Cover Page for Protocol

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Protocol

Trial ID: NN7170-4345

Evaluation of safety following Immune Tolerance Induction treatment with turoctocog alfa in patients with haemophilia A following inhibitor development in NN7170-4213 trial

Final Protocol version 1.0 (18 November 2016), Final Global Protocol Amendment no 1 (19 Dec 2018)

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

Protocol originator

[redacted]

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List of abbreviations

AE	Adverse event
BP	Blood pressure
BU	Bethesda Units
CRF	Case report form
DCF	Data clarification form
DFU	Direction for use
DUN	Dispensing unit number
ECG	Electrocardiogram
EOT	End-of-treatment
FDA	U.S. Food and Drug Administration
FVIII	Factor VIII
FPFV	First patient first visit
GCP	Good Clinical Practice
HCP	Host Cell Protein
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
ITI	Immune tolerance induction
IU	International Units
i.v.	Intravenous(ly)
LAR	Legally acceptable/authorised representative
LLoQ	Lower limit of quantification
LPLV	Last patient last visit
MIDF	Monitor-initiated discrepancy form
N8-GP	turoctocog alfa pegol
OD	On demand
PK	Pharmacokinetic

PPX	Prophylaxis
PTP	Previously treated patients
PUP	Previously untreated patients
rFVIII	Recombinant factor VIII
SAE	Serious adverse event
SAS	Safety Analysis Set
s.c.	Subcutaneous(ly)
SC N8-GP	Subcutaneous turoctocog alfa pegol
SDV	Source data verification
SUSARs	Suspected unexpected serious adverse events reactions
TMM	Trial Materials Manual
UTN	Universal Trial Number

1 Summary

Objective(s) and endpoint(s):

Primary Objective

- To evaluate safety of immune tolerance induction treatment with turoctocog alfa in patients who have developed neutralising antibodies against factor VIII after exposure to subcutaneous turoctocog alfa pegol during participation in NN7170-4213.

Secondary objective

- To evaluate efficacy of immune tolerance induction treatment with turoctocog alfa.

Primary Endpoint

- Number of adverse events during immune tolerance induction treatment with turoctocog alfa.

Secondary endpoints

- Response to immune tolerance induction treatment (success, partial success, failure, other) within a maximum immune tolerance induction treatment duration of 24 months.

Trial design:

This trial is a single arm, open label interventional trial evaluating safety and efficacy of immune tolerance induction treatment with turoctocog alfa.

The maximum treatment period for this trial is 24 months and the patient(s) will be called for visit to the clinic every 3rd month. Upon confirmed successful immune tolerance induction treatment, the patient will leave the trial after attending visit 10 and 11.

Trial population:

The patients eligible for participation in this trial are patients who have developed clinically relevant inhibitors upon exposure to subcutaneous turoctocog alfa pegol during participation in NN7170-4213 trial. A confirmed inhibitor is defined as two consecutive tests at the central laboratory in NN7170-4213.

Key inclusion criteria:

- Previous participation in the NN7170-4213 trial (male, age ≥ 18 years (part A) and age ≥ 12 years (part B)).
- Development of a confirmed high titre neutralising antibody towards factor VIII (>5 Bethesda Unit) after exposure to subcutaneous turoctocog alfa pegol in the NN7170-4213 trial or development of a confirmed clinically relevant low titre inhibitor (≥0.6 to ≤5 Bethesda Unit), defined as factor VIII activity measures (recovery) and/or bleed pattern indicating a lack of clinical response to factor VIII treatment.

Key exclusion criteria:

- Known or suspected hypersensitivity to trial product(s) or related products, defined as allergic reactions.
- Participation in another clinical trial within 1 month before screening (except participation in NN7170-4213).
- Any disorder, except for conditions associated with Haemophilia A which in the investigator's opinion might jeopardise patients' safety or compliance with the protocol.
- Currently receiving immune tolerance induction treatment with a factor VIII containing product other than turoctocog alfa.

Assessments:

The key assessments are:

- Changes in factor VIII inhibitor levels will be monitored throughout the trial.
- Safety (adverse events and clinical safety evaluation).
- Incremental recovery will be calculated throughout the trial.

Trial product(s):

- turoctocog alfa 2000 IU/vial for intravenous administration.
  turoctocog alfa will be supplied as a freeze-dried powder to be reconstituted with sodium chloride solution for injection.
- Sodium Chloride, 10 mL (0.9% w/v).

Investigational medicinal products:

- Test product: turoctocog alfa 2000 IU/vial.

2 Flow chart

Trial Periods	Screen	Treatment				Stop/ Go	Treatment			End of treatment	Follow-up	Section
Visit number	1	2	3	4	5	6	7	8	9	10	11	
Timing of visit (Months)		0	3	6	9	12	15	18	21	24	25	
Visit window (Days)		0-180 after Visit 1[a]	± 14	± 14	± 14	± 14	± 14	± 14	±14	± 14	plus 14	
PATIENT RELATED INFO/ASSESSMENTS												
In/exclusion criteria	X											6.2
Criteria for premature discontinuation of trial product		X	X	X	X	X	X	X	X			6.4, 6.5
Concomitant illness	X											8.2.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	8.2.2
Informed consent	X											18.2
Body measurements		X				X						8.3.4
EFFICACY												
Bleeding episodes		X	X	X	X	X	X	X	X	X		8.3.1
Coagulation parameters[b]		X	X	X	X	X	X	X	X	X		8.5.2.2
FVIII recovery[c]		X	X	X	X	X	X	X	X	X		8.5.2.2
FVIII trough level[c,d]		X	X	X	X	X	X	X	X	X		8.5.2.2
FVIII inhibitor[d]		X	X	X	X	X	X	X	X	X	X	8.5.2.1
SAFETY												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	12
ECG	X											8.4.2.1
Physical examination	X										X	8.4.2.2
Vital signs	X	X				X					X	8.4.2.3
Antibodies[d,e]		X	X	X	X	X	X	X	X	X	X	8.5.4, 8.5.4.1
TRIAL MATERIAL												
Administration of trial product		X	X	X	X	X	X	X	X	X		
Drug accountability			X	X	X	X	X	X	X	X		9.4
REMINDERS												
End of trial											X	
Affirmation statement											X	

Drug preparation and dispensing training		X										
Direction for use hand-out		X										

Footer	Description
X[a]	End of Trial visit of NN7170-4213 (visit 4 in part A or visit 10 in part B) can be the same as visit 1 (screening) in NN7170-4345. Visit 1 and 2 can take place on the same day.
X[b]	Includes only Lupus anticoagulant.
X[c]	Incremental recovery will be calculated based on FVIII recovery and FVIII trough level.
X[d]	Blood samples should be taken before dosing.
X[e]	Appendix A should be followed for handling of antibody blood samples.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (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 Haemophilia

Haemophilia A is a rare congenital bleeding disorder that manifest as abnormal bleeding tendency due to deficiency in coagulation factor VIII (FVIII). Haemophilia A has an incidence of approximately 1 in 5,000 male births[3]. Currently, it is recommended to treat haemophilia with coagulation factor replacement therapy; either on demand (OD) treatment of bleeding episodes or regular prophylaxis (PPX) for prevention of bleeds[4]. The factor replacement therapy is administered as intravenous (i.v.) injections of the deficient clotting factor. Regular PPX has increasingly become preferred over OD treatment in order to prevent progressive destructive joint damage, which is one of the most significant late stage effects of repeated joint bleeds potentially progressing into crippling disability, chronic pain, and functional limitations severely impairing quality of life[5, 6].

The most serious complication of factor replacement therapy is development of inhibitory antibodies (inhibitors) compromising or completely eliminating the effect of factor replacement therapy. This complication occurs in about 30% of patients with severe haemophilia A[7].

