxis treatment and treatment of bleeding episodes. This design is similar to the pivotal NN7008-3543 (guardian™1) trial design and it is deemed adequate to fulfil the post-approval commitment requirements form the Indian Health Authority. The timeframe of 8 weeks (corresponding to ≥20EDs on standard prophylactic treatment) provides an opportunity to detect an inhibitory response after initiation of treatment with turoctocog alfa in previously treated patients.

5.3 Treatment of patients

Patients will receive standard prophylaxis treatment and treatment of bleeding episodes, according to label. Trial product will be administered as intravenous injections (i.v.) at home by the patient or parent/LAR, 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.

Dosing for prophylaxis should be according to the approved prescribing information. The frequency of dosing can be either every second day or 3 times weekly, at a dose in the range 20-50 IU/kg. 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 starting dose should be defined by the investigator within the recommended range based on clinical status. Dose adjustments can be made during the treatment period of 8 weeks within this range based on the patient's clinical status (bleeding frequency) at a visit.

Bleeding episodes 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[3] and according to approved prescribing information.

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 5–1 as well as the WFH guideline 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 highest dose per injection mentioned in this protocol should though not be exceeded.

Table 5–1 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%.

Bleeding treatment should start as soon as a bleeding episode is identified. The investigator should in advance provide the patient the doses needed to treat the bleed episode 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 8–4 for a definition of severe bleeding episodes. 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 bleeding episode to ensure as correct information as possible. Any dose used for treatment of an active bleeding episode must be recorded as a treatment of a bleeding episode. When symptoms of active bleeding episode have stopped (e.g. pain is reduced and no increase in swelling/swelling diminishes), the patient or parent/caregiver can resume the prophylactic treatment. The timing of the next dose should be according to the prophylaxis dosing schedule.

For treatment in case of a minor surgical procedure, doses 30-60 IU/kg should be used. Treatment should be repeated every 24 hours as needed.

If the procedure takes place at another location than at the trial site (e.g. surgery site or dental practice), the surgeon/dentist must be informed that the patient is participating in the trial, and the investigator should give instructions in advance about the dosing and handling of the trial product.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products, either at the scheduled end of trial visit or if trial product is discontinued prematurely, the patient should be switched to a suitable marketed product at the discretion of the investigator.

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 in India and worldwide.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 70

Number of patients planned to start on trial product: 60

Number of patients planned to complete the trial: 50

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, age above or equal to 12 years at the time of signing informed consent.
3. Patients with the diagnosis of congenital moderate or severe Haemophilia A based on medical records. (FVIII ≤ 5%).
4. Documented history of at least 150 EDs to FVIII containing products.

6.3 Exclusion criteria

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

1. Confirmed inhibitors to FVIII (≥ 0.6 BU) at screening as assessed by central laboratory.
2. 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 signed informed consent.
5. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 1 month before screening (visit 1).
6. Any disorder, except for conditions associated with haemophilia A, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol.
7. Immunocompromised patients due to HIV infection (defined as viral load ≥400.000 copies/mL and/or CD4+ lymphocyte count ≤200/µL). HIV status and CD4+ lymphocyte count /viral load results may be obtained at screening or from available medical records; results must be not older than 6 months.
8. Known congenital or acquired coagulation disorders other than haemophilia A.
9. Mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation.

6.4 Withdrawal from trial

A patient may withdraw consent at will at any time either by the patient or by the patient's parent or the patient's legally acceptable representative. The patient's request to withdraw from the trial must always be respected. See section 8.1 for procedures to be performed for patients withdrawing consent.

6.5 Criteria for premature discontinuation of trial product

A patient must be prematurely discontinued from trial product if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria.
2. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
3. High titer FVIII inhibitor (>5 BU), confirmed by central laboratory.
4. Planned or emergency major surgery.
5. Severe allergic or anaphylactic reaction to trial product.
6. Clinically relevant thromboembolic event which requires treatment with anticoagulants.
7. Lack of haemostatic effect of the trial product.
8. Use of other FVIII products
9. Use of FVIII containing products (blood components, PCC) for more than 5 EDs.

The subject may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.
See section 8.1 for procedures to be performed for subjects discontinuing trial product prematurely.

6.6 Patient replacement

Patients who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

Patients with moderate or 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. 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 without inhibitors to FVIII products are selected. These selection criteria are in accordance with the EMA guideline.[21]

7 Milestones

Planned duration of recruitment period: First patient first visit until last patient first visit (FPFV – LPFV): 16 months

- Planned FPFV: 28-Feb-2018

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

- Planned LPLV of the trial: 28-Oct-2019

The screening and recruitment rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further patients may be screened and the IWRS will be closed for further screening.

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[22], it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[23], the Food and Drug Administration Amendment Act (FDAAA)[24], European Commission Requirements[25-27] 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. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and for this trial it is last treatment (8 weeks after Baseline visit), corresponding to end of trial visit, see section 2. If the last patient is withdrawn early the PCD is considered the date when the last patient would have completed the end of trial visit. The PCD determines the deadline for the results disclosure at Clinicaltrials.gov according to FDAAA.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2). It is important to comply with the visit window stated in the flow chart, to ensure that the trial products do not expire while they are in the patient's possession (see section 2).

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 at the information visit, in accordance with GCP[1] and local requirements, see section 18.2. Informed consent must be obtained before any trial related activity. A separate informed consent must be obtained for genotype and future research, see section 18.3 and 18.4.
A child assent form may be provided to children (below the age of 18). The child assent can be performed on a separate day. 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 visit 2, 3 and unscheduled visits. A trial product injection at visit 2 must be performed at the trial site to assess if the patient or parent/LAR can handle the trial product injection. If assessed necessary, training sessions must be planned for and documented in the patient's medical records.
If injection of trial product is performed at site between scheduled visits, this must be recorded at an unscheduled visit

Screening failures: For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. The following must be collected and documented:

- Date of visit
- Date of informed consent
- Violated Inclusion and exclusion criteria
- Screen failure reason
- Date patient left the trial
- Data relating to AE/SAEs if applicable
- Demography

Follow-up on serious adverse events (SAEs) must be carried out according to section 12.3.
A screening failure session must be made in the IWRS and the case book must be signed in eCRF.