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

3.1.2 Subcutaneous turoctocog alfa pegol (SC N8-GP)

turoctocog alfa pegol (N8-GP) is a long-acting recombinant factor eight (rFVIII) compound currently in clinical development for i.v. treatment of haemophilia A (NN7088; pathfinder™ clinical programme). In non-human primates, N8-GP has a significantly increased bioavailability in comparison to rFVIII after subcutaneous (s.c.) administration, indicating that FVIII activity levels suitable for prophylactic treatment may be obtainable also in humans. No safety signal in terms of increased incidence has been observed in the N8-GP i.v. programme.

An isotonic and close to neutral pH formulation of N8-GP has been developed for s.c. administration (SC N8-GP) and it could provide clinically relevant benefit of increased convenience in regular prophylaxis for patients with haemophilia A, while at the same time

maintaining a sufficient average FVIII activity level comparable to or above the trough level achieved with i.v. FVIII treatment.

The purpose of the NN7170-4213 trial is to evaluate safety including immunogenicity (anti-drug antibody development), local tolerability, pharmacokinetics (PK), and preliminary efficacy of SC N8-GP used as regular prophylaxis in previously treated patients (PTPs) with severe haemophilia A. The NN7170-4213 trial is the first clinical trial with SC N8-GP, and thus follows a cautious approach, starting with single dose exposure of ascending dose levels with safety assessments between dose levels prior to multiple dose exposure.

3.1.3 Immune Tolerance Induction

Formation of neutralising antibodies (inhibitors) against FVIII is a known complication in the management of individuals with haemophilia A. The risk of inhibitor formation varies depending on patient population. In PTPs the cumulative risk of inhibitor formation is 2-3 per 1000 patients/ year whereas in previously untreated patients (PUPs) the risk is around 30%[7]. Inhibitors in haemophilia A are usually IgG immunoglobulins directed against the FVIII pro-coagulant activity, which are quantified in Bethesda Units (BU). Inhibitor development is a serious complication for patients with haemophilia A due to the increased risk of uncontrolled bleeding and therefor an increased morbidity and mortality. Additionally, patients with inhibitors experience a decrease in quality of life and an increase in health related cost of treatment compared to haemophilia A patients without inhibitors[8]. s.c administration of therapeutic proteins (including N8-GP) may potentially have a higher immunogenicity compared to i.v. administration[9], and should a patient develop an inhibitor towards FVIII during NN7170-4213, immune tolerance induction (ITI) may be indicated. Should the FVIII activity measures (recovery) and/or bleed pattern indicate a lack of clinical response to treatment in patients with low titre inhibitor, the patient will be regarded as having a clinically relevant inhibitor.

ITI constitutes of regular administration of usually high doses of factor concentrate to haemophilia A patients with inhibitors. By repeated exposures, ITI treatment aims at inducing immunologic tolerance and hereby disappearance of the inhibitor and thereby making regular FVIII replacement therapy feasible. Various ITI treatment regimens exist with differences in dose, frequency and with or without use of immunosuppression. Bleeding episodes in patients undergoing ITI and in chronic inhibitor patients are usually treated with “bypassing agents” e.g. recombinant activated factor VII (rVIIa) or plasma derived activated prothrombin complex concentrate[4].

The International Immune Tolerance study compared a high dose FVIII regimen (200 units/kg/day) with a low dose regimen (50 units/kg/3 times per week) and found that the overall success rate did not differ between the two study arms[10]. However, they showed that time to achieve defined success of ITI was significantly shorter in the high-dose regimen and that

patients in the low-dose arm experienced more bleeds compared to patients in the high-dose treatment arm.

ITI therapy is the first-choice approach in patients with high titre FVIII inhibitors, and the only proven strategy for eradicating FVIII inhibitors[11].

3.2 Rationale for the trial

The purpose of this exploratory trial is to provide ITI treatment using turocotocog alfa and to evaluate safety and efficacy of ITI treatment in patient(s) who have developed neutralising antibodies (inhibitors) against FVIII, after exposure to SC N8-GP in the NN7170-4213 trial.

ITI treatment is not an authorised indication for turoctocog alfa, therefore it is considered as investigational use, and the ITI treatment will for that reason be conducted in the setting of a separate exploratory trial.

With current knowledge, the benefit/risk ratio for using turoctocog alfa for ITI treatment is expected to be favourable.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary Objective

- To evaluate safety of ITI treatment with turoctocog alfa in patients who have developed neutralising antibodies against FVIII after exposure to SC N8-GP during participation in NN7170-4213.

4.1.2 Secondary Objective

- To evaluate efficacy of ITI treatment with turoctocog alfa.

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Number of adverse events during ITI treatment with turoctocog alfa.

4.2.2 Secondary endpoints

- Response to FVIII ITI treatment (success, partial success, failure, other) within a maximum ITI treatment duration of 24 months.

ITI treatment response categories are defined as patients who fulfil the following criteria:

- Success (all criteria need to be fulfilled):
  - Undetectable inhibitor titre <0.6 BU (or lower limit of quantification (LLoQ) if above 0.6 BU).
  - Normalised FVIII *in vivo* recovery, defined as ≥ 0.013 (IU/ml)/(IU/kg) (66% of expected incremental recovery).
  - turoctocog alfa half-life ≥ 7 hours (based on FVIII activity) after 72-hrs treatment-free washout period[1].

- Partial success (all criteria need to be fulfilled):
  - Inhibitor titre ≤5 BU.
  - Clinical effect of turoctocog alfa therapy as judged by the investigator.

- Failure (one criterion need to be fulfilled):
  - Failure to attain defined success or partial success after 24 months of ITI treatment with turoctocog alfa.
  - Decrease in inhibitor titre after 12 months of ITI treatment <20% compared to peak titre.

- Other:
    - Patients not fulfilling the above criteria e.g. early withdrawal from ITI treatment, lack of adherence to recommended ITI protocol etc.

[1]If turoctocog alfa half-life is not calculated, the success criteria is achieved if the patient fulfils the first two criteria.

5 Trial design

5.1 Type of trial

The trial is a single arm, open-label, interventional trial. In this trial, PTPs with haemophilia A, who have developed clinically relevant inhibitors during the NN7170-4213 trial, will be offered ITI treatment with turoctocog alfa.

The trial duration for a single patient will be maximum 31 months (visit 1 to visit 11) with a maximum treatment period of 24 months. During treatment period, patients will be called for visits to the clinic every 3rd month (Figure 5–1). After approximately 12 months treatment, a stop/go visit (visit 6) will take place where ITI treatment response will be evaluated based on the inhibitor titre.

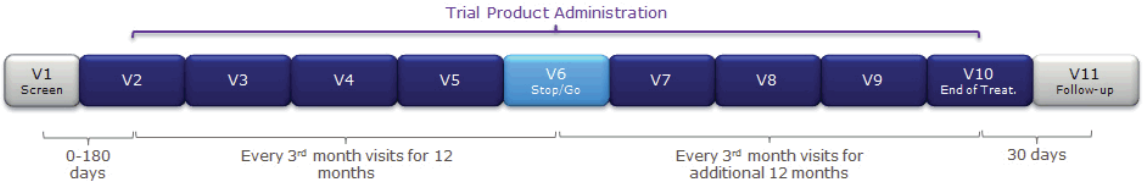


Figure 5–1 Trial overview

Each box represents one visit. The Stop/Go visit taking place after 12 months of ITI treatment with turoctocog alfa is represented by the light blue box (visit 6).

5.2 Rationale for trial design

The concept of this trial design is to follow local clinical practice for offering and monitoring ITI treatment.

5.3 Treatment of patients

All patients entering this trial will receive the same trial product: turoctocog alfa for i.v. administration.

ITI dosing will be decided at the investigators discretion in accordance with local practice. However, a maximum dose of 200 IU/kg daily is defined. The trial product should be administered by the patient or patient's caregiver between the scheduled visits.

Besides the 11 planned visits, monitoring and evaluation of ITI treatment response can be done during ITI response visits at the investigators discretion (see Section 8.1.7). The ITI treatment response visits can be done at any time during the trial.