Re-screening is NOT allowed if the patient has failed one of the inclusion or exclusion criteria, this includes re-sampling if the patient has failed one of the inclusion or exclusion criteria related to laboratory parameters.

Premature discontinuation of trial product: If a patient prematurely discontinues trial product, the investigator must withdraw the patient from trial and undertake procedures similar to those for end of trial visit as soon as possible.

If a patient prematurely discontinues trial product (see section 6.5), the patient should attend a follow-up visit in addition to the end of trial visit (see section 8.1.6).

The primary reason for premature discontinuation of trial product must be specified in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

Withdrawal from trial: Withdrawal criteria must be evaluated at every visit after consent. If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for end of trial visit as soon as possible (see section 8.1.6)
The end-of-trial form must be completed in the eCRF, and final drug accountability must be performed even if the patient is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS. The case book must be signed.
Although a patient is not obliged to give his reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

Data review: Review of diaries and laboratory reports etc. must be documented either on the documents or in the patient's medical record.
If clarification of entries or discrepancies in the diary is identified then the patient must be questioned and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

8.1.1 Visit 0 - Information visit

The purpose of the information visit is to inform the patient and/or parent/LAR about the trial. If the patient decides to participate, the patient or parent/LAR must give signed dated informed consent prior to any trial-related activities. All patients will be provided with a copy of the patient information and a copy of the signed and dated informed consent form, see section 18.2.

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 trial and at the latest before sampling for genotyping.

A washout period for minimum of 72 hours for FVIII containing products is needed, when collecting FVIII activity and FVIII inhibitor laboratory samples at the next visit (visit 1). 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. The purpose of these analyses is to determine whether or not the

patient can continue in the trial according the inclusion and exclusion criteria (see section 6.2 and 6.3).

Table 8–1 Minimum requirements for washout periods

Laboratory test	Washout period
Visit 1 – FVIII activity level	72 hours
Inhibitor sampling	48 hours

In case a patient does not fulfil the requirements of a washout period (e.g. the patient has received treatment for a bleeding episode), the visit should be rescheduled. Beside the washout period, the patient should stay on his normal treatment regime between information visit and visit 2.

Key reminders:

- Informed consent must be obtained before any trial related activities starts
- Inform about the washout period
- Schedule next visit

8.1.2 Visit 1 - Screening

Visit 1 is characterised as the screening visit. The visit must be scheduled 1 week after the information visit with a window of ±2 days.
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 evaluating the laboratory results taken at this visit. Furthermore an inhibitor test and a FVIII activity test will be performed so the patient must withhold FVIII containing products for 72 hours prior to this visit to ensure there is no interference of a FVIII product with the assay.

Each patient will be assigned a unique 6-digit subject number which will remain the same 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 subject identification code list and a patient enrolment log. Only patients who have signed the informed consent form should be included on the logs. The patient screening log and patient enrolment log may be combined in one log.

Patient 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.

All assessment to be performed at this visit are listed in section 2

Key reminders:

- Informed consent must be obtained before any trial related activities starts
- Ask for concomitant illness
- Ask for concomitant medications
- Screening session IWRS must be performed
  - In case of screening failure a screening failure session in IWRS must be performed and the case book must be signed off
- Check for 72 hours washout of FVIII containing products before FVIII activity test and inhibitor test
- Ask if the patient has experienced any AEs during his visit
- Trial card must be dispensed
- Schedule next visit

8.1.3 Visit 2 - Baseline

Visit 2 is characterised as the baseline visit. The visit must be scheduled 3 weeks after visit 1 with a window of ±7 days. This is to allow sufficient time for the arrival of the laboratory reports as all results are necessary for evaluation of the inclusion and exclusion criteria. These results must be available before determining whether or not the patient can continue in the trial.

After the final evaluation of the inclusion and exclusion criteria, the investigator has to inject the trial product the first time: After the first dose of turoctocog alfa the patient's medical status must be assess.

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

The diary must be handed out to the patient or parent/LAR 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 bleeding episode has occurred or after the treatment has been injected to ensure as accurate information as possible.

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

All 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 and hand out the Direction for Use
- Hand out the diary and train how to use it
- Dispensing session for the first dose and dispensing trial product until next visit must be performed in the IWRS
- Schedule next visit.

8.1.4 Visit 3 - Treatment

Visit 3, must be scheduled 4 weeks after visit 2 with a visit window of ±3 days. The main reasons for these visits are to review the patient's diary and to dispense trial product.

The diary must be collected and reviewed by the investigator or delegated site staff (see section 8.6.2). The review will include the haemostatic efficacy for treatment of bleeding episodes and evaluate the severity rating. The review should be performed together with the patient or parent/LAR, see section 8.6.2.

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
- Collect and review the diary
- Dispensing session for trial product until next visit must be performed in the IWRS
- Schedule next visit
- Remind the patient about the coming 48 hours washout period

8.1.5 Visit 4 - End of trial visit

For patients who withdraw from the trial, an end of trial visit must be performed as soon as possible. For patients completing the trial, the end of trial visit must be 8 weeks after visit 2 with a window of ±3 days. The main reason for the visit is to collect samples analysing for FVIII inhibitors, see section 8.4.2. The patient must therefore withhold FVIII treatment for 48 hours prior to this visit to ensure there is no interference of a FVIII product with the assay.

The diary must be collected and reviewed by the investigator or delegated site staff (see section 8.6.2). The review will include the haemostatic efficacy for treatment of bleeding episodes and evaluate the severity rating. The review should be performed together with the patient or parent/LAR, see section 8.6.2. The assessments to be performed at this visit are listed in Section 2

Key reminders:

- Ask of the patient has experienced any AEs since last visit
- Ask for any concomitant medications since last visit
- Ensure 48 hours washout of trial product before the inhibitor test
- Collect sample for inhibitor test
- Collect and review the patient diary
- Completion or treatment discontinuation session must be performed in IWRS

8.1.6 Follow up visit

Patients withdrawn, after visit 2, due to inhibitors must attend a follow up visit in order to evaluate the patient's inhibitor status. This visit should be performed within 4 weeks after end of trial visit with a visit window of ± 3 days.

Patients who have completed the trial must attend a follow up visit in order to assess any possible AEs. Patients, who have completed the trial, must attend 12 weeks after visit 2, with a window of ±3 days.

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

Key reminders:

- Ask if the patient has experiences any AEs since last visit

8.1.7 Unscheduled visit

An unscheduled visit can be performed after the visit 1 has been performed. The date and time of the unscheduled visit must be recorded in the eCRF.

Several reasons can be given for the necessity for the unscheduled visit. The main purpose could be to record information that is important and is not covered by the scheduled visits. This information can be (but not limited to) laboratory tests, dosing adjustments, lab samples to confirm a positive inhibitor test or trial drug administration at site. Please note AEs, withdrawal criteria and concomitant medication must be assessed at every unscheduled visit.

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

8.2 Patient related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth
- Sex
- Race
- Ethnicity

8.2.2 Concomitant illness and medical history other than haemophilia

A **concomitant illness** is any illness, other than haemophilia A, that is present at the start of the trial (i.e. at the first visit, visit 1) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

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

It must be possible to verify the patient's medical history in source documents such as patient's medical record. If a patient is not from the investigators own practice; the investigator must make reasonable effort to obtain a copy of patient's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication for treatment or prevention of a disease, other than the trial products, which is taken during the trial, from visit 1 (screening visit) to end of trial visit.

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 12. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Details of the haemophilia

Historical information regarding the patient's underlying disease (haemophilia A) will be collected in the eCRF at visit 1.

- Classification of haemophilia, as per medical record.
- Family history of inhibitors.

8.2.5 Haemophilia treatment and bleed history

Haemophilia treatment and bleed history should be collected for a period of 12 months prior to visit 1. The following information on the patient's current treatment regimen and previous regimens up to 12 months prior to visit 1 will be collected in the eCRF.

- Type of treatment regimen
  - Prophylaxis or on-demand
  - Start date of regimen
  - Stop date of regimen
- Number of bleeding episodes during the regimen period (may be an estimate if not documented)
- Coagulation factor product(s) during regimen period
  - Type of product (plasma derived or recombinant
- Dose used for prophylaxis (IU/kg)
- Dosing frequency, if patient is on prophylaxis regimen
- Total number of previous exposure days.

Total number of previous exposure days (≥150 or exact number of EDs). The "total number of previous exposure days" must be assessed to ensure that 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).

8.2.6 Body measurements

Body weight must be measured at visit 1-4, if necessary the weight can also be measured at an unscheduled visit. Height will only be measured at visit 1.

- Body weight
- Height

8.3 Efficacy assessments

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 must be entered in the diary, see section 8.6.2.

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

- Bleeding episode start date and time
- Bleeding episode stop date and time, see Table 8–2
- Bleeding episode location (joint, muscle, skin, stomach (gastrointestinal bleeding episode), mucosal (mouth, gums, nose), urinary system, central nervous system, other)
  - If joint is chosen, specify location: knee, ankle, wrist, fingers, elbow, shoulder, hip, toes, jaw
  - If muscle or skin is chosen, specify location: arm, leg, hand, buttocks, head/neck, chest, back, stomach, foot
- Cause of bleeding episode (spontaneous, traumatic, surgical bleeding episode) see Table 8–5
- Other non-medical therapy used
- Evaluation of the achieved haemostatic response (Excellent, Good, Moderate or None), see Table 8–3
- Severity (mild/moderate or severe) evaluated by investigator, see Table 8–4

Table 8–2 Definition of stop of a bleeding episode

Stop time is: When the patient/parent or LAR experiences/observes signs of cessation of the active bleeding episode 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 8–3 Definition of haemostatic response

Category	Definition
Excellent	abrupt pain relief and/or unequivocal improvement in objective signs of bleeding episode within approximately 8 hours after a single injection
Good	definite pain relief and/or improvement in signs of bleeding episode within approximately 8 hours after an injection, but possibly requiring more than one injection for complete

Category	Definition
	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/LAR must in the diary assess the haemostatic efficacy for treatment of bleeding episodes, but the investigator must together with the patient during the diary review evaluate the correctness of the evaluation.

Table 8–4 Definition of bleeding episode severity

Category	Definition	Comment
Mild/Moderate	Minor bleeding episodes which are uncomplicated joint bleeding episodes, muscular bleeding episodes without compartment syndrome, mucosal or subcutaneous bleeding episodes	
Severe	Major bleeds that require hospitalisation; intracranial, retroperitoneal, iliopsoas and internal neck bleeds; muscle bleeding episodes with compartment syndrome; bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl). Traumatic bleeding episodes 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 8–5 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	Bleeding episodes during surgery

8.3.2 Injection of trial product

The following information will be recorded in the diary when injecting trial product:

Actual dose:

- Dose (volume)
- Start date and time of injection

- Reason for dosing (prophylactic or treatment of bleeding episode)
- Injection method

Prophylaxis

1. Dosing frequency
2. Planned dose (volume and vial strength)

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

8.4 Safety assessments

To ensure standardisation of safety assessment across trial sites a centralised laboratory is used for laboratory assays. All the safety assessments are standard assessments widely used for haemophilia care, see section 8.5

The evaluations must follow the categories:

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

8.4.1 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.1.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product involved
- Classification of medication error
- Whether the patient experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.2 Antibodies

8.4.2.1 FVIII inhibitors

FVIII inhibitors will be measured at visit 1 and end of trial visit. 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. 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.

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

If either tests are below or equal to 5 BU the patient can continue in the trial, unless the patient fulfil withdrawal criteria such as ineffective treatment (see section 6.5).