Bleeding episodes that occur during the trial can be treated with FVIII or bypassing agents according to local practice (see Section 8.3.2).

5.4 Treatment after discontinuation of trial product

When discontinuing trial product, either at the scheduled end of treatment (EOT) visit or if trial product is discontinued prematurely according to discontinuation criteria 1 or 2 (see section 6.4), the patient can be switched to a suitable marketed product at the discretion of the investigator.

Upon successful ITI treatment in accordance with the outlined criteria (see Section 4.2.2), the patient will leave the trial. The patients may then be switched to a suitable marketed FVIII product at the discretion of the investigator.

5.5 Rationale for treatment

The key rationale for using turoctocog alfa for ITI treatment in this trial, is the long term safety record and the fact that turoctocog alfa has the same protein backbone as SC N8-GP which is based on the approved Novo Nordisk product NovoEight® (active substance, turoctocog alfa).

Furthermore, a newly published article has presented the first published case on the use of turoctocog alfa for ITI treatment where a rapid success of ITI treatment was found even though the inhibitor was elicited by a plasma derived FVIII product[12].

Due to the s.c. route of administration, SC N8-GP is not considered a feasible choice for ITI treatment where high plasma concentrations are targeted. Moreover, N8-GP for i.v. use is currently undergoing investigation (including use for ITI in PUP's) in an ongoing Novo Nordisk development programme, and the results are not yet available.

The dose and the dosing regimen will be chosen at the investigators discretion in accordance with local practice.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: Maximum 6, the number of patients participating in this trial depends on whether any patients participating in NN7170-4213 develop FVIII inhibitors.

Number of patients planned to be started on trial product(s): Maximum 6, the number of patients participating in this trial depends on whether any patients participating in NN7170-4213 develop FVIII inhibitors.

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. Previous participation in the trial NN7170-4213 (male, age ≥ 18 years (part A) and age ≥ 12 years (part B)).
3. Development of a confirmed high titre neutralising antibody towards FVIII (>5 Bethesda Unit) after exposure to subcutaneous turoctocog alfa pegol in the NN7170-4213 trial or development of a confirmed clinically relevant low titre inhibitor (≥0.6 to ≤5 Bethesda Unit), defined as FVIII activity measures (recovery) and/or bleed pattern indicating a lack of clinical response to FVIII treatment.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products, defined as allergic reactions.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Participation in another clinical trial within 1 month before screening (except participation in NN7170-4213).
4. 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.
5. Currently receiving immune tolerance induction treatment with a FVIII containing product other than turoctocog alfa.

6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

The 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.

See Section 8.1 for procedures to be performed for patients discontinuing trial product prematurely.

6.5 Withdrawal from trial

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

See Section 8.1 for procedures to be performed for patient's withdrawing consent.

6.6 Rationale for trial population

The rationale is to include patients who have developed inhibitors in the SC N8-GP trial (NN7170-4213) in order to offer and evaluate ITI treatment.

The inclusion and exclusion criteria reflect that only patients who develop an inhibitor during participation in the NN7170-4213 trial are eligible for participating in this trial.

7 Milestones

Planned duration of recruitment period (first patient first visit (FPFV) – last patient first visit (LPLV): 51 months.

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

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[13], it will also be disclosed according to other applicable requirements such as those of the International Comm ittee of Medical Journal Editors (ICMJE)[14], the Food and Drug Administration Amendment Act (FDAAA)[15] European Commission Requirements[16-18] 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.

8 Methods and assessments

8.1 Visit procedures

The following sessions describe the assessments and procedures (see Section 2) and outline of visit procedures (see Figure 8–1).

Informed consent must be obtained before any trial related activity, see section 18.2.

A screening session will be completed at visit 1. At the screening, patients will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Patients should be instructed to return the card to the investigator at the last trial visit, or to destroy the card after the last visit.

The investigator must keep a patient screening log, a patient identification code list and a patient enrolment log. The patient screening log and patient enrolment log may be combined into one log. Only patients who have signed the informed consent form should be included in the logs.

Each patient entering this trial will keep the unique 6-digit subject number from the trial NN7170-4213 at the time point when FVIII inhibitor development was confirmed (part A or part B from NN7170-4213). This unique 6-digit subject number will remain the same throughout the trial.

An unscheduled visit can be performed at any time during the trial at the discretion of the investigator. The unscheduled visit must be documented in the case report form (CRF).

Screening failures: For screening failures the following must be completed in the screening failure form in the CRF:

- Date of screening visit
- Date of informed consent
- Demographics (sex, date of birth and race)
- Violated inclusion/exclusion criteria
- Screening failure form
- SAE

Follow-up on SAEs must be carried out according to Section 12.

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 according to discontinuation criteria 1 and 2 (see Section 6.4), the investigator must undertake procedures similar to those for visit 10 as soon as possible after discontinuation of trial product. In

addition, the follow up visit should be performed approximately 30 days after discontinuation of trial product.

The primary reason for premature discontinuation of trial product must be specified in the end-of-treatment form in the CRF and final drug accountability must be performed. The affirmation statement in the CRF must be signed.

Withdrawal from trial: If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for visit 10 as soon as possible after discontinuation of trial product. If patient agrees, follow-up visit should be performed approximately 30 days after discontinuation of trial product.

The end-of-trial form must be completed, and final drug accountability must be performed even if the patient is not able to come to the trial site. The affirmation statement 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 CRF.

Data review: Review of laboratory reports etc. must be documented either on the documents or in the patient's medical record.

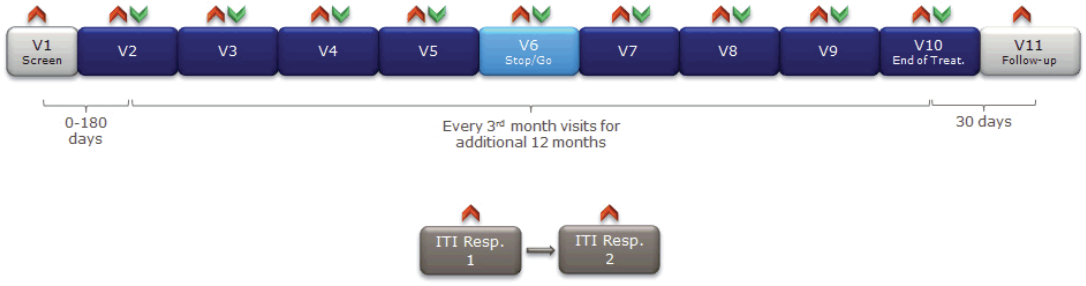


Figure 8–1 Outline of visit procedures
Each box represents one visit. The light-blue box (visit 6) represents the Stop/Go visit taking place after 12 months of ITI treatment with turoctocog alfa. Upright (red) arrow represents blood sampling and downright (green) arrow represents trial product administration. ITI response visits (ITI Resp. 1 and ITI Resp. 2) can be performed any time during the trial, if deemed relevant by the investigator.

8.1.1 Visit 1: Screening

Visit 1 is a screening visit to assess the eligibility of patients for the trial and should be documented in the CRF. EOT visit in the NN7170-4213 trial can be the same as visit 1 (screening) in this trial.

For more detailed assessment and procedures that should take place during this visit, see flow chart in Section 2.

The following must be recorded in the CRF:

- Patient related information/assessments, and safety results according to flowchart (see Section 2).

Training and reminders

- Trial card dispensing.
- The patient should be reminded to return for the next planned visit.

8.1.2 Visit 2: Trial product administration

Visit 2 is the first treatment visit involving a single administration of i.v. turoctocog alfa in the ITI treatment regimen and should be documented in the CRF. Visit 2, if not combined with visit 1, should preferably take place approximately 14 days after the screening visit (visit 1), and can at the investigators discretion take place up to, but no later than, 180 days after the screening visit. Direction for use should be handed out and documented.

For more detailed assessment and procedures that should take place during this visit, see flow chart in Section 2.