If the second confirmatory is positive (≥0.6 BU) and if one of the two tests is above 5 BU, then the patients must be withdrawn from the trial, see section 6.5. The patient must be followed up at the follow-up visits, see section 8.1.6.

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 Antibody characterization

Antibody characterization will only be done to identify any FVIII inhibitors in this trial, see section 8.4.2.1. Upon request from authorities antibody characterization, or as well for future research, may be performed on the frozen and stored antibody sample, see further information in section 8.5.3.2 and 8.5.3.3 for handling of the stored samples.

8.4.3 Physical examination

Physical examination must be performed at screening and 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
- Cardiovascular system
- Genito-Urinary System, Breasts
- Gastrointestinal System incl. Mouth
- Skin
- Respiratory system
- Musculoskeletal system
- Central and peripheral nervous system

The investigator must evaluate the results of the examination and record the outcome in the eCRF as:

- Normal or abnormal
- If abnormal the investigator must:
  - Specify the abnormality
  - Record if the result is clinically significant
  - If observed before or at visit 1: recorded as medical history (see section 8.2.2)
  - If observed after screening: report a AE/SAE (see section 12)

If the patient experiences any changes during the visits which fulfil the criteria of an AE it must be recorded as such, please see Section 12.

8.4.4 Vital signs

Vital signs must be assessed at screening 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 see Section 12.

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.

8.4.5 Surgery

Only minor surgery is allowed during this trial. See Table 8–6 for definition of a minor and major surgery. Treatments must be recorded (concomitant medication and turoctocog alfa) in the diary and the surgery data must be recorded in the eCRF (see section 8.6.2). In case of major surgery, patient must be withdrawn from the trial, and complete the end of trial visit, see section 8.1.5.

Table 8–6 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 cut down 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/guide wire. Dental surgery will be classified as minor or major based on above definitions

The following data must be recorded for minor surgery:

- Surgical indication
- Surgical procedure
- Surgery location
- Start date and time of surgery
- Stop date and time of surgery
- Surgery doses

Date patients resume regular prophylaxis treatment

8.5 Laboratory assessments

The collection of all blood samples for the laboratory tests will be performed before injection of the trial product.

Laboratory results for biochemistry and haematology 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 12.1.1 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.

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.

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.

Furthermore the results of the future research (Biospecimen) and the antibody characterisation 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).[28] 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.[28]

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.

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 visit 1 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.

CVADs (central venous access device) should preferably not be used for blood sampling due to risk of contamination and dilution.

8.5.2 Safety laboratory parameters

The below listed parameters will be sampled for safety reasons:

- FVIII inhibitors
- Haematology
- Biochemistry

8.5.2.1 Haematology

The assessment will be performed at visit 1 and at the end of trial visit. Analysis of Haematology is performed according to the normal practice of the central laboratory and includes:

- Haemoglobin
- Leucocytes
- Thrombocytes

8.5.2.2 Biochemistry

The assessment will be performed at visit 1 and end of trial visit.

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

- Creatinine
- Alanine aminotransferase (ALT)
- C-reactive protein (CRP)
- Bilirubin

8.5.2.3 Coagulation parameter, FVIII activity

FVIII baseline level:
In order to determine 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 see Section 6.2

Any anti-haemophilic treatment with blood components or FVIII concentrates should not be administered for at least 72 hours prior to blood sampling to ensure there is no interference of the trial product with the assay.

- FVIII activity (IU/mL)

8.5.2.4 Hepatitis

Blood samples for Hepatitis B and C are sampled at visit 1.

- Hepatitis B
- Hepatitis C

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

8.5.2.5 HIV

Blood samples HIV testing is sampled at visit 1.

- HIV viral load
- HIV antigen/antibody screening test
- CD4+ T Cells count

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

8.5.3 Other laboratory parameters

8.5.3.1 Genotype

Genotype tests is optional in this trial and can only be performed after a separate informed consent has been signed, see section 18.3. The blood sample for the test can be taken at any visits, but it is recommended to sample for genotype at screening visit. Note that the test can only be analysed once.

- FVIII genotyping

The FVIII genotype test will only characterise the genes in relation to haemophilia A. 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.

8.5.3.2 Samples for future research, biospecimen samples

In order to explore immunogenicity and perform further analysis of turoctocog alfa the remaining part of the blood sample for FVIII inhibitors and FVIII activity 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, which at present have not been included in the scientific hypotheses of haemophilia A.

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 18.4. The biospecimen sample should only be sampled one time and should not be taken 48 hours after dosing with a FVIII containing product. It is recommended to take the biospecimen sample at visit 1 or end of trial visit.

Table 8–7 Overview of samples for future research (biospecimen)

Test	Remaining sample of	Sampled at
FVIII Inhibitors	FVIII Inhibitors	Visit 1, and end of trial visit
FVIII Activity	FVIII activity sample	Visit 1
Extra blood sample	NA as this is a separate blood sample	Any visit

The investigator may not be given all the tests results, to review these 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.

8.5.3.3 Retention of blood samples

Biospecimen samples will be collected and stored at a Novo Nordisk appointed referral bio-repository. All biospecimens will be shipped out of India. 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 prophylaxis treatment related to haemophilia. All treatments, including treatment of bleeding episodes and any treatment for minor surgery 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 2, the patient or parent/caregiver will receive the first diary and they will be trained in the use by the investigator.

The investigator should train the patient and/or parent/LAR 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 bleeding episode has occurred or after the treatment has been injected to ensure as accurate information as possible.

The diary is split in two, a bleeding episode part and a treatment diary part (treatment of bleeding episodes, treatment for minor surgery and prophylaxis treatment). The patient will only receive one bleed diary for the whole trial but will receive many treatment diaries during the trial. The diary must be returned at every scheduled visit and a new diary will be handed out to the patient or parent/LAR. During trial site visits, the diary must be reviewed by the investigator together with the patient or parent/LAR including the correctness of the haemostatic efficacy for treatment of bleeding episodes. The severity rating of the bleeding episode must be entered by the trial site staff into 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. 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. 24-01-17)

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 2, 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 direction for use, explaining the reconstitution and injection process, must be handed-out to the patient or parent/LAR at visit 2.

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.

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 supplies

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

Trial products must not be dispensed to any person not included in the trial. This does not include the patient's parent/LAR.

The reconstituted turoctocog alfa must not be used, if it does not appear as a clear to slightly opalescent solution. If visible particles or discolouration are noticed, the product must not be used. 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, see table Table 9–1.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/delivery device
Turoctocog alfa (Investigational medicinal product, IMP), test product	2000 IU/vial	Powder for solution for injection	Intravenous injection	Vial
Sodium chloride	0.9%	Solvent for solution for injection	Intravenous injection	Pre-filled syringe

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[29], local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS (see section 10). Trial product will be distributed to the trial sites according to enrolment.

The investigator must document that direction for use is given to the patient orally and in writing at the first dispensing visit, (visit 2, see section 8.1.3). The DFU can be handed out at subsequent visits.

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use-time[a]
Turoctocog alfa 2000 IU/vial	Store in refrigerator (2°C-8°C)	For single use	After reconstitution: Use within 4 hours when stored at room temperature (below 30°C) or 24 hours when stored in refrigerator (2°C-8°C)
	Do not freeze	Do not freeze	
	Protect from light	Protect from light	
	May be stored at room temperature (below 30 °C) for a single period not exceeding 9 months. Do not return the product to the refrigerator.[b]		
	Write the start date for the storage at room temperature on the label.		
Sodium chloride, 0.9%	Store at 2°C-30°C	For single use	N/A (specified by turoctocog alfa)
	Do not freeze		
	Protect from light		

[a] In use starts from when the reconstitution procedure is initiated

[b] At the clinical sites, the product must be stored in a refrigerator (2°C-8°C) at all times. When in patient's possession, the product can be stored at room temperature for a single period not exceeding 9 month

The investigator must ensure that trial product is kept under 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). Additional details regarding handling of temperature deviations can be found in the TMM.

Trial product that has been stored improperly must not be dispensed to any patient before it has been 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 of all trial products received at site is the responsibility of the investigator.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial products including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Drug accountability for turoctocog alfa should be performed at vial level in the IWRS. Unused trial product must be stored separately from used trial product. Drug accountability must also be performed for the sodium chloride solvent.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

9.5 Auxiliary supplies

The following auxiliary supplies will be supplied by Novo Nordisk:

- Directions for Use (DFU)
- Trial injection kits (for reconstitution and administration of trial product)

Only needles provided by Novo Nordisk must be used for administration of trial product.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Medication arrival
- Dispensing
- Dispensing verification (when barcode scanner is used)
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

Not applicable for this trial.

12 Adverse events and technical complaints

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal 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 or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or concomitant illness)
- Surgical procedures (If the condition for which the procedure was performed has emerged or worsened from the first trial related activity after the patient has signed the informed consent, the condition should be reported as AE)
- Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. In case of a life-threatening bleeding episode, it must always be reported as an SAE. All bleeding episodes and other findings related to underlying disease will be captured in the CRF.

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**
  Relationship between an AE and the relevant trial product:
  - **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

- Final outcome
  - **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 sequelae** - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae 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 sequelae" 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

12.1.2 Serious adverse event

A serious adverse event (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 dyscrasia 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:

- Inhibitor development (confirmed by two consecutive tests (≥ 0.6 BU))
- 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)

Note: A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be an SAE.

12.1.3 Non-serious adverse event

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

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug
  - Note: Use of wrong DUN is not considered a medication error.
- Wrong route of administration, such as intramuscular instead of intravenous
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt) misuse or abuse of trial product.
- Accidental administration 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 they did not necessarily occur

Medication errors must be reported on an AE form and a specific event form, see section 8.4.1.

12.1.5 Adverse events requiring additional data collection

AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

In this trial the following AE require the completion of specific event forms in the eCRF

- Hypersensitivity reaction including anaphylactic reactions

Clinical criteria for diagnosing anaphylaxis (Sampson et al.[30]).
Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   - Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

12.1.6 Technical complaints

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

12.2 Reporting of adverse events

All events meeting the definition of an AE, SAE and AEs leading to discontinuation of trial product 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. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

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?"

All AEs, observed by the investigator or patient, must be reported by the investigator and evaluated.

All AEs must be recorded by the investigator on an AE form. The investigator must report the diagnosis, if available. If no diagnosis is available, the investigator must 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.

For all non-serious AEs, the applicable forms must be signed when the event is resolved or at the end of the trial at the latest.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

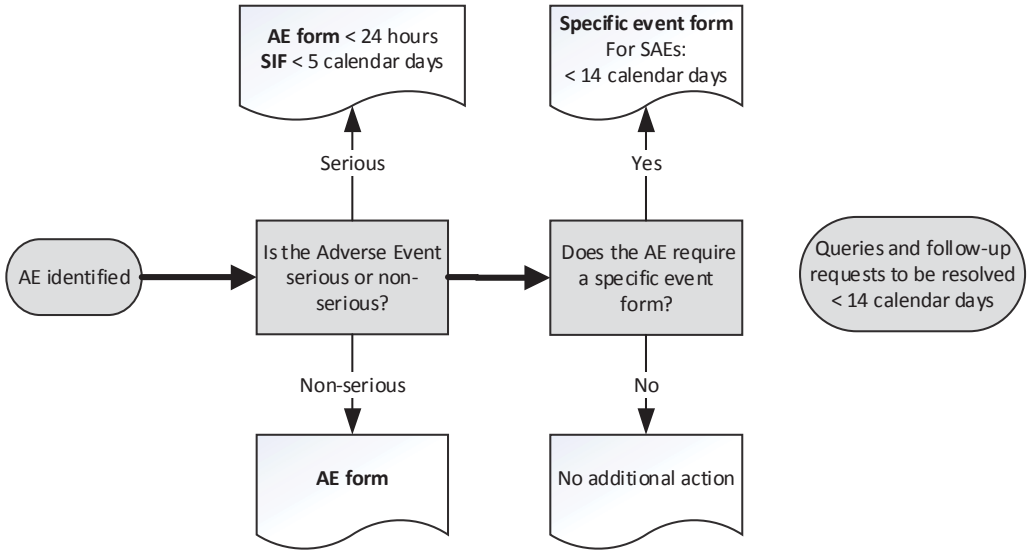
- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE

Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For AEs/SAEs requiring reporting on a specific event form: In addition to the above the specific event form within 14 calendar days from the investigator's first knowledge of the AE.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form 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 enter the information on the form into the eCRF.