Trial product administration (dosing)
Patients will receive a dose of i.v. turoctocog alfa. The trial product will be administered by site staff or the patient/caregiver, as preferable during the visit.
The actual dose level will be calculated and provided by the investigator.

The following must be recorded in the CRF:

- Trial product dispensed.
- Prescribed dose according to investigators discretion and local practice.
- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).
- Incremental recovery calculation (see Section 8.3.3).

Training and reminders

- Dispensing of Direction for Use.
- Training in preparing and dispensing the drug.
- The patient should be reminded to return for the next planned visit.
- Patients should be reminded to bring all used and unused trial product back to the site for the next visit.

8.1.3 Visit 3, 4 and 5: Dosing and treatment effect evaluation

Visit 3, 4 and 5 are treatment visits and should take place approximately 3, 6 and 9 months after trial product administration at visit 2. All three visits should be documented in the CRF. Visit 3, 4 and 5 involve blood sampling for evaluation of treatment effect. Drug dispensing will be performed at these visits.

For more detailed assessment and procedures that should take place during this visit, see flow chart in Section 2.

Trial product administration (dosing)
Patients will receive a dose of i.v. turoctocog alfa during visit 3, 4 and 5. The trial product will be administered by site staff or the patient/caregiver, as preferable.
The actual dose level will be calculated and provided by the investigator.

The following must be recorded in the CRF:

- Trial product dispensed and drug accountability (see Section 9.4).
- Prescribed dose according to investigators discretion and local practice.
- If the prescribed dose has been followed in between the scheduled visits.
- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).
- Incremental recovery calculation (see Section 8.3.3).

Training and reminders

- The patient should be reminded to return for the next planned visit.
- At visit 5, patient should be reminded that visit 6 will be a stop/go visit where ITI treatment response will be evaluated.
- Patients should be reminded to bring all used and unused trial product back to the site for the next visit.

8.1.4 Visit 6: Stop/Go decision visit

Visit 6 should take place approximately 12 months after trial product administration at visit 2 and should be documented in the CRF. Visit 6 is a stop/go visit involving evaluation of ITI treatment response based on inhibitor titre.

For more detailed assessment and procedures that should take place during this visit, see flow chart in Section 2.

If the patient is still inhibitor positive after 12 months, but the decline from peak titre level is ≥20%, ITI treatment may be continued for a total maximum period of 24 months.

If the decline from peak titre level is <20%, a confirmatory inhibitor test must be performed at an unscheduled visit taking place approximately 1 month after visit 6. If the inhibitor titre at the unscheduled visit has declined < 20% from peak titre, the patient will continue to visit 10 as soon as possible and the follow-up visit approximately 30 days later.

Trial product administration (dosing)
Patients will receive a dose of i.v. turoctocog alfa during the planned visit. The trial product will be administered by site staff or the patient/caregiver, as preferable.
The actual dose level will be calculated and provided by the investigator.

The following must be recorded in the CRF:

- Trial product dispensed and drug accountability (see Section 9.4).
- Prescribed dose according to investigators discretion and local practice.
- If the prescribed dose has been followed in between the scheduled visits.
- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).
- Incremental recovery calculation (see Section 8.3.3).

Training and reminders

- The patient should be reminded to return for the next planned visit.
- Patients should be reminded to bring all used and unused trial product back to the site for the next visit.

8.1.5 Visit 7, 8 and 9: Dosing and treatment effect evaluation

Visit 7, 8 and 9 are treatment visits and should take place approximately 15, 18 and 21 months after trial product administration at visit 2. All three visits should be documented in the CRF. Drug dispensing will be performed at these visits.

For more detailed assessment and procedures that should take place during this visit, see flow chart in Section 2.

Trial product administration (dosing)
Patients will receive a dose of i.v. turoctocog alfa. The trial product will be administered by site staff or the patient/caregiver, as preferable.
The actual dose level will be calculated and provided by the investigator.

The following must be recorded in the CRF:

- Trial product dispensed and drug accountability (see Section 9.4).
- Prescribed dose according to investigators discretion and local practice.
- If the prescribed dose has been followed in between the scheduled visits.
- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).
- Incremental recovery calculation (see Section 8.3.3).

Training and reminders

- The patient should be reminded to return for the next planned visit.
- At visit 9, patients should be reminded that visit 10 will be the EOT visit.
- Patients should be reminded to bring all used and unused trial product back to the site for the next visit.

8.1.6 Visit 10 and 11: End of Treatment and follow-up visit

Visit 10 defines EOT and should take place approximately 24 months after trial product administration at visit 2 or earlier if a patient is withdrawn, premature discontinued treatment with trial drug or achieved ITI success. The patient will continue in the trial for additional 30 days in order to complete a follow up visit for monitoring adverse events. Both visit 10 and the follow up visit should be documented in the CRF.

For more detailed assessment and procedures that should take place during these visits, see flow chart in Section 2.

Trial product administration (dosing)
Patients will receive a dose of i.v. turoctocog alfa at visit 10. The trial product will be administered by site staff or the patient/caregiver, as preferable.
The actual dose level will be calculated and provided by the investigator.

The following must be recorded in the CRF at visit 10:

- Drug accountability should be performed (see Section 9.4).
- If the prescribed dose has been followed in between the scheduled visits.

- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).
- Incremental recovery calculation (see Section 8.3.3).
- Clinical effect of turoctocog alfa therapy as judged by the investigator.
- Rating of response to ITI treatment (success, partial success, failure or other).

The following must be recorded in the CRF at follow-up visit:

- If the prescribed dose has been followed in between the scheduled visits.
- Patient related information/assessments, safety and laboratory sample results according to flowchart (see Section 2).

8.1.7 ITI response visit

If the investigator suspects ITI treatment success at any time during the trial, the patient should be called in for ITI response visits. If ITI treatment success is confirmed, the patient must attend a second confirmatory ITI response visit. If the success criteria are not met, the patient will continue with ITI treatment. The details of any ITI response visit will be decided for each individual patient according to local practice and at the discretion of the investigator. ITI response visits should be preceded by a 72-hour treatment-free washout period prior to the visit to avoid that any residual FVIII impact on inhibitor analysis. The 72-hour treatment-free washout should be recorded in the CRF.

8.1.7.1 First ITI response visit

During the first ITI response visit, the following assessments must be performed and recorded in the CRF:

- Blood sampling (trough, recovery and inhibitor).
- Incremental recovery calculations (see Section 8.3.3).
- PK session to determine turoctocog alfa, half-life, (if deemed relevant by the investigator (see Section 8.3.5.1)). The recommended dose of turoctocog alfa during the PK session is 50 IU/Kg.

8.1.7.2 Second ITI response visit

The second ITI response visit should preferably take place within 14 days after the first ITI response visit. The same parameters as for the first ITI response visit will be tested as a confirmatory test during the second ITI response visit. If the success criteria are achieved, ITI treatment will be stopped and the patient will attend visit 10 as soon as possible. The follow-up visit should be performed approximately 30 days after discontinuation of trial product. The following assessments must be performed and recorded in the CRF:

- Blood sampling (trough, recovery and inhibitor).
- Incremental recovery calculations (see Section 8.3.3).
- PK session to determine turoctocog alfa, half-life, (if deemed relevant by the investigator (see Section 8.3.5.1)) The recommended dose of turoctocog alfa during the PK session is 50 IU/Kg.

8.1.8 Unscheduled visit

If the patient is still inhibitor positive after 12 months of ITI treatment (visit 6), a confirmatory FVIII inhibitor peak titre decline level should be measured during unscheduled visit and recorded in the CRF.

If the patient attends the clinic outside the visit schedule, the unscheduled visit form in the CRF should be completed if trial related. The unscheduled visit form in the CRF should not be completed if the patient attends the clinic only to obtain trial supplies or for re-scheduling visits. The investigator may at any time during the trial perform an unscheduled visit.

The investigator may at any time during the trial perform inhibitor analysis at an unscheduled visit.