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



Timelines are for the completion of forms from the time of investigator's awareness.
AEs requiring specific event forms are descibed in Section 12.1.4 *and 12.1.5*.

AE: Adverse Event SIF: Safety Information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference document: Current version of the Company Core Data Sheet (CCDS, version 7) and any updates thereto.

Reporting of trial product-related SUSARs by Novo Nordisk:

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 IRBs/ IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP[1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication

If an AE 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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

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 sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing 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 sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing 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 investigator must ensure that the recording of 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 patient after the patient has

ended the trial, the investigator must report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Turoctocog alfa 2000 IU/vial
- Isotonic Sodium Chloride 0.9% for injection in prefilled 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 product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

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

The investigator must assess whether the technical complaint is related to any AEs or SAEs. 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. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 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 copy of the technical complaint form must be included in the shipment of 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 batch, code or lot number and, if available, the DUN. All parts of the DUN must be returned.

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.

12.5 Precautions and/or overdose

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

If an overdose is suspected, further turoctocog alfa administration must be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines.

12.6 Committees related to safety

12.6.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal turoctocog alfa safety committee to perform ongoing safety surveillance. The turoctocog alfa safety committee works according to written guidelines and will meet regularly to discuss and evaluate the overall safety of turoctocog alfa.

The Novo Nordisk safety committee can take action with regard to patient safety for the trial based upon observations of the overall safety information for turoctocog alfa.

13 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, 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 will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- Safety information forms
- Technical complaint forms

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. 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 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.

13.1 Corrections to case report forms

13.1.1 Corrections to paper CRFs

Corrections to the data in 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 delegated staff after the date of the investigator's signature on the casebook in eCRF, the casebook must be signed again.

13.1.2 Corrections to eCRFs

Corrections to the eCRF data may be made by the investigator or the investigator's delegated 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 delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. 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 will be supplied as paper-set including two different coloured copies. 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 data management. One copy (bottom page) of the CRF will be retained at the site. The CRA will keep the middle copy of the CRFs.

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

13.3 Diary

Two set of paper diaries will be provided by Novo Nordisk A/S and will be handed to the patients at visit 1 (see section 8.6.2). The completed diary will be returned by the patient at every visit to the site and at the end of the trial. The data from the diaries will be checked by the investigator or site staff and reported into the eCRF. Corrections to this data may be made by investigator or the investigator's delegated staff after a discussion with patient and the same should be documented in the patient's medical or source records.

14 Monitoring procedures

Monitoring will be conducted using risk based approach including risk assessment, monitoring plans centralised monitoring and visits to trial sites. 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 centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), 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 other than the eCRF, except for the data in the diary.

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
- Any disorder which, in the opinion of investigator, might jeopardise patient's safety or compliance with the protocol
- Mental incapacity
- Haemophilia treatment and bleeding episode 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 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.

If paper CRF are used, each copy of the paper CRF are considered to be source and this allows that the top page of the paper CRF 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 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. The following data will be source data verified for screening failures:

- Date of informed consent
- Violated Inclusion and exclusion criteria
- Screen failure reason
- Date patient left the trial
- Data relating to AE/SAEs if applicable
- Demography
- Date of visit

Monitors must review the patient's medical records and other source data (e.g. the diaries) 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.

15 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. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer. The central 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.

16 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.

17 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

No formal statistical testing will be performed. When confidence intervals are provided they will be two-sided 95% intervals.

17.1 Sample size calculation

Sample size is based on Indian Health Authorities (HA) requirements. Indian HA has mandated Novo Nordisk to perform a trial with 50 patients (completers). Based on Hanley's formula[31] "the rule-of-three" we know that with approximately 95% power we will observe at least one patient with FVIII inhibitor (≥0.6 BU) if the incidence rate is as low as 6%. The same holds for any other type of adverse events.

17.2 Definition of analysis sets

All main descriptions and analyses of efficacy will be based on the Full Analysis Set, as defined in ICH E9 Guidelines (Statistical Principles for Clinical Trials).[32] The Full Analysis Set includes all

dosed patients with data after dosing. Only in exceptional cases will patients be excluded from the full analysis set. The patients to be excluded and the reasons for their exclusion must be documented and signed by those responsible before database lock. Only in exceptional cases data points will be excluded from analysis based on the full analysis set. The observations to be excluded from such analysis and the reasons for their exclusion must be documented and signed by those responsible before database lock. The patients and observations excluded from analysis sets or any analyses, and the reason for this, will be described in the clinical trial report.

The Safety Analysis Set will be identical to the full analysis set. The analyses of the safety endpoints will be based on the Safety Analysis Set. The observation period for safety analysis will be the on-treatment period with a post treatment window until the follow-up visit to capture all treatment emergent events. The observation period is therefore from fist treatment with trial drug (visit 2) until the follow-up visit.

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

Missing inhibitor test will not be counted as a positive result. This is based on the plausible assumption that in case of any clinical signs of inhibitor development inhibitor testing will be performed in practice, so missing test is unlikely to indicate positive inhibitor.

In general the statistical analysis will be based on the available data, unless otherwise explicitly stated below.

17.3 Primary endpoint

- Occurrence of confirmed FVIII inhibitors (≥0.6 BU) during 8 weeks of treatment.