8.2 Patient related information/assessments

8.2.1 Concomitant illness other than haemophilia

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

The information collected for concomitant illness should include diagnosis, date of onset and date of resolution or continuation, 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. If the change influences the patient's eligibility to continue in the trial then the monitor must be informed.

8.2.2 Concomitant medication

A **concomitant medication** is any medication, other than the trial product which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at visit 1. 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 continuation. The dose should also be collected if available.

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.

Concomitant medication also includes use of haemostatic medication other than trial product used to treat or prevent a bleed during the trial.

8.3 Efficacy assessments

8.3.1 FVIII inhibitors

The patient will be assessed for FVIII inhibitors before dosing in all visits during the treatment period, as well as during the safety follow-up visit.

Blood samples for measurement of inhibitors towards FVIII will be analysed. All analyses for inhibitors will be performed by the local laboratory.

An inhibitor test with a result <0.6 BU (or LLoQ if above 0.6 BU) will be considered a negative inhibitor test. Once the first negative inhibitor results are available, the patient must attend ITI response visits as soon as possible. A patient is verified inhibitor negative (<0.6 or LLoQ if above 0.6 BU) if two consecutive samples are negative after 72 hour washout-out. A patient having an initial negative inhibitor test and a second positive inhibitor test will be regarded as inhibitor positive and can continue in the trial.

Upon successful ITI treatment (see Section 4.2.2) the patient will leave the trial after attending the two ITI response visits, visit 10, and follow-up visit. The patients may be switched to a suitable marketed FVIII product at the discretion of the investigator.

All per protocol inhibitor analyses will be performed by the local laboratory, and only these results will be used in the trial data analysis.

8.3.2 Bleeding episodes

Bleeding episodes that occur during the trial can be treated with trial product (turoctocog alfa), FVIII other than trial product, or bypassing agents (recombinant FVIIa or Activated prothrombin complex concentrates) with a treatment regimen according to local practice.

Use of turoctocog alfa for treatment of bleeds is mainly indicated in relation to final stage of a successful ITI treatment, when the inhibitor is almost eradicated and the patient experiences clinical response to FVIII treatment. It is therefore expected that only a minor fraction of the total turoctocog alfa consumption for each patient will be used for treatment of bleeds.

Bleeding episodes will be recorded in the CRF during planned visits. The following must be recorded for all periods in between scheduled visits:

- Number of bleeds requiring treatment since last visit.
- Treatment evaluation of the haemostatic effect for bleeding episodes treated with factor product (effective or ineffective), as judged by the investigator.

Only report the bleeding episode as an AE/SAE if fatal, life threatening or evaluated as related to trial product.

8.3.3 Incremental Recovery

Incremental recovery should be calculated at every scheduled visit, including ITI response visit (see Section 8.1.7). The investigator should calculate the incremental recovery based on FVIII recovery 30 ± 15 min post dose, FVIII trough level, administered dose and patient weight, see Section 17.4.1.3. All the above assessments must be recorded in the CRF.

8.3.4 Body measurements

The following will be recorded in the CRF:

- Weight wearing light clothing only (whole Kg).

8.3.5 Other efficacy assessments

8.3.5.1 Pharmacokinetic assessments

PK sessions can be performed during the ITI response visits (see Section 8.1.7), if deemed relevant by the investigator, and will be based on FVIII recovery and FVIII trough level. The half-life should be calculated by the investigator (see Section 17.4.1.2) and recorded in the CRF.

Guidance for PK assessments
As a recommendation; In addition to a pre-dose sample and a recovery sample, a minimum of three PK samples (LLoQ) should be taken between 6-28 hours after administration of turoctocog alfa for half-life determination. Further, there must be at least 20 hours between the first and the last (of minimum 3) PK samples used for half-life calculation (see Figure 8–2 for guidance).

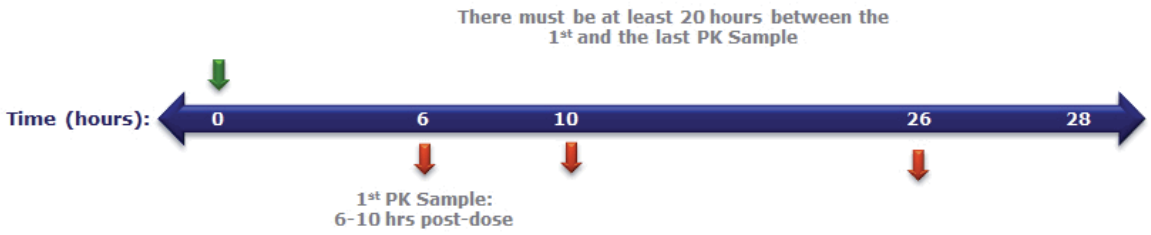


Figure 8–2 Example of PK assessment to be used as guidance
Administration of turoctocog alfa is indicated by the green arrow (at 0 hours) and blood sampling for PK assessments is indicated by red arrows (at 6, 10 and 26 hours).

The following must be recorded in the CRF for PK session:

- Timing of PK samples.
- FVIII activity values.
- Dose used for PK session.

8.4 Safety assessments

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 CRF in addition to the AE form:

- Trial product(s) involved.
- Classification of medication error.
- Whether the patient experienced 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.

8.4.1.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the CRF in addition to the AE form. AEs requiring additional data collection are hypersensitivity reactions (see section 12.5).

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

8.4.2 Other safety assessments

8.4.2.1 Electrocardiogram

In the CRF, the investigator must evaluate the electrocardiogram (ECG) and record the outcome as:

- Normal or abnormal
- If abnormal the investigator must:
    - Specify the abnormality (free text in CRF).
    - Record if the result is clinically significant (Yes/No).
    - If clinically significant and observed at screening: record as concomitant illness, see Section 8.2.1.

- If clinically significant and observed after screening: report a AE/SAE, see Section 12.

8.4.2.2 Physical examination

In the CRF, the physical examinations will be performed according to local procedure and should include:

- General appearance.
- Head, ears, eyes, nose, throat, neck.
- Respiratory system.
- Gastrointestinal System including mouth.
- Cardiovascular system.
- Genito-urinary system.
- Musculoskeletal system.
- Central and peripheral nervous system.
- Skin.
- Lymph node palpation.

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

- Normal or abnormal
- If abnormal the investigator must:
  - Specify the abnormality (free text in CRF).
  - Record if the result is clinically significant (Yes/No).
  - If clinically significant and observed at screening: record as concomitant illness, see Section 8.2.1.
  - If clinically significant and observed after screening: report a AE/SAE, see Section 12.

8.4.2.3 Vital signs

Before measurement of vital signs the patient should preferably rest comfortably for at least three minutes and all measurements should, if possible, be performed using the same method and position (e.g. sitting) throughout the trial for each individual patient.

Vitals signs include assessment of:

- Body temperature, ear.
- Systolic blood pressure, sitting (mmHg).
- Diastolic blood pressure, sitting (mmHg).
- Pulse, sitting (beats/min).
- Respiratory rate (breath/min).

Measurements will be reported in the CRF.

Clinically significant findings as judged by the investigator present at screening must be documented as concomitant illness and during the trial as AEs.

8.5 Laboratory assessments

FVIII inhibitor analyses (see Section 8.3.1) and other laboratory parameters deemed relevant by the investigator will be performed by local laboratory in accordance with local practice. Further, in order to characterise the underlying immunogenicity, antibodies towards N8-GP will be analysed in a specialised laboratory (see Section 8.5.4.2).

Antibody samples will be stored as described in Section 24.2.

8.5.1 Blood sampling volume

The total maximum volume of blood to be drawn for an individual patient during one visit is expected to be 20 ml, and should not exceed 1% of the total blood volume at one occasion or 3% within 28 days.

8.5.2 Local laboratory assessments

8.5.2.1 FVIII Inhibitor test

Assessments of FVIII inhibitor test will be done at the local laboratory as per standard practice at the participating site. Laboratory results from the local laboratory will be recorded in the CRF.

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

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

8.5.2.2 FVIII plasma activity and Coagulation parameters

FVIII plasma activity as well as coagulation parameters will be measured in local laboratories according to normal procedures.

The following FVIII plasma activity will be determined:

- FVIII recovery.
- FVIII trough level.

The following coagulation parameters will be determined:

- Lupus anticoagulant.

8.5.3 Specialised laboratory assessments

Analysis of antibody samples (see Section 8.5.4) will be analysed, if deemed relevant, by a specialised laboratory. If applicable, these antibody analyses will take place using the same appointed specialised laboratory as for the NN7170-4213 trial. The antibody analysis will take place at end-of-trial. The detailed description of the assay methods and the antibody results will be included in the antibody analysis report at the end of the study.

For description of procedures for obtaining biospecimens, storage, handling and disposition of biospecimens, see Section 24.2.

8.5.4 Laboratory assessments for safety

8.5.4.1 Antibody assessments

If applicable, antibody assessment will include samples for:

- Anti-PEG antibodies (see Section 8.5.4.2).
- Anti-HCP antibodies (see Section 8.5.4.2).
- N8-GP binding antibodies including immunoglobulin isotype analysis (see Section 8.5.4.2).

8.5.4.2 Antibodies

The underlying immunogenicity will, if applicable, be investigated by analysing for antibodies towards N8-GP, PEG and HCP. These analyses will be performed using validated antibody analysis and further antibody characterisation e.g. immunoglobulin isotyping may be performed if relevant. Antibodies (anti-N8-GP, anti-HCP, anti-PEG) will be analysed at the end of trial. If deemed relevant, i.e. due to an antibody relevant adverse event, or based on request from the safety committee, specific samples may be analysed during the trial.

Antibodies will be analysed for all planned visits (and unscheduled visit, if relevant). The analyses will be performed at the same specialised laboratory as for the NN7170-4213 trial.

For handling antibody blood sample at local lab, Appendix A should be followed. Samples should be shipped to the same Novo Nordisk A/S specialised laboratory as for the NN7170-4213 trial. The address of the specialised lab will be provided to you after study initiation of the trial.

8.5.4.3 Antibody Assessments in case of an Hypersensitivity/Anaphylactic reaction

In the event of a severe immediate hypersensitivity reaction to trial product, blood sampling will be collected and analysed according to investigators discretion and local guidelines.

8.6 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.

Treatment compliance:
In order to ensure that the patients have taken all doses as required according to investigators discretion and local guidance, full drug accountability on all used, partly used and unused vials must be performed in the CRF to document treatment compliance. The number of used and partly used vials should correspond to the expected amount of doses taken during the trial. The drug accountability must include both doses given at site and doses taken at home by the patient.

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.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Turoctocog alfa (investigational medicinal product)	2000 IU/vial	Powder for solution for injection	Intravenous injection	Single-use vial
Isotonic sodium chloride for injection 0.9% w/v, 10 mL	Not applicable	Solvent for solution for injection	Intravenous injection	Single-use vial

The trial products will be packed open labelled.

turoctocog alfa is supplied as a sterile freeze-dried powder for injection in single-use vials with a nominal content of 2000 IU/vial to be reconstituted with 4.3 mL isotonic sodium chloride for injection (0.9% w/v), see Table 9–1. After reconstitution, the 2000 IU/vial will contain 500 IU/mL of turoctocog alfa.

The reconstituted solution will be clear to slightly opalescent. The reconstituted solution must not be used if it does not appear clear to slightly opalescent.

After reconstitution, the appropriate volume of solution will be drawn from the vial into a syringe. The content of several vials of turoctocog alfa may be combined into one syringe. Turoctocog alfa must not be added to, or mixed with any other material.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13[19], local regulations and trial requirements.

Each trial site, with patients enrolled in this trial, will be supplied with sufficient trial products for the trial on an on-going basis.

The investigator must document that direction for use is given to the patient orally and in writing at the first dispensing visit (visit 2). The Direction for use (DFU) can be given to the patients 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 (Investigational medicinal product (IMP), test product)	Store in refrigerator (2°C – 8°C) Do not freeze 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.	For single use Protect from light Do not freeze	**For US only**: Use within 4 hours after reconstitution when stored at room temperature (below 86°F). **For all other countries that US:** Use within 4 hours after reconstitution when stored at room temperature (below 30 °C) or 24 hours when stored in refrigerator (2°C-8°C).
Isotonic sodium chloride 0.9% w/v	Store at 2°C – 30°C Protect from light Do not freeze	For single use	For single use

[a]The in-use time starts when the reconstitution procedure is initiated.
[b]At the clinical sites, the product must be stored in a refrigerator (2°C – 8°C). However, at the patients home the product can be stored at room temperature below 30°C for a single period up to 9 months.

The investigator must ensure that trial product is kept under proper storage conditions and 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 is the responsibility of the investigator and should be performed at vial level in the CRF. Drug accountability must also be performed for isotonic sodium chloride solvent vials used for reconstitution.

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.

9.5 Auxiliary supplies

Novo Nordisk will provide the following auxiliary supplies for this trial:

- DFUs.
- Trial injection kits (containing vial adapters, syringes for administration and butterfly-needles).

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

10 Interactive voice/web response system

Not applicable for this trial.

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: 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 concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the patient has signed the informed consent.
- Bleeding events and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AE/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 should always be reported as 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**
  - **Mild** – no or transient symptoms, no interference with the patient's daily activities.
  - **Moderate** – marked symptoms, moderate interference with the patients's daily activities.
  - **Severe** – considerable interference with the patients's daily activities; unacceptable.

- **Causality**
  Relationship between an AE and the relevant trial product(s):
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely** - The event is most likely related to aetiology other than the trial product.

- 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 sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with 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 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:
- Suspicion of transmission of infectious agents via the trial product
- Risk of liver injury defined as alanine aminotransferase or aspartate aminotransferase >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

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 Dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular.
- 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 8.4.1.1

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 AEs require the completion of specific event forms in the CRF:

- Hypersensitivity reaction.

For details, see Section 8.4.1.2.

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 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 CRF 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, either 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 should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a paper 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 should be signed when the event is resolved or at the end of the trial at the latest.

Timelines for initial reporting of AEs:

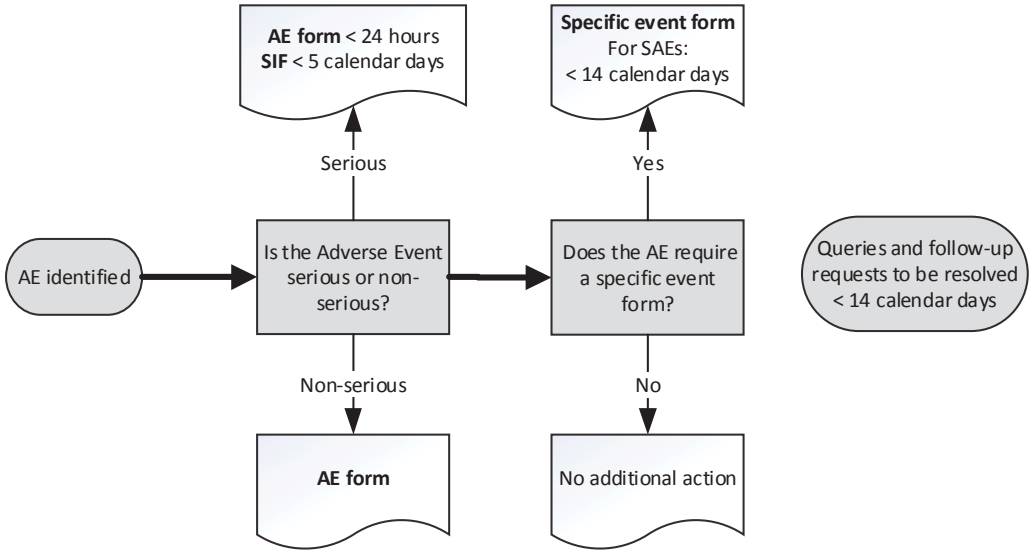
The investigator must complete the following forms in the CRF within the specified timelines:

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

For 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.