A patient is said to have confirmed FVIII inhibitor when two consecutive tests are positive. In case of confirmation the inhibitor is considered to have been present from the first of the two tests. The estimand for the primary endpoint is an effectiveness estimand among all exposed subject. The incidence rate of inhibitors will be calculated and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the incidence rate the numerator will include number of all patients with confirmed inhibitors anytime after baseline visit while the denominator will include the number of patients in the safety analysis set.

Furthermore, listings will be provided displaying inhibitor status including pertinent clinical information such as gene mutation.

17.4 Secondary endpoints

17.4.1.1 Efficacy endpoints

Classification of re-bleeds will be done by Novo Nordisk as part of the statistical analysis based on bleeding information: A re-bleed is defined as a bleed (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping treatment 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. Relevant data listings will be repeated for re-bleeds separately. Minor surgery periods will be excluded from the prophylaxis treatment period. Data related to bleeds during these periods will be listed separately.

- Successful haemostatic effect of turoctocog alfa on treatment of bleeding episodes during the trial.

Haemostatic effect is assessed on a predefined four point scale: Excellent, Good, Moderate and None. Successful haemostatic response is defined by the categories: success (good or excellent) and failure (none, moderate, missing).

The haemostatic effect and successful haemostatic of turoctocog alfa will be will be summarised by frequency tables containing count and percentages of all bleeds. Summaries will be made separately by severity of haemophilia A assessed at baseline.

The haemostatic effect and successful haemostatic effect of turoctocog alfa will also be summarised by the following subgroups: Cause of bleeding episode (Spontaneous, Traumatic), Site of bleeding (Central nervous system, Haemarthrosis (Joint), Gastrointestinal, Subcutaneous, Muscular or other), and Classification of bleeding (Mild/Moderate or Severe). Details (cause, site, classification and time) about the bleeding episodes will also be summarised and listed.

All bleeding episodes during trial will be listed including pertinent clinical information.

- Total annualised consumption of turoctocog alfa measured during the 8 weeks of treatment

Total consumption of turoctocog alfa (IU/kg/year) during the trial (given for either prevention, treatment of bleeding episodes or during surgery) will be summarised for moderate and severe haemophilia A patients and listed by patient.

Additionally, number of turoctocog alfa infusions (injections/bleed) required per bleeding episode during the 8 weeks of treatment will be summarised. The number of infusions of turoctocog alfa required per bleed will be calculated as the number of infusions of turoctocog alfa used in the time period from start of the bleed to stop of the bleed. The number of infusions will be presented using count and percentages of all bleeds. Presentation will be done separately for moderate and severe haemophilia A patients. Further, the turoctocog alfa consumption per bleeding episode during the 8

weeks of treatment will be summarised. The consumption of turoctocog alfa (IU/kg BW/bleed) will be calculated as the consumption of turoctocog alfa used from start of the bleed to stop of the bleed. The consumption will be summarised for moderate and severe haemophilia A patients and listed by patient.

17.4.1.2 Safety endpoints

- Frequency of ARs and SARs reported until follow-up, 12 weeks after the first treatment.

An AR is an AE where the causality is rated as probable or possible by the investigator, similar for SAR. ARs and SARs will be analysed by severity of haemophilia A assessed at baseline.

All ARs and SARs will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity will be made.

All AE's and SAEs will be summarised by frequency of events and frequency of patients with an y event. Similar summaries cross-classified by severity will be made. These summary will be made by severity of haemophilia A assessed at baseline.

ARs, SARs, AEs, SAEs will be summarised by SOC and PT.

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

Separate list will be performed for adverse events with onset before first trial drug or after the follow up visit (if any).

- Frequency of allergic or infusion reactions related to the trial product reported until follow-up,12 weeks after first treatment.

This endpoint will be reported without additional summaries or listings. The reporting will be based on the overall summaries and listings for ARs and SARs.

17.5 Interim analysis

No interim analysis is planned for this trial.

17.6 Sequential safety analysis and safety monitoring

No safety analysis is planned for this trial.

17.7 Explorative statistical analysis for pharmacogenetics and biomarkers

No analysis of pharmacogenetics and biomarkers are planned for this trial.

17.8 Pharmacokinetic and/or pharmacodynamic modelling

Pharmacokinetic and pharmacodynamic modelling is not planned for this trial, but data may be included in cross-trial meta-analysis PK modelling should the need for such analyses arise.

17.9 Health economics

Not applicable for this trial

18 Ethics

The trial will be conducted in compliance with ICH GCP [1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki. [2]

No patient will consent to the trial before all required IRB/IEC and regulatory approvals have been obtained for the trial.

18.1 Benefit-risk assessment of the trial

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, 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.

The potential benefits to the patients treated with turoctocog alfa include 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.

18.2 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 Indian 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.

If the minor reaches legal age while participating in the trial and has only signed an age specific informed consent/assent form, the patient has to re-consent to the informed consent form signed by the patient’s LAR.

18.3 Informed consent for genotyping

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

They can abstain from the genetic testing and still participate in the trial.

18.4 Informed consent for future research (biospecimen)

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. They can abstain from the additional blood sample and still participate in the trial.

Furthermore, this informed consent also request to store other blood samples for future research, see section 8.5.3.2.

18.5 Data handling

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

- Data already collected and any data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the clinical 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.

18.6 Information to the patients during 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 written information to patients must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.7 Premature termination of the trial and/or trial site

Novo Nordisk, 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 the 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 regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk 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.

19 Protocol compliance

19.1 Protocol deviations

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.

20 Audits and inspections

Any aspect of the clinical trial may be subject 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.

21 Critical documents

An Investigator Portal, Global Haemophilia Network (GHN), will be used as primary media for exchange and handling of investigator trial master 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, written notification from Novo Nordisk must be received and 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, subject 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 (or a general assurance number/statement of compliance)
- 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[17]
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

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

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

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented 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 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 trial master file. The documents including the subject identification code list must be kept in a secure locked facility, so no unauthorized persons can get access to the 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).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as 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. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One investigator will be appointed by Novo Nordisk 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.[33]

23.1 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 subject to public disclosure on external web sites according to international and national regulations, as reflected in t he Novo Nordisk Code of Conduct for Clinical Trial Disclosure.[22]

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 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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[33] (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.