The paper forms or safety information form and specific event forms for AESIs must be forwarded to Novo Nordisk either by fax, e-mail or courier.

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

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 European Medicines Agency, 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 forward follow-up information as corrections to the original forms or by using a new form marked as follow-up.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with 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 should 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 for injection 0.9% w/v vial.
- 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 and/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 and forward the technical complaint form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, 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**.

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 should 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 blood pressure may occur. If

hypersensitivity reaction is suspected, further turoctocog alfa administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines prior to further treatment with turoctocog alfa

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

12.5.1 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

In this trial, the CRF will be paper-based.

CRFs will be provided by Novo Nordisk A/S. The activities for preparation of the CRFs will be under the direction of Novo Nordisk A/S.

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 signing the affirmation statement, the investigator confirms that the information in the CRF and related forms is complete and correct.

13.1 Corrections to case report forms

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

Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the patient has not yet been signed, any corrections must be approved by the investigator or her/his delegated staff. If the affirmation statement for the patient has already been signed, the investigator must approve any correction.

13.2 Case report form flow

The investigator must ensure that data is recorded in the CRF as soon as possible after the visit.

CRFs will be supplied on paper-sets including the required different coloured original and a copy. The original will be collected by the monitor. Once monitored, the CRFs are provided to Data Management. From this stage, the CRFs are not modified anymore and all requested modifications are traced on paper DCFs or MIDFs. One copy of the CRF will be retained at the site.

Results from central laboratory will be provided in a format which is loadable into the clinical database of the sponsor.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the CRFs are completed correctly and the protocol adhered to, to perform source data verification, monitor drug accountability and collect completed CRF pages. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site.

The monitor must be given direct access to all 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 trial, 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 CRF, except for the following data that may be recorded directly in the CRFs, and will be considered source data:

- Body measurements.
- Vital signs.
- Physical examination.
- ECG evaluation.

If source data is entered directly in a paper CRF, each data entry or clear series of data entry must be signed and dated separately by the trial staff making the entry.

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 signed laboratory reports are source data and should be archived at the trial site.

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

The monitor will ensure that the CRFs are completed and collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent.
- Screening failure reason.

Monitors will review the patient's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these.

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 patient and any biological material obtained from the patient will be identified by subject number and trial ID. 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

Novo Nordisk will be responsible for the statistical analysis.

No testing of statistical hypotheses will be performed. Evaluation of data will be based on descriptive statistics, i.e. summary tables and listings.

Generally, data will be presented according to whether they occur prior to ITI treatment (from Visit 1 to Visit 2), during ITI treatment with turoctocog alfa or after ITI treatment. End of ITI treatment is either defined as; the second ITI response visit at which successful ITI is confirmed and terminated or at Visit 10, if ITI is not terminated before a second ITI response visit.

Summaries will not be prepared if the trial only enrols 3 or fewer patients.

When calculating actual dose in IU/kg based on reported volume, the last measured body weight must be used.

17.1 Sample size calculation

No formal sample size calculations have been performed, since the number of patients in the trial depends on the number of patients developing inhibitors in the preceding NN7170-4213 trial that require ITI treatment. This number is expected to be low, but cannot otherwise be robustly predicted.

17.2 Definition of analysis sets

All patients initiating ITI treatment with turoctocog alfa will be included in the Safety Analysis Set (SAS), as well as the Full Analysis Set.

17.3 Primary endpoint

The primary endpoint is the number of adverse events during ITI treatment with turoctocog alfa.

AEs will be summarised by preferred term during ITI treatment (from visit 2), before ITI treatment, after ITI treatment as well as total AEs. Similar summaries will be presented by severity and causal relation to trial product.

In addition, listings of all AEs and SAEs will be provided with indication of which period they have occurred in.

17.4 Secondary endpoints

17.4.1 Supportive secondary endpoints

17.4.1.1 Secondary efficacy endpoints

As secondary efficacy endpoint, the trial defines response to ITI treatment (success, partial success, failure, other) within a maximum ITI treatment duration of 24 months.

The ITI treatment response categories referred in the endpoint are defined according to the following criteria:

- **Success** (all criteria need to be fulfilled):
  - Undetectable inhibitor titre < 0.6 BU (or LLoQ if above 0.6 BU).
  - Normalised FVIII in vivo recovery, defined as ≥ 0.013 (IU/ml)/(IU/kg) (66% of expected incremental recovery).
  - turoctocog alfa half-life ≥ 7 hours (based on FVIII activity) after 72-hrs treatment-free washout period[1].

- **Partial success** (all criteria need to be fulfilled):
  - Inhibitor titre ≤5 BU.
  - Clinical response to turoctocog alfa therapy as judged by the investigator.

- **Failure** (one criterion need to be fulfilled):
  - Failure to attain defined success or partial success after 24 months of ITI treatment with turoctocog alfa.
  - Decrease in inhibitor titre after 12 months of ITI treatment <20% compared to peak titre.

- **Other** (one criterion needs to be achieved):
  - Patients not fulfilling the above criteria e.g. early withdrawal from ITI treatment, lack of adherence to recommended ITI protocol etc.

[1]If turoctocog alfa half-life is not calculated, the success criteria is achieved if the patient fulfils the first two criteria.

17.4.1.2 Pharmacokinetic endpoints

It is up to the discretion of the investigator to decide whether actual PK sampling session will be conducted in order to calculate the half-life as supplement in the evaluation of inhibitor status and response to ITI treatment. PK parameters are therefore optional and not defined as actual endpoints. The PK parameters are described in the subsequent section 17.4.1.3.

17.4.1.3 Pharmacokinetic assessments

FVIII trough level and FVIII recovery will be summarised and listed. Incremental recovery is calculated as the baseline subtracted FVIII activity post dosing (IU/ml) divided by the actual dose (IU/kg).

If blood sampling is conducted as specifies in Section 8.3.5.1, half-life should be calculated as $t_{½} = \ln(2) / \lambda_z$, where λ_z is the elimination rate (slope) estimated using linear regression on the logarithm of the collected minimum 3 values larger than LLoQ as described in section 8.3.5.1. The time-points and FVIII activity values used for calculating $t_{½}$ should be recorded in the CRF, see Section 8.1.7.

17.5 Other assessments

A number of assessments not specified as endpoints are collected during the trial, covering the following:

- Concomitant medication.
- Bleeding episodes.
- Lupus anticoagulant.
- Antibodies.

The following data collected in trial NN7170-4213 will be transferred and presented in this trial (NN7170-4345).

- Demography.
- Medical history.
- Haemophilia treatment and bleed history.
- Details of Haemophilia.

The listed assessments will be summarized by trial period (before, during and after ITI treatment) as well as listed. Bleeding episodes are reported by the patient at the planned visits to the clinic, see Section 8.3.1.

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

The key arguments for offering turoctocog alfa for ITI is its long term safety record and because turoctocog alfa has the same protein backbone as SC N8-GP that is based on the approved Novo Nordisk product NovoEight® (active substance, turoctocog alfa). Further, a newer article has presented the first published case on the use of turoctocog alfa for ITI treatment, and found a rapid success of ITI treatment, this despite that the inhibitor was elicited by a plasma derived FVIII product[12]. So far no FVIII product has been approved for ITI treatment and therefor the risk profile for this mode of treatment is still not fully established. However; ITI therapy is the first-choice approach in patients with high responding FVIII inhibitors, and the only proven strategy for eradicating FVIII inhibitors[11]. It is expected that the risk/benefit profile of turoctocog alfa is similar to that of other FVIII contacting product currently used for ITI treatment.

The safety profile of turoctocog alfa is similar to that of other marketed rFVIII products, which has been confirmed in the completed clinical trials. No special clinical risks have been identified for turoctocog alfa. The risk of transmission of viral and other blood-borne diseases has been virtually eliminated as the product is produced by a serum-free process and using a 20 nm filtration step. As with any intravenous protein product allergic hypersensitivity reactions may occur.

It is evaluated that the potential benefits of turoctocog alfa for ITI treatment outweigh the recognised risks.

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 patient's LAR verbal and written information about the trial and the procedures involved in a form that the patient or the patient's LAR can read and understand. This includes the use of an impartial witness where required according to local requirements.

The patients or the patient's LAR must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the patient and/or the patient's LAR before any trial-related activity.

All minors under the age of 18 must sign an assent form. 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.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent 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 be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient and/or the patient's LAR in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

18.3 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 including follow up visits 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.

18.4 Information to patients during trial

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.

18.5 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 the trial is temporary halted, a substantial amendment will be submitted to the Regulatory Authorities to support a restart of the trial.

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, and the action(s) taken.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The importance of patient retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The patients will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of patient retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed and data is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

20 Audits and inspections

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

21 Critical documents

An Investigator Portal 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, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials.
- List of IRB/IEC members and/or constitution (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.
- 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.
- Insurance statement, if applicable.
- Financial disclosure form from investigator and sub-investigator(s).

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations of Financial Conflict of Interest.
- For US trial sites: U.S. Food and Drug Administration (FDA) form 1572 must be completed and signed by the investigator at each site.

FDA form 1572:

For US sites:

- Intended for US sites.
- Conducted under the IND.
- All US investigators, as described above, will sign FDA Form 1572.

For sites outside the US:

- Intended for participating sites outside of the US.
- Not conducted under the IND.
- All investigators outside of the US will not sign FDA form 1572.

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

If a local laboratory is used:

- Laboratory normal ranges.
- Laboratory certification, QA scheme or similar documentation.
- Laboratory assay methods (only non-standard assays) and/or analytical methods.

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 patient 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.

If this trial becomes a multicentre trial, depending on how many patients that develop inhibitors while participating in NN7170-4213 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[20].

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 patient to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[13].

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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[20] (sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publication(s) by investigator(s)

If this trial becomes a multicentre trial, depending on how many patients that develop inhibitors while participating in NN7170-4213 trial, then the following section will apply:

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.

Individual investigators will have their own research patients' data.

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

Antibody samples will be retained for later analysis for further characterisation of antibody responses towards drug, if deemed relevant or if required by health authorities or for safety reasons.

In the event that the collected blood samples will be used in the future, the investigator will become directly informed by Novo Nordisk about the results if the findings are deemed clinically relevant and analytically valid and quantifiable. Patient or parent(s) can contact the investigator if they wish to be informed about results derived from stored blood samples obtained from their own body.

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.

The samples will be stored after end of trial 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 antibody 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 com mencement 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, 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:

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBI Nr. 162/2013.

Only applicable for France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I,IX, Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical the research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research).

27 References

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Appendix A

NN7170-4345
Blood sampling for antibody analysis

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1 Sampling of blood for analysis

NB: The patient name must NOT be listed on shipped vials. The tubes should be marked with patient ID, visit ID and visit date.

Sampling: The blood sample should be collected in 2 x 4.5 mL tubes with 3.2% (0.109 M) sodium citrate.
The blood **must** be obtained and prepared for shipment as follows:

1. Draw blood into 4.5 mL vacutainer tubes, containing 3.2% (0.109 M) sodium citrate. Be sure to draw the full volume to ensure correct blood-to-anticoagulant ratio.
2. Invert the vacutainer tubes carefully 3-4 times if using BD vacutainer (blue top). Otherwise according to manufacture´s instructions.
3. Samples should be centrifuged immediately. This should be carried out at room temperature for 15 minutes at 1500 RCF (approximately 2000 g) for BD vacutainers (or refer to speed and times recommended by manufacturer). Do not use brake to stop centrifugation.
4. This will give three layers: (from top to bottom) plasma, leucocytes (buffy coat), erythrocytes.
5. Carefully aspirate the supernatant (plasma) at room temperature and transfer into 6 cryovials, each with minimum 0.6 mL separated plasma (e.g. Nunc with star foot). Take care not to disrupt the cell layer or transfer any cells.
6. Inspect plasma for turbidity. Turbid samples should be centrifuged and aspirated again to remove remaining insoluble matter.
7. The cryovials should immediately be stored at minus 20 °C and be stored on site until patient's last visit.
8. Ensure that the cryovials are adequately labelled with relevant information, including; Patient ID, Visit ID and Visit date.
9. After patients last visit, the samples should be sent to the same Novo Nordisk A/S specialised laboratory as for the NN7170-4213 trial. The address of the specialised lab will be provided to you after study initiation of the trial.

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

Protocol Amendment

no 1

to Protocol, version *1.0* dated *18 Nov 2016*

Trial ID: NN7170-4345

Evaluation of safety following Immune Tolerance Induction treatment with turoctocog alfa in patients with haemophilia A following inhibitor development in NN7170-4213 trial

Trial phase: 3b
Applicable to *all countries*

Table of Contents

1 Introduction including rationale for the protocol amendment

The rational for this amendment is to align with new internal procedures in Novo Nordisk. Summary of Product Characteristics will no longer be the source of the Reference Safety Information (RSI) for assessment of AE expectedness. Instead, we will use the Investigator Brochure (IB). Furthermore, the RSI is no longer specified in the protocol, but in the cover letter. A cover letter and the IB (Edition 9) are enclosed in this amendment application.

Continued, a small change has been done in the treatment of patient section, in order to allow investigators to treat the patients as deemed relevant and according to local guidelines.

In addition to the above changes, testing for non-neutralising antibodies will only be performed if deemed relevant or for safety reasons, e.g. in case of adverse events suspected of being related to antibodies. Patients enrolled in the trial already have confirmed neutralising antibodies (inhibitors) and these are being monitored in accordance with local standard of care. The patients receive immune tolerance inducing therapy (ITI) using marketed unmodified recombinant FVIII (NovoEight). Given the circumstances, there is limited value of additional antibody testing.

In this protocol amendment:

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

2 Changes

2.1 Section 5.3 Treatment of patients

…

ITI dosing will be decided at the investigators discretion in accordance with local practice. However, a maximum dose of 200 IU/kg daily is defined. ~~If deemed relevant by the investigator, patients can be switched from a higher dose to a lower dose while participating in this trial.~~ The trial product should be administered by the patient or patient's caregiver between the scheduled visits.

2.2 Section 8.5.3 Specialised laboratory assessments

Analysis of antibody samples (see Section 8.5.4) will be analysed*, if deemed relevant,* by a specialised laboratory. *If applicable, t*~~T~~hese antibody analyses will take place using the same appointed specialised laboratory as for the NN7170-4213 trial. The antibody analysis will take place at end-of-trial. The detailed description of the assay methods and the antibody results will be included in the antibody analysis report at the end of the study.

For description of procedures for obtaining biospecimens, storage, handling and disposition of biospecimens, see Section 24.2.

2.3 Section 8.5.4 Laboratory assessments for safety

2.3.1 Section 8.5.4.1 Antibody assessments

If applicable, a~~A~~ntibody assessment will include samples for:

- Anti-PEG antibodies (see Section 8.4.2.1).
- Anti-HCP antibodies (see Section 8.4.2.1).
- N8-GP binding antibodies including immunoglobulin isotype analysis (see Section 8.4.2.1).

2.3.2 Section 8.5.4.2 Antibodies

The underlying immunogenicity will*, if applicable,* be investigated by analysing for antibodies towards N8-GP, PEG and HCP…

2.4 Section 12.2 Reporting of adverse events

…

~~**Novo Nordisk assessment of AE expectedness:**~~

~~Novo Nordisk assessment of expectedness is performed according to the following reference documents: Summary of Product Characteristics for NovoEight®, current version.~~