23.1.2 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 of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 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 supplied by Novo Nordisk. These data must be retained by the trial site. If the 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 at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

The files from the trial site/institution must be retained for 15 years after end of trial as defined in section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

Biospecimens will be collected and stored for potential future assessments. The samples will be stored by a biorepository for up to 15 years from end of trial after which all samples will be destroyed according to standard operating procedures by the biorepository. The potential future assessments may address issues such as unexpected safety events, refinement of the PK or anti-drug antibody assessments and to improve the understanding of the mechanism of action. As new biomarkers related to the disease and/or safety, efficacy, immunogenicity, or mechanism of action may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. In the event that the collected biospecimens (specific whole blood, plasma and serum samples) will be used in the future, the investigator will be informed directly 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. Patients may at any time contact the investigator if they wish to be informed about results derived from stored biospecimens obtained from their own body.

The samples might be transferred to other countries, if not prohibited by local regulations. The patient's identity will remain confidential and samples will be marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and biorepository personnel will have access to the stored biospecimens. Antibody and inhibitor samples will be retained for later analysis for further characterisation of antibody responses towards trial drug if required by health authorities or for safety reasons. Remaining blood from the samples already collected may be used for further development of Anti-Drug antibody assays, and will not be reported in this study.

The samples will be stored at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed. The patient's identity will remain confidential and the samples will be identified only by subject number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored anti-body samples.

Patient can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 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 Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure[17], 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 benefit-risk 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 trial master 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.

26 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 any country, 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 Indian law and guidelines

27 References

1. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Current Step 4 version. 09 Nov 2016.
2. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. 1 Oct 2013.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1-47.
4. Kar A, Phadnis S, Dharmarajan S, Nakade J. Epidemiology & social costs of haemophilia in India. Indian J Med Res. 2014;140(1):19-31.
5. World Federation of Hemophilia. Report on Annual Global Survey 2014.
6. Resolution of the world federation of haemophilia. General Assembly on the Supply of Safe High-Quality Clotting Factor 2010 [cited 2015 28 Dec].
7. Ghosh K, Joshi SH, Shetty S, Pawar A, Chipkar S, Pujari V, et al. Transfusion transmitted diseases in haemophilics from western India. Indian J Med Res. 2000;112:61-4.
8. Khaja MN, Madhavi C, Thippavazzula R, Nafeesa F, Habib AM, Habibullah CM, et al. High prevalence of hepatitis C virus infection and genotype distribution among general population, blood donors and risk groups. Infect Genet Evol. 2006;6(3):198-204.
9. Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. Haemophilia. 2008;14(4):671-84.
10. Farrugia A. WFH Guideline for the assessment of clotting factor concentrates [cited 2015 28 Dec].
11. Government of India. Form 45. Permission to import finished formulation of the new drug. IMP 182/2015. Letter of communication from Ministry of Health and Fa mily Welfare, Government of India to Novo Nordisk India Pvt Ltd; dated 19 August 2015. 2015.
12. Ezban M, Vad K, Kjalke M. Turoctocog alfa (NovoEight(R))--from design to clinical proof of concept. Eur J Haematol. 2014;93(5):369-76.
13. Lentz SR SS, Staber J, Kulkarni R. Turoctocog alfa and drug development for haemophilia A. Expert opinion on orphan drugs. 2014;2(4):419-31.
14. Kulkarni R, Karim FA, Glamocanin S, Janic D, Vdovin V, Ozelo M, et al. Results from a large multinational clinical trial (guardian™3) using prophylactic treatment with turoctocog alfa in paediatric patients with severe haemophilia A: safety, efficacy and pharmacokinetics. Haemophilia. 2013;19(5):698-705.
15. Ozelo M, Misgav M, Abdul Karim F, Lentz SR, Martin-Salces M, Matytsina I, et al. Long-term patterns of safety and efficacy of bleeding prophylaxis with turoctocog alfa (NovoEight(®)) in previously treated patients with severe haemophilia A: interim results of the guardian(™) 2 extension trial. Haemophilia. 2015;21(5):e436-9.
16. Ozelo MC. Updates from guardian™: a comprehensive registration programme. Eur J Haematol. 2015;95 Suppl 81:22-9.
17. Novo Nordisk A/S. Investigator's brochure, turoctocog alfa (NovoEight®), project NN7008 (edition 8). 2016.

18. Xi M, Makris M, Marcucci M, Santagostino E, Mannucci PM, Iorio A. Inhibitor development in previously treated hemophilia A patients: a systematic review, meta-analysis, and meta-regression. J Thromb Haemost. 2013;11(9):1655-62.
19. Matino D, Lillicrap D, Astermark J, Dolan G, Kessler C, Lambert T, et al. Switching clotting factor concentrates: considerations in estimating the risk of immunogenicity. Haemophilia. 2014;20(2):200-6.
20. Fischer K, Lassila R, Peyvandi F, Calizzani G, Gatt A, Lambert T, et al. Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. Thromb Haemost. 2015;113(5):968-75.
21. EMA/CHMP/BPWP/144533/2009. Committee for Medicinal Products for Human Use (CHMP), Guideline on the Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products. 2009 2009. p. 1-19.
22. Novo Nordisk A/S. http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx.
23. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
24. U.S. Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
25. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities. 01 May 2001.
26. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
27. The European Parliament and the Council of the European Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, article 41. Official Journal of the European Communities. 27 Dec 2006.
28. European Medicines Agency. Ethical considerations for clinical trials on medicinal products with the paediatric population. Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.
29. European Commission. The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products. Brussels. 03 February 2010.
30. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second Symposium on the Definition and Management of Anaphylaxis: Summary report -

Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine. 2006;47(4):373-80.

31. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA. 1983;249(13):1743-5.
32. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline E9. Statistical Principles for Clinical Trials. 5 Feb 1998.
33. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff