Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03528551
Sponsor trial ID:	NN7088-4410
Official title of study:	Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A
Document date*:	18 June 2019

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

List of contents

Protocol

pathfinder8

Protocol title: Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Final protocol version 1.0 (13-Dec-2017) including:

- Final Substantial Amendment no 1 version 2.0, FR (10-Aug-2018)
- Final Substantial Amendment no 2 version 1.0, Global (18-Jun-2019).

Substance NNC0129-1003 (turoctocog alfa pegol)

Universal Trial Number: U1111-1202-2780

EUdraCT Number: 2017-003788-36

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3b

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1 Synopsis

Rationale:

The rationale for performing this trial is to allow the continued evaluation of the safety and efficacy of turoctocog alfa pegol in order to obtain additional data on long-term use. Introducing a twice or three times weekly prophylactic dosing regimen to the majority of patients is intended to show potential improvement in clinical outcomes by converting patients to a milder bleeding phenotype. Joint health and target joints will be assessed and evaluated at inclusion and at end of trial.

Objectives and endpoints:

Primary objective
To investigate the safety of turoctocog alfa pegol during continuous use for prevention and treatment of bleeding episodes of previously turoctocog alfa pegol treated severe haemophilia A patients.

Secondary objectives
To investigate the following in severe haemophilia A patients previously treated with turoctocog alfa pegol

- Development of FVIII inhibitors
- Efficacy of turoctocog alfa pegol prophylaxis
- Haemostatic efficacy of turoctocog alfa pegol when used for treatment of bleeds

Primary endpoint
Number of adverse events reported

Key secondary endpoints

- Incidence of FVIII inhibitors ≥0.6 BU
- Number of bleeding episodes on prophylaxis
- Number of spontaneous bleeding episodes on prophylaxis
- Haemostatic effect of turoctocog alfa pegol when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None
- Number of turoctocog alfa pegol injections required per bleeding episode

Overall design:

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety and efficacy of turoctocog alfa pegol during prophylaxis treatment and treatment of bleeds. There will be three turoctocog alfa pegol treatment arms (dosing once weekly, twice weekly, and three times weekly) and no comparator.

Key inclusion criteria

- Male patients of all ages with the diagnosis of severe congenital haemophilia A (FVIII activity <1%) based on medical records
- On-going participation in NN7088-3859 (pathfinder2), or NN7088-3885 (pathfinder5) at the time of transfer

Key exclusion criteria

- Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products
- Any disorder, except for conditions associated with haemophilia, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol
- Current participation in any clinical trial (except NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5)) of an approved or non-approved investigational medicinal product

Number of patients:

170 patients are expected to be assigned to trial product during the 8 months recruitment period

Treatment groups and duration:

Duration of treatment period will be 104 weeks (2 years).

The following trial products will be supplied by Novo Nordisk A/S:

- Turoctocog alfa pegol 2000 IU vials
- Turoctocog alfa pegol 3000 IU vials

Turoctocog alfa pegol is supplied as a sterile, freeze-dried powder in a 2-8°C (36-46°F) stable formulation single use vial with a nominal content of 2000 IU/vial or 3000 IU/vial to be reconstituted with 4.3 mL 0.9% Sodium Chloride solution for intravenous injections.

2 Flowchart

Visit number	1 (Screening and treatment)	2	3	4	5	6	7	8	EoT	Unscheduled	Follow-up (Inhibitors)	Follow-up (Discontinued)
Timing of visit (week)	**0**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**When applicable**	**When applicable**	**1 month after EoT**
Visit window (weeks)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**	**N/A**	**N/A**
Treatment month	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**			
PATIENT RELATED INFO / ASSESSMENTS												
Informed consent	•											
In/exclusion criteria	•											
Demography [b]	•[a]											
Concomitant illness/Medical history	•											
Details of Haemophilia/Haemophilia treatment and bleed history	•[a]											
Genotype	•[a]											
AB0 blood group	•											
Physical examination	•		•		•		•		•			
Concomitant medication	•	•	•	•	•	•	•	•	•		•	•
Discontinuation criteria		•	•	•	•	•	•	•	•			
EFFICACY ASSESSMENTS												
Bleeding episodes	•[c]	•	•	•	•	•	•	•	•		•	
Target joint assessment	•								•			
Haemophilia Joint Health Score	•								•			
PHARMACO-ECONOMIC ASSESSMENTS												
PRO questionnaire (Hemo-SAT)	•[g]								•			
SAFETY ASSESSMENTS												

Visit number	1 (Screening and treatment)	2	3	4	5	6	7	8	EoT	Unscheduled	Follow-up (Inhibitors)	Follow-up (Discontinued)
Timing of visit (week)	**0**	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**When applicable**	**When applicable**	**1 month after EoT**
Visit window (weeks)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**N/A**	**N/A**	**N/A**
Treatment month	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**			
Adverse events		•	•	•	•	•	•	•	•		•	•
Vital signs	•				•				•	•	•	
Body measurements [h]	•	•[i]	•	•[i]	•	•[i]	•	•[i]	•			
ECG (patients ≥18 years)	•[a]											
Urinalysis	•		•		•		•		•			
Biochemistry	•[a]		•		•		•		•			
Haematology	•[a]		•		•		•		•			
Coagulation parameters	•									•[e,f]	•[e]	
FVIII activity [d]	•[a]		•		•		•		•	•[e]	•	
Antibodies [d]	•[a]		•		•		•		•	•[k]	•	
TRIAL MATERIAL												
IWRS call	•	•	•	•	•	•	•	•	•			
Dispensing visit (IWRS)	•	•[i]	•	•[i]	•	•[i]	•	•[i]				
Administration of trial product	•		•		•		•					
Drug Accountability	•	•	•	•	•	•	•	•	•			
REMINDERS												
Human biological specimen for storage [j]			•						•			
Hand out ID Card and Direction for Use	•											
Hand out of Diaries	•[c]	•	•	•	•	•	•	•				
End of treatment/ End of trial									•			

Footer	Description
a.	Transferred from previous trial by sponsor. Note that FVIII recovery cannot be transferred and must be sampled. Date of birth will not be transferred.
b.	Demography consists of date of birth and age (unless not allowed according to local regulation, see Appendix 8), ethnicity and race (unless not allowed according to local regulation, see Appendix 8).
c.	Training must take place at visit 1 and whenever needed afterwards.
d.	Sampling for FVIII activity and antibodies should be scheduled to allow for a wash out of approximately 3 days. Post-dose FVIII activity must be collected 30± 10 min at visits including administration of trial product.
e.	Post-dose FVIII activity and Lupus anticoagulant should be collected if reduced effect of N8-GP or FVIII inhibitor development is suspected.
f.	Lupus anticoagulant sample only.
g.	Will be transferred from previous trial. Patients who have turned 17 years during their participation in NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5) will have to fill in the questionnaire.
h.	For patients > 18 years of age, height will only be assessed at visit 1, 5 and EoT.
i.	For selected countries, and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries to the patient's home by courier service. The bodyweight and height may be re-used from the previous visit. For these patients visit 2, 4, 6 and 8 may be conducted as a phone visit.
j.	Only applicable for patients, who have signed the informed consent for Human biological specimen for long term storage. Patients < 12 years will only have blood samples taken, if maximum limit for blood sampling is not exceeded ([16]).
k.	In case of severe allergic reactions see section 9.8.8.3

2.1 Flowchart for major surgery

Time	Day of surgery	Post-surgery	End of surgery period
PATIENT RELATED INFO / ASSESSMENTS			
Indication for surgery	•		
Surgical procedure	•		
Anatomical location	•		
Date for surgery	•		
N8-GP dose pre-surgery	•		
N8-GP dose(s) during the day of surgery	•		
N8-GP doses until return to prophylaxis schedule		•	
Date of return to trial treatment			•
Days hospitalised due to surgery			•
EFFICACY ASSESSMENTS			
Clinical evaluation of haemostatic response	•		
Haematology	•	•*	
Blood product transfusions	•	•*	
SAFETY ASSESSMENTS			
Vital signs	•		
Antibodies	•		
FVIII activity	•		

*To be collected if blood product transfusions are needed

3 Introduction

3.1 Trial rationale

The rationale for performing this trial is to allow the continued evaluation of the safety and efficacy of turoctocog alfa pegol (N8-GP) in order to obtain additional data on long-term use of N8-GP. Introducing a twice or three times weekly prophylactic dosing regimen to the majority of patients is intended to show potential improvement in clinical outcomes by converting patients to a milder bleeding phenotype. Joint health and target joints will be assessed and evaluated at inclusion and at end of trial (EoT).

3.2 Background

3.2.1 Haemophilia A

Haemophilia A is a recessive X-linked congenital bleeding disorder, resulting from deficiency of the essential blood coagulation factor VIII (FVIII) and is characterised by increased bleeding tendency. Haemophilia A is classified as "severe (<1%)", "moderate (1-5%)" or "mild (>5%)" according to the plasma activity of the affected clotting factor. Patients with severe haemophilia A lack production of functional FVIII molecules and hence have unmeasurable FVIII levels (<1%). With an absence of FVIII the normal haemostasis gets insufficient resulting in joint damage and derived disabilities caused by repeated, often spontaneous and sometimes life-threatening bleedings.

The primary goals of haemophilia care are the prevention of bleeding episodes (prophylaxis), rapid and definitive treatment of bleeding episodes that do occur, and provision of adequate haemostasis during surgery and other major challenges to haemostasis. Currently, these goals are essentially met for patients with haemophilia A by intravenous (i.v.) injections of the commercially available plasma derived or recombinant FVIII products (pdFVIII and rFVIII, respectively). Extended half-life therapies like N8-GP have the advantage of either requiring less frequent dosing which may reduce the overall burden of prophylactic treatment or could contribute to increased FVIII activity levels thereby potentially reducing the occurrence of spontaneous bleeding episodes.

The most serious complication of haemophilia treatment with current FVIII products is FVIII inhibitor development. These inhibitors are antibodies formed as an immune response to allogeneic FVIII, which reduce or eliminate the activity of FVIII proteins. This condition develops in about 30% of previously untreated patients with severe haemophilia A following exposure to FVIII products[1,2].For previously treated patients without any historical or current inhibitor, the risk of inhibitor formation following FVIII exposure is expected to be approximately 2–3 per 1,000 patient years of exposure [3, 4].

3.2.2 Turoctocog alfa pegol

N8-GP is a glycopegylated recombinant coagulation FVIII and represents a new recombinant FVIII (rFVIII) with a longer terminal half-life than unmodified rFVIII products. N8-GP is under development for control and prevention of bleeding episodes, including routine prophylaxis and treatment of bleeds and prevention of bleeding during surgery.

For full information on medicinal aspects and qualities of the N8-GP product please refer to the Investigator's Brochure (IB)[5].

3.2.3 Turoctocog alfa pegol clinical data

In accordance with the European Medicines Agency (EMA) guidelines[6] and other regulatory advices the clinical programme for N8-GP was initiated with a first-human-dose trial to document the essential pharmacokinetic characteristics of the product and to obtain initial safety information.

In the first human dose trial NN7088-3776 (pathfinder1), a single dose of N8-GP (25 IU/kg body weight (BW), 50 IU/kg BW or 75 IU/kg BW) was administered to 26 adult previously treated patients with severe haemophilia A being in a non-bleeding state. N8-GP was well-tolerated and the safety profile of N8-GP appeared similar to that of marketed FVIII products. The mean half-life of N8-GP was shown to be 18.4 hours, corresponding to a 1.6-fold prolongation compared to the half-life of un-modified FVIII products (patient's previous product including rFVIII and pdFVIII).

Four clinical trials investigating the safety and efficacy of N8-GP are on-going – a pivotal phase 3 trial NN7088-3859 (pathfinder2) which includes an extension phase divided in two parts, part 1 and part 2, a phase 3 surgery trial NN7088-3860 (pathfinder3), a paediatric phase 3 trial NN7088-3885 (pathfinder5), and a previously untreated patients phase 3 trial NN7088-3908 (pathfinder6).

The pivotal part of trial NN7088-3859 (pathfinder2) in adolescents and adults documented the safety and efficacy of a prophylactic regimen with 50 IU/Kg BW of N8-GP given every four days. The annualised bleeding rate (ABR) was estimated to 3.70 and the median ABR rate was estimated to 1.33. The estimated success rate for treatment of all bleeds was 84.2% and the haemostatic effect of N8-GP was confirmed. The extension phase part 2 is on-going.

In the trial NN7088-3860 (pathfinder3) the efficacy and safety of N8-GP during major surgical procedures in patients with severe haemophilia A is evaluated. The haemostatic effect of N8-GP during surgery for the first interim was demonstrated. All surgeries were effectively performed with N8-GP. The haemostatic effect of N8-GP was rated as "excellent" or "good" in 17 out of 18 surgeries (94.4%), and as "moderate" in 1 surgery. The haemostatic effect of N8-GP during the post-operative period, Days 1−14, was also demonstrated. No FVIII inhibitory antibodies were detected, no thromboembolic events occurred and no other clinically significant safety issues were identified. The trial is on-going.

The main phase of the paediatric trial NN7088-3885 (pathfinder5) assessed safety including immunogenicity, and efficacy of N8-GP prophylaxis in previously treated patients with severe haemophilia A < 12 years of age. Patients were treated with approximately 60 IU/kg BW N8-GP twice weekly. The haemostatic effect of N8-GP used for treatment of bleeding episodes was confirmed by an estimated success rate of 78.6% (including n=3 missing observations counted as 'failure'). Prophylactic protection of N8-GP was demonstrated by an estimated mean ABR of 2.13 and a median ABR of 1.95. No confirmed inhibitory antibodies (FVIII ≥0.6 BU) and no safety signals were observed. The extension phase is on-going.

For further information on medical aspects, non-clinical data and quality of N8-GP please refer to the IB[5].

3.3 Benefit-risk assessment

Participation in this trial could be a possible benefit for the patients as it will allow them to continue their replacement therapy. Additionally, the trial will provide assessments of longer-term safety of N8-GP and establish information on joint health and target joints.

Currently available clinical data from the pathfinder programme support that N8−GP has the intended haemostatic potential.

The key risks associated with N8-GP administration are inhibitor development and allergic/hypersensitivity reactions, which are well-known class effects for FVIII products.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of N8-GP may be found in the IB[5].

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objective(s)

4.1.1 Primary objective

To investigate the safety of N8-GP during continuous use for prevention and treatment of bleeding episodes of previously N8-GP treated severe haemophilia A patients during the 104 weeks trial period.

4.1.2 Secondary objectives

To investigate the following in severe haemophilia A patients previously treated with N8-GP during the 104 weeks trial period.

- Development of FVIII inhibitors
- Efficacy of N8-GP prophylaxis
- Haemostatic efficacy of N8-GP when used for treatment of bleeds
- Joint health status
- Haemostatic efficacy during major surgical interventions
- Treatment satisfaction in patients receiving N8-GP prophylaxis
- To evaluate the health economic impact of N8-GP treatment

4.1.3 Exploratory objectives

- To investigate the incidence of antibodies other than inhibitors

4.2 Primary, secondary and exploratory endpoint(s)

4.2.1 Primary endpoint

Number of adverse events reported

4.2.2 Secondary endpoints

- Incidence of FVIII inhibitors ≥0.6 BU
- Number of bleeding episodes on prophylaxis
- Number of spontaneous bleeding episodes on prophylaxis
- Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None
- Number of N8-GP injections required per bleeding episode
- Pre-dose FVIII activity levels on N8-GP prophylaxis (IU/dL)
- Change in joint health status from start to end of trial (based on Haemophilia Joint Health Score)

- Haemostatic response during major surgical interventions assessed as: Excellent, Good, Moderate, or None
- Consumption of N8-GP (number of infusions and IU/kg) per bleed
- Consumption of N8-GP (number of infusions and IU/kg per month and per year) during prophylaxis treatment
- Change from start till end of trial in treatment satisfaction (based on Hemo-SAT score)

4.2.3 Exploratory endpoints

- Incidence of anti-N8-GP antibodies
- Incidence of anti-PEG antibodies

5 Trial design

5.1 Overall design

This phase 3b trial is a multi-centre, multi-national, open labelled, non-randomised, interventional trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously N8-GP treated severe haemophilia A patients of all age groups. There will be three N8-GP treatment arms and no comparator.

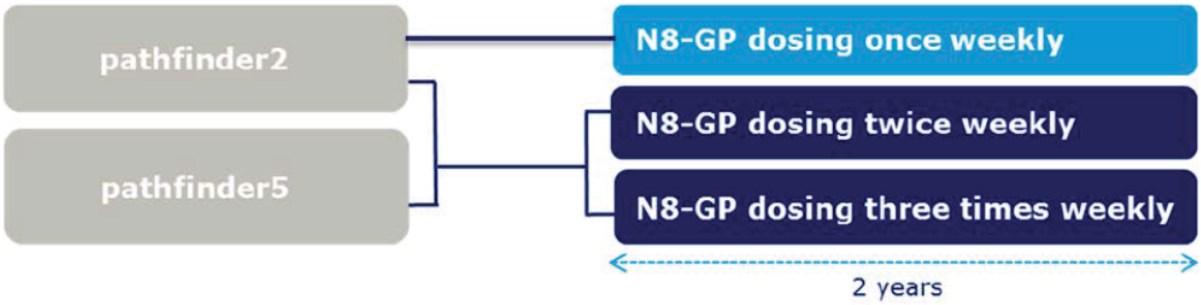


Figure 5-1: Overview of prophylaxis regimen options in pathfinder8

The investigator will decide which treatment arm the patient should be allocated to taking previous treatment regimen and bleeding tendency into account. Only patients on once weekly dosing or on-demand treatment upon entry into pathfinder8 are allowed to enter the once weekly treatment arm. Twice and three times weekly dosing is allowed for all patients. The investigator should evaluate the need for an intensification to the three times weekly dosing regimen if a patient experienced/experiences recurrent spontaneous bleeding episodes.
The treatment regimen can be changed to twice or three times weekly during the course of the trial if deemed clinically relevant by the investigator.

Table 5-1: Prophylaxis doses for the regimen options

previous trial	age at screening	once weekly dosing	twice weekly dosing	three times weekly dosing
pathfinder5	patients <12 years	N/A	60 IU/kg BW	50 IU/kg BW
	patients ≥12 years	N/A	50 IU/kg BW	50 IU/kg BW
pathfinder2	all	75 IU/kg BW	50 IU/kg BW	50 IU/kg BW

The total duration of treatment for a patient will be 104 weeks.

The follow-up period is 1 month after EoT and is only applicable for patients who have developed an inhibitor or discontinued trial product due to lack of haemostatic effect of the trial product (discontinuation criteria no. 2), or anaphylaxis to the trial product (discontinuation criteria no. 4) (France only; or experience a major thromboembolic event [discontinuation criteria no. 9]).

5.2 Patient and trial completion

- Approximately 174 patients will be offered to participate in the trial
- Approximately 170 patients are expected to be assigned to trial product.
- Expected number of patients to complete the trial: 153

Planned duration of recruitment period: FPFV to LPFV is approximately 8 months
FPFV: 01 May 2018
LPLV: December 2020

Patients are recruited from NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5).

5.2.1 Trial period completion for a patient:

Trial period completion is defined as when the patient has completed the final scheduled visit ('end of trial' according to the flowchart).
'Date of trial completion' is the date the patient completed the final scheduled visit.

The patients may be completed from the trial when N8-GP becomes commercially available in their respective country. The completion should be performed as an EoT visit according to the flowchart independent of the visit window.

5.3 End of trial definition

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

5.4 Scientific rationale for trial design

Historically, the aim of prophylactic treatment in severe haemophilia A has been to maintain at least a 0.01 IU/mL (1 IU/dL) FVIII activity level. However, recent studies have suggested that the maintenance of higher FVIII activity levels is desirable in order to further reduce and potentially even eliminate the risk of spontaneous bleeding episodes by converting patients from a severe to a mild haemophilia A phenotype [7, 8, 9].

Apart from investigating the overall safety of N8-GP during continuous use, the purpose of this trial is to demonstrate that N8-GP can convert patients to a milder bleeding phenotype, and to evaluate the clinical benefit of maintaining higher FVIII trough levels with FVIII replacement. To achieve this, there is an option to intensify the N8-GP dosing regimen from every four days dosing (previous regimen in NN7088-3859 (pathfinder2)) to twice weekly or three times weekly.

In addition, the trial aims to provide additional clinical outcome data – e.g. target joint status and clinical safety data in patients with haemophilia A after on-going N8-GP treatment.

The trial is not controlled by a placebo group. It is considered unethical to administer an ineffective treatment to patients with haemophilia.

For clinical efficacy of N8-GP in the prevention and treatment of bleeding episodes, data on ABR may be compared within the trial's treatment arms and to data from patients' previous participation in the pathfinder trial program (patient serves as his own control).

The rationale for choosing a multi-centre design is to ensure a sufficient number of patients with this rare disorder.

The non-randomised trial design will allow flexibility relative to the patient's current treatment in the N8-GP clinical trial program as it will offer prophylactic treatment with either once, twice or three times weekly N8-GP dosing dependent on current treatment regimen and bleeding tendency for all adolescent and adult patients.

The trial population reflects a patient population of severe haemophilia A patients of which some might benefit from intensified N8-GP treatment.

Paediatric, adolescent and adult patients will be recruited from the NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) trials. This will allow severe haemophilia A patients on N8-GP treatment to continue treatment with N8-GP after completion of the initial phase 3 pathfinder trials. Patients will be evaluated over an additional two year treatment period to provide additional data on long term safety and efficacy of N8-GP.

5.5 Justification for dose

Justification for introducing a twice or three times weekly prophylactic dosing regimen to the majority of patients, is to show potential improvement in clinical outcome by converting patients to a milder bleeding phenotype.

N8-GP is a longer-acting rFVIII compound, with a PEG attached to the truncated B-domain of the rFVIII turoctocog alfa prolonging its half life. It is intended for prevention and treatment of bleeding episodes as replacement therapy in patients with congenital haemophilia A. The only approved route of administration for coagulation factor products is i.v. administration.

N8-GP has been administered i.v. to over 270 patients for more than 800 patient years of exposure and the observed safety profile of N8-GP is consistent with what is expected with other FVIII-containing products [5].

NN7088-3859 (pathfinder2), the pivotal trial in adolescents and adults, aimed to document the safety and efficacy of a prophylactic regimen with 50 IU/kg BW of N8-GP administered every four days. This regimen was chosen based on the first human dose trial, NN7088-3776 (pathfinder1), and the same dose will be used for prophylactic treatment in pathfinder8 for adolescents and adults.

The administered dose of 75 IU/kg BW corresponds to the highest single dose tested in the clinical trial programme for N8-GP. Selected patients that during participation in the NN7088-3859 (pathfinder2) trial, due to a low bleeding frequency (less than 2 bleeding episodes over the previous 6 months), could switch to once weekly dosing (75 IU/kg BW). These patients will be allowed to continue on this regimen in pathfinder8.

Patients currently receiving episodic treatment for bleeding episodes (on-demand treatment) will upon entry into pathfinder8 be allowed to switch to either of the prophylaxis regimens as this is seen as beneficial compared to their current episodic treatment.

Based on a weighted mean from published studies representative numbers for mean ABR in severe haemophilia A patients are 24 bleeds/year for patients treated on-demand and 6.8 bleeds/year for patients on prophylactic treatment. The mean observed ABR for patients on on-demand 12 months prior to entry into pathfinder2 was 28.95. At the end of main phase on prophylaxis the mean observed ABR was 6.66. For all patients on on-demand and once weekly prophylaxis regimen the mean ABR at cut-off for submission were 32.52 and 3.89 respectively [10, 11].

Intensification to twice weekly or even three times weekly prophylaxis can take place at the investigators discretion. Apart from patients dosed once weekly, all patients should preferably stay on a dosing regimen for at least 6 months.

In the NN7088-3885 (pathfinder5) trial the prophylactic dosing regimen is 60 IU/kg BW twice weekly. Due to an expected increased clearance in younger patients. The same dosing will apply for patients < 12 years of age enrolled in pathfinder8 initiated on twice weekly dosing.

For prevention of bleeding during surgery and for treatment of bleeding episodes doses of 20-75 IU/kg BW are to be administered, depending on the surgical procedure and location and severity of the bleed, respectively. The N8-GP dosing regimens are based on phase 1 data from NN7088-3776 (pathfinder1), the first human dose trial, and the treatment guidelines from the World Federation of Hemophilia regarding prevention of bleeding during surgical interventions and treatment of bleeding episodes [12, 13].

6 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent from the patient or the child's parent/LAR obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients of all ages with the diagnosis of severe congenital haemophilia A (FVIII activity <1%) based on medical records
3. On-going participation in NN7088-3859 (pathfinder2), or NN7088-3885 (pathfinder5) at the time of transfer
4. The patient or child's parent/LAR is willing to follow one of the defined turoctocog alfa pegol prophylaxis regimens
5. The patient and/or caregiver is capable of assessing a bleeding episode, capable of home treatment of bleeds and otherwise able to follow trial procedures

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

6.1.1 Rationales for the inclusion criteria

No. 1 is included in accordance with International Conference on Harmonisation/Good clinical Practice (ICH-GCP).
No. 2 is included to select target age and previous haemophilia treatment history group in accordance with the EMA guideline.
No. 3 is included to be able to collect long term treatment data on a well defined and known patient population.
No. 4 and 5 are included to ensure compliance with protocol requirements and to protect the patient's safety.

6.2 Exclusion criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products
2. Any disorder, except for conditions associated with haemophilia, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol
3. Current participation in any clinical trial (except NN7088-3859 or NN7088-3885 (pathfinder2 or 5 respectively)) of an approved or non-approved investigational medicinal product

4. Mental incapacity, unwillingness to cooperate, or a language barriers precluding adequate understanding and cooperation

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

6.2.1 Rationales for the exclusion criteria

No. 1 and 2 is included to protect the patient's safety.
No.3 is included to reduce the risk of confounding factors.
No. 4 is included to ensure compliance with protocol requirements and to protect the patient's safety.

6.3 Lifestyle restrictions

There are no lifestyle restrictions during the conduct of the trial.

6.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. A screen failure session must be made in the IWRS (Interactive Web Response System).

Individuals who do not meet the criteria for participation in this trial may not be rescreened.

7 Treatments

7.1 Treatments administered

This non-randomised trial will allow flexibility relative to the patient's current treatment as it will offer prophylactic treatment with either once, twice or three times weekly N8-GP dosing for adolescent and adult patients. All children (< 12 years of age) will be treated with twice or three times weekly N8-GP prophylaxis.

Table 7-1 Trial products and solvent provided by Novo Nordisk A/S

Trial product name:	N8-GP 2000 IU/vial	N8-GP 3000 IU/vial	N/A
Solvent name	N/A	N/A	Sodium Chloride
Dosage form:	Powder for solution for injection	Powder for solution for injection	Solvent for solution for injection
Route of administration:	Intravenous injection	Intravenous injection	Intravenous injection
Packaging	Vial	Vial	Pre-filled syringe

The investigator must document that directions for use are given to the patient orally and in writing at the first dispensing visit.

Novo Nordisk A/S will provide the following auxiliaries for this trial:

- For N8-GP administration: Trial injection kit and direction for use (DFU)

Only needles provided and/or approved by Novo Nordisk must be used for administration of trial product

7.1.1 Prophylaxis treatment

All prophylactic and preventive doses of N8-GP should be reported in a diary or the eCRF. All doses must be transcribed by trial staff into the eCRF preferably within 2 days after site visit.

7.1.1.1 Once weekly prophylaxis regimen (NN7088-3859 (pathfinder2) patients only)

In a sub-set of patients N8-GP may be administered once weekly at a dose of 75 IU/kg BW. Patients are eligible for the once weekly N8-GP dosing regimen if they were treated once weekly or were on the on demand regimen in NN7088-3859 (pathfinder2) upon entry into pathfinder8. The once weekly treatment arm is only available at screening/V1.

If the patient experiences more than 2 bleeds within an 8 week period or experiences a severe bleed requiring hospitalisation, it should be considered to change the patient to a twice weekly regimen. This decision is per investigators discretion in collaboration with the patient.

7.1.1.2 Twice weekly prophylaxis regimen

For twice weekly prophylaxis doses of N8-GP 50 IU/kg BW for patients ≥ 12 years of age and 60 IU/kg BW for patients < 12 years of age are to be administered. If a patient reaches the age of 12 years during the trial, he must be switched to 50 IU/kg BW.
At the investigators discretion an intensification of the dosing regimen to three times weekly should be considered if the patient experiences spontaneous bleeding episodes.
If clinically warranted a patient can be switched to three times weekly at any time. Otherwise any treatment regimen should preferably be kept for a minimum of 6 months..

7.1.1.3 Three times weekly prophylaxis regimen

For three times weekly prophylaxis doses of 50 IU/kg BW apply for all patients.
If clinically warranted a patient can be switched to twice weekly at any time. Otherwise any treatment regimen should preferably be kept for a minimum of 6 months.

7.1.2 Treatment of bleeding episodes

All bleeding episodes and treatment doses of N8-GP should be reported in a diary or the eCRF. All doses must be transcribed by trial staff into the eCRF preferably within 2 days after site visit.

For treatment of bleeding episodes doses of 20-75 IU/kg BW are to be administered, depending on location and severity of the bleed. For recommended dose levels see Table 7-2.

Bleeding episodes should be treated with N8-GP as soon as identified. If two doses are not sufficient to treat a bleeding episode or in case of a severe bleeding episode, the patient should contact the clinic as soon as possible for further instructions. Single doses should not exceed 75 IU/kg BW and the total daily dose should not exceed 200 IU/kg BW.
If a satisfactory haemostatic effect cannot be achieved after 48 hours using adequate doses of N8-GP, another FVIII product may be selected at the discretion of the investigator. This will result in discontinuation of the patient, see section 8.1.

Table 7-2: Recommended dose levels for treatment of bleeding episodes

Type of bleeding episode	Recommended dose range
Joint, muscle (except iliopsoas)	20-60 IU/kg BW
Central nervous system/head, throat, neck, iliopsoas, gastrointestinal	40-75 IU/kg BW

If a planned prophylaxis dosing is administered during the occurrence of a bleeding episode, the dose should be recorded as treatment of a bleed. All doses administered due to/during a bleeding episode should be registered as treatment of bleed. After a bleed has stopped the patient should continue to follow the original prophylaxis regimen.

For detailed information on what data to capture and definitions, see section 9.5.1.

7.1.3 Treatment of suspected bleeding episodes

In case of abdominal or head trauma where there is a risk of a severe traumatic bleeding episode it is allowed to initiate treatment before symptoms arise. This is defined as preventive treatment of suspected severe traumatic bleeding episode. The recommended dose is equivalent to treatment of a severe bleeding episode, see Table 7-2.
In case of a suspected severe bleeding episode the patient should contact trial site as soon as possible for further instructions.

7.1.4 Surgery

Both minor and major surgeries are allowed during this trial.

Definition of minor surgery
Minor surgery is defined as any invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated.
Examples of minor surgery include implanting catheters or ports in subcutaneous tissue, skin biopsies, simple dental procedures, uncomplicated cataract, and uncomplicated emergent procedures.

Definition of major surgery
Major surgery is defined as any invasive procedure that require several days of substitution therapy and/or where any one or more of the following occur:

- A body cavity is entered
- A mesenchymal barrier (e.g. pleura, peritoneum or dura) is crossed
- A fascial plane is opened
- An organ is removed
- Normal anatomy is operatively altered
- Major elective orthopaedic surgery

This definition includes e.g. circumcision since this requires several days of substitution therapy.

7.1.4.1 Minor surgery

Minor surgeries, can be performed by administering a preventive dose of N8-GP according to local practice and at the investigator's discretion.

7.1.4.2 Major surgery

Surgical procedures should be performed in coordination and co-operation with a team experienced in the management of haemophilia in a centre with adequate laboratory support for reliable monitoring of the FVIII activity levels.

The dose level of N8-GP should be chosen to target a FVIII activity as recommended by WFH guidelines[14]. Higher FVIII levels may be clinically warranted depending on type of surgery to ensure effective prevention of bleeding during and after the surgery or surgical procedure. Doses of N8-GP should be adjusted based on measured FVIII activity and the investigator's discretion.

All patients must receive a planned pre-operative loading dose of N8-GP, within 1 hour prior to expected surgical procedure ("knife to skin") and before any procedures are undertaken, including anaesthesia. Subsequent dosing on the day of surgery should be considered approximately 12 hrs. after the loading dose to maintain plasma levels of FVIII above 50%. For patients <12 years of age administration of a subsequent dose after 8 hours may be considered.

The major surgery period ends when patient is able to return to his prophylaxis regimen.

Scheduled visits according to the flowchart must be conducted independently of the surgery period. Scheduled visits should be avoided during hospitalisation.

Preventive treatment during major surgery period
Patients undergoing major surgery should receive bleeding preventive treatment with N8-GP (20-75 IU/kg BW) before, during and after surgery.

Treatment of bleeding episodes during major surgery period
If a patient experiences a post surgery treatment requiring bleeding episode at home, treatment with N8-GP (20-75 IU/kg BW) should be initiated as soon as it is identified. The patient should contact the trial site as soon as possible and irrespective of severity of the bleeding episode (within 2 weeks post discharge from hospital). Patients with severe bleeding episodes should visit the site within 24 hours.

7.2 Dose modification

Not applicable for this trial

7.3 Method of treatment assignment

All screened patients will receive a unique patient number at the screening visit, which will be assigned to the patient throughout the trial. Trial product will be dispensed/allocated using IWRS at the trial visits summarised in the flowchart, see section 2.

The investigator will decide which treatment arm the patient should be allocated to taking previous treatment regimen and bleeding tendency into account. Only patients on once weekly dosing or on-demand treatment upon entry into pathfinder8 are allowed to enter the once weekly treatment arm. Twice and three times weekly dosing is allowed for all patients. The investigator should evaluate the need for an intensification to the three times weekly dosing regimen if a patient experienced/experiences recurrent spontaneous bleeding episodes.

7.4 Blinding

This is an open-label trial.

7.5 Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Table 7-3 Trial product and solvent storage conditions

Trial product name	Solvent name	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
N8-GP 2000 IU/vial	N/A	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Protect from light Do not freeze	24 hours at 2°C-8°C or 4 hours at 8°C-30°C upon reconstitution.
N8-GP 3000 IU/vial	N/A			
N/A	0.9% Sodium Chloride Solution	Store at 2°C-30°C Do not freeze Protect from light	For single use	N/A

[a] The in-use time starts when the trial product is reconstituted.

N8-GP powder must be reconstituted prior to administration. After reconstitution with 4.3 mL 0.9% Sodium Chloride Solution, each 2000IU vial will contain 500 IU/ml and each 3000 IU vial will contain 750 IU/ml.

For a patient weighing <80 kg at the last scheduled visit conducted in trial NN7088-3859 or 3885, 2000 IU vials will be dispensed, and for a patient weighing ≥ 80 kg at the last scheduled visit conducted in trial NN7088-3859 or 3885, 3000 IU vials will be dispensed. The patient will remain on the same N8-GP product strength throughout the trial.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to the patient's treatment regimen.

The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the trial materials manual (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.

7.5.1 Drug accountability

The investigator or other delegated staff (according to local regulation, see Appendix 8) is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
Drug accountability also include the responsibility to check that the calculated amount of drug to be used correspond the amount actually used by the patient.

Destruction of trial products can be performed on an on-going basis and will be done according to local procedures after accountability is finalised by the site.

Destruction of trial products must be documented in the IWRS.

All returned, expired or damaged trial products (for technical complaint samples see Appendix 6) must be stored separately from non-allocated trial products. No temperature monitoring is required.

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

Used/unused Sodium Chloride may be discarded at home and accountability is not required.

7.6 Shipment of trial product to patient's home

For selected countries, and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the patient's home by courier service. For these patients visit 2, 4, 6 and 8 may be conducted as a phone visit.

The process for sending trial product from the trial site or pharmacy to a patient's home is described in the "Trial site/pharmacy instruction for shipment of trial product to patients' homes" document. This document contains detailed instructions for preparing packaging and setting up the pick-up of trial product, handover of trial product from the trial site or pharmacy staff to the courier, required

temperature monitoring of trial product, delivery to and receipt of trial product by the patient. The process for returning trial product to the trial site or pharmacy by courier is also described in this document.

Investigators, trial site/pharmacy staff and patients who will be involved in shipment of trial product to the patient's home will be adequately trained in this process.

7.7 Treatment compliance

- Drug accountability of all dispensed trial product will be performed on an on-going basis by trial staff and monitor
- Review of patient diary will be performed at every visit by the investigator/trial staff

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.

7.8 Concomitant medication

Any medication other than the N8-GP that the patient is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication (including route of administration)
- Dates of administration including start and stop dates or continuing

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 9.6.

The following medications may not be used during the trial period:

- Bypassing products: activated recombinant factor VII (rFVIIa), plasma-derived prothrombin complex concentrates (pd-PCC) and plasma-derived activated prothrombin complex concentrates (pd-aPCC).
- Coagulation factor containing products: FVIII, FIX and FVII-containing products other than N8-GP, including fresh frozen plasma (FFP) and cryoprecipitate.
- Anti-coagulants such as heparin and vitamin-K antagonists in therapeutic doses. Heparin is only allowed for surgery prophylaxis (if clinically warranted) and sealing of central venous access catheters.

7.8.1 Rescue medication or Rescue therapy

No rescue medication will be provided, and rescue therapy with other medication than trial product is not allowed. Patients treated with coagulation factors or anti-coagulants (therapeutic doses) other than N8-GP must be discontinued from the trial.

7.9 Treatment after the end of the trial

When discontinuing trial product, at the scheduled EoT visit, the patient should be transferred to a suitable marketed product at the discretion of the investigator. Even if N8-GP is not commercially available at EoT, Novo Nordisk will not provide N8-GP after EoT.

8 Discontinuation/Withdrawal criteria

The patient may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the patients, who discontinue trial product, attend EoT visit to collect the required data for the analysis of the primary (and confirmatory secondary) endpoint. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

For patients shifting to commercial products see section 5.2.1.

8.1 Discontinuation of trial treatment

The patient must be discontinued from trial product, if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Lack of haemostatic effect of the trial product. The bleed is not controlled after 48 hours of appropriate turoctocog alfa pegol treatment
3. FVIII inhibitor (>5 BU) as confirmed by re-testing by Central Laboratory
4. Allergy/anaphylaxis to the trial product requiring systemic treatment
5. Treatment with other FVIII containing products other than trial product turoctocog alfa pegol or anti-coagulants (therapeutic doses)
6. Incapacity or unwillingness to follow the trial procedures
7. FVIII inhibitor (≥0.6 and ≤ 5 BU) as confirmed by re-testing by Central Laboratory that makes treatment (prophylaxis and/or treatment of bleeding episodes) with turoctocog alfa pegol clinically ineffective
8. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
9. Applicable for France only; In the case of a major thromboembolic event (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as per investigator.

See the flowchart for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

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

8.1.1 Rationale for discontinuation of trial treatment criteria

No 1-4 are included to protect the patient's safety.
No 5 and 8 are included not to confound the effects of the investigational product.
No 6 and 7 (and no. 9 for France only) are included to protect the patient's safety.

8.2 Withdrawal from the trial

A patient may withdraw consent at any time at his own request, or at the request of the patient's parent or the patient's legally acceptable representative (LAR).

If a patient withdraws consent, the investigator must ask the patient if he is willing, as soon as possible, to have assessment performed according to EoT visit. See the flowchart for data to be collected.

Final drug accountability must be performed even if the patient is not able to come to the trial site.
A treatment discontinuation session must be made in the IWRS.

If a patient withdraws from the trial, he may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

If the patient withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

Although a patient is not obliged to give his reason(s) for withdrawing, 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 withdrawal must be specified in the EoT form in the eCRF.

If relevant a follow-up phone call may be requested.

8.2.1 Replacement of patients

Patients who discontinue trial product or withdraw from trial will not be replaced.

8.3 Lost to follow-up

A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the trial site for a required visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit

schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.

- Before a patient is deemed lost to follow-up, the investigator must make every effort to regain contact with the patient (where possible, at least three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's source document.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the trial with a primary reason of lost to 'follow-up'.

9 Trial assessments and procedures

Trial procedures and their timing are summarised in the flowchart, see section 2.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

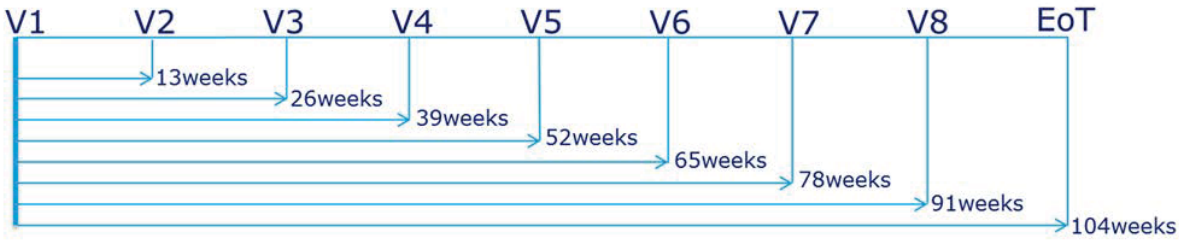
The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, patients will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.

Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.

Any scheduled assessment visit (V1, V3, V5, V7, and EoT) must be rescheduled if the patient has experienced a treatment required bleeding episodes within the last 7 days prior to the visit date.

Figure 9-1 Visit structure



Next visit in line must be calculated based on screening/V1.

Review of completed diaries, PRO questionnaires for possible AEs, and laboratory reports must be documented either on the trial documents or in the patient's source documents. If clarification of entries or discrepancies in the diary or possible AEs in PRO questionnaires is needed, the patient must be questioned and a conclusion made in the patient's source documents. Care must be taken not to bias the patient.

Informed consent must be obtained before any trial related activity, see Appendix 3.

9.1 Follow-up visit (only for patients who have developed a FVIII inhibitors)

For patients who discontinues trial product due to an inhibitor development:
1 month after the EoT visit the patient should attend a FU Visit. Assessments should be according to flowchart, see section 2. Additional follow-up visits may be arranged at intervals as long as

clinically warranted. If the patient refuses to attend the follow-up visit, the persuading attempts should be documented in the patient's source document.

For patients who continues on trial product with a low titre inhibitor:

Patients with low titre inhibitor (≥0.6 and ≤ 5 BU) continuing in the trial must follow the prescribed regimen and the scheduled visits as described in the flowchart. If closer monitoring is needed patients with low titre inhibitors should attend a follow-up visit with blood collection for the assessments specified in the flowchart Appendix 20 (Follow-up (inhibitors)). Closer monitoring is highly recommended but this decision will be Investigator's discretion.

9.2 Follow-up visit (only for patients discontinued trial product due to lack of efficacy or anaphylaxis)

In case of discontinuation of trial product due to lack of efficacy (discontinuation criteria no. 2) or anaphylaxis to the trial product (discontinuation criteria no. 4), the patient should be scheduled for an EoT visit as soon as possible and asked to attend a follow–up visit 1 months after EoT.

Assessment should be done according to the flowchart in section 2

If the patient refuses to attend the follow-up visit, the patient should be considered as lost to follow-up, see section 8.3.

The follow-up visit can be performed as either a telephone call or a site visit at the investigator's and/or patient's discretion.

9.3 Unscheduled visit

The Unscheduled visit form in eCRF must be filled in if the patient attends an unscheduled visit due to the following reasons:

Suspicion/confirmation of inhibitor development

- Vital signs according to section 9.6.4
- Coagulation parameters according to Appendix 2
- FVIII activity according to Appendix 2
- Antibodies according to Appendix 2

Re-sampling of inhibitor blood samples

- Antibodies according to Appendix 2

Severe allergic reaction/anaphylaxis

- Vital signs according to section 9.6.4

- Antibodies (in case of severe allergic reactions) according to Appendix 2

For any other reason, the visit should be documented according to local practice.

9.4 Patient related info/assessments

Demography consists of date of birth and age (unless not allowed according to local regulation, see Appendix 8), ethnicity and race (unless not allowed according to local regulation, see Appendix 8)

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

Medical history is a medical event other than haemophilia that the patient has experienced in the past. This will include joint status at screening:

- List of joints which during the patient's life have caused special problems, in terms of repeated or frequent bleeding episodes. This list can be compiled through discussion between the patient/parent(s) and investigator
- List of joints with arthropathy

In case of an abnormal and clinically significant finding other than haemophilia, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 4) during the trial and any clinically significant worsening from baseline (Screening/V1) must be reported as an AE (see Section 9.6).

Details of haemophilia / haemophilia treatment and bleed history is any data from the previous trial NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5) in relation to previous regimens and bleeding episodes.

Genotype testing during trials NN7088-3859 (pathfinder2) and NN7088-3885 (pathfinder5) was offered to all patients unless not allowed according to local regulation.

AB0 blood group will be collected in eCRF as A, B, AB, 0 or not assessed based on medical records

Concomitant medication is any medication, other than the trial product, that is taken during the trial

Available demography, details of haemophilia treatment and bleeding episodes, and genotype will be transferred from previous trial NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5).

9.4.1 Physical examinations

A physical examination will include assessments of the general appearance, head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system, including mouth, musculoskeletal system, central and peripheral nervous system (general evaluation and neurological assessment), skin, and lymph node palpation.

Following aspects of the neurological examination [1] will be assessed:

- General appearance including language, social and developmental aspects
- Parameters including handedness, head circumference and level of consciousness
- Cranial
- Extremity and truncal tone
- Strength of extremities
- Reflexes
- Sensory aspects
- Gait with regards to walking, running, and standing
- Coordination and fine motor skills

Remember to update medical history if clinical findings have been recorded previously.

9.5 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart.

9.5.1 Bleeding episodes

The following must be recorded for any bleeding episode, also bleeding episodes that do not require treatment with trial product:

- Start date and time
- Stop date and time (see Table 9-1 for definition)
- Anatomical location(s)
- Cause (see Table 9-2 for definitions)
    - spontaneous
    - traumatic
    - post minor surgery
    - post surgical
- Severity (see Table 9-3 for definitions)
    - mild/moderate, severe
    - classification and recording of severe bleeding episodes is the responsibility of the investigator

[1] Kitchen L, Westmacott R, Friefeld S, et al. The pediatric stroke outcome measure: a validation and reliability study. Stroke. 2012;43(6):1602-1608

- Treatment, if any
  - Trial product administration(s)
    - Dose, date, time (see section 7.1.2)
  - Other medicinal treatments related to the bleeding episode (haemostatic treatment e.g. tranexamic acid, pain relieving medication etc.)
    - record as concomitant medication (see section 7.8)
- Clinical evaluation of the haemostatic effect for bleeding episodes treated with trial product (see Table 9-4 for the project specific 4-point scales)
- **Only** report the bleeding episode as an AE/SAE if fatal, life threatening or evaluated as related to trial product and/or trial procedure (see Table 9-5)

Table 9-1 Definition of stop of bleed

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

Table 9-2 Definitions of bleeding episodes

Category	Definition
Spontaneous	Not linked to a specific, known action or event
Traumatic	Caused by a specific, known action or event (e.g. injury or exercise)
Post Minor surgery	Bleed caused by or after minor surgery procedure
Post-surgical	Bleeds after surgery from the surgical site. Bleeding episodes during surgery does not fall under this category

Table 9-3 Definition of bleeding episode severity and treatment recommendation

Category	Definition	Treatment recommendation
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeds (joint, muscular bleeds without compartment syndrome), mucosal- or subcutaneous bleeds Mild/moderate bleeds may occur in other anatomical locations	Mild/moderate bleeding episodes can be treated at home without contact to the investigator
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeds; muscle bleeds with compartment syndrome; bleeds associated with a significant decrease in the haemoglobin level (>3g/dL) Severe bleeds may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes	Severe bleeding episodes must be treated immediately
Instruction for patients	The patient/parent or LAR must be instructed to contact the investigator immediately if in doubt regarding treatment of a bleeding episode and to discuss what other actions may need to be taken	

Table 9-4 Definition of haemostatic effect of N8-GP when treating bleeding episodes

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

Table 9-5 Reporting of bleeding episodes and/or adverse event

Reporting requirement	Definition
Report as bleed only	Bleeding episodes and other symptoms that are caused by the underlying disease (for example synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes are adverse events but should not be reported as AEs/SAEs
Report as bleed *and* AE/SAE	The event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. In case of a fatal or a life-threatening bleeding episode, it should always be reported as an SAE
Report as AE/SAE	In association with bleeding episodes (mostly traumatic) there may be other concurrent events that qualify for normal AE reporting, this could be bone fracture, ligament damage etc.

9.5.2 Target Joint assessment

A joint status including target joints must be assessed.

- Joint status based on the Haemophilia Joint Health Score, see section 9.5.2.1
- Current target joint(s), including number of spontaneous bleeding episodes for the last 12 months in each current target joint. - A target joint is defined as a joint with three or more spontaneous bleeding episodes within a consecutive period of 6 months. When there has been no spontaneous bleeding episode in the joint for 12 months, it is no longer considered a target joint.

Clinically significant findings present at screening should be recorded as concomitant illness and during the trial as AEs. Any changes in the examination which fulfil the criteria of an AE (see section 9.6) or an update to concomitant illness (see section 9.8) must be recorded as such.

9.5.2.1 Haemophilia Joint Health Score

The Haemophilia Joint Health Score was originally designed to be used by physiotherapists. The developers of the tool strongly recommend that the tool should be used by physiotherapists/healthcare professionals who have haemophilia-related expertise/experience and have been trained in the use of clinical measure, musculoskeletal assessment specifically administration of Haemophilia Joint Health Score. This is to ensure the precision and validity of the tool [15].

This assessment comprises an evaluation of the elbow, knee and ankle joints with regards to swelling, muscle atrophy, loss of motion, crepitus, strength, joint pain and global gait. The assessment should preferably be done by same person. If not possible, then the same profession.

9.5.3 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart and the laboratory manual.

9.5.4 Efficacy assessment during major surgery

9.5.4.1 Surgical intervention

Surgical procedure and duration:

- Date and time of surgery
- Surgical procedure (e.g. arthroscopy)
- Indication for surgery (e.g. haemarthrosis)
- Anatomical location (e.g. left knee joint)
- N8-GP dose(s) during the day of surgery
- N8-GP doses until return to prophylaxis schedule
- Clinical evaluation of haemostatic response during major surgery
- Date of return to trial treatment

9.5.4.2 Clinical Evaluation of Haemostatic response of N8-GP during major surgery

After completion of surgery (defined as "last stitch") a clinical evaluation of haemostatic response during surgery will be assessed by the Surgeon, Anaesthesiologist or Investigator using a 4-point scale based on experience as follows:

Table 9-6 definition of clinical evaluation of haemostatic response

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

9.6 Adverse events

The definitions of AEs and SAEs can be found in Appendix 4.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.6.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until EoT visit or follow-up visit if relevant, at the time points specified in the flowchart.

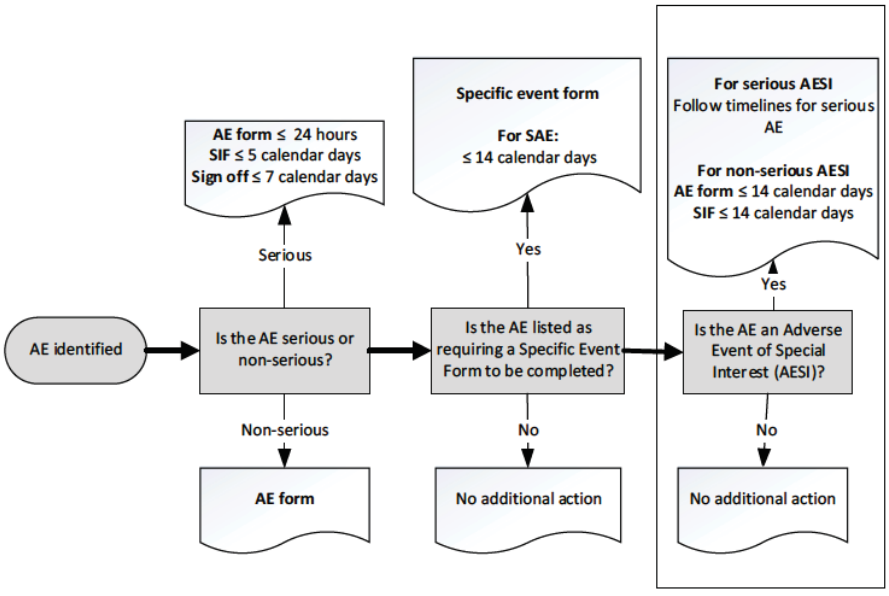
All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 4. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

Timelines for reporting of AEs, including AESIs, Appendix 4, are listed in Figure 9-2.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific event(s) are listed in Table 9-7 and the reporting timelines in Figure 9-2.



Timelines are from the awareness of an AE.
Queries and follow-up requests to be resolved ≤ 14 calendar days.

AE: Adverse Events, SAE: Serious Adverse Events, SIF: Safety Information Form

Figure 9-2 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 9-7 AEs requiring additional data collection (via specific event form) and AESIs

Event type	AE requiring additional event form	AESI
Hypersensitivity	X	
Medication error	X	
Inhibitors		X

9.6.1.1 Adverse event of special interest

The definition of AESIs can be found in Appendix 4.

The AESIs for this trial are listed in Table 9-7 and must be reported according to Figure 9-2.

9.6.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non leading verbal questioning of the patient is the preferred method to inquire about events.

9.6.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 9.6.1.1), will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the patient is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.6.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.6.5 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to AE/SAEs description in Section 9.6.1.

9.6.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following Disease-Related Events (DREs) are common in patients with Haemophilia A and can be serious/life threatening:

- Bleeding episodes

Bleeding episodes

Because bleeding episodes are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of AEs/SAEs, even though the event may meet the definition of an AE/SAE. These events, both serious and non-serious will be recorded in the AE form within the timeframe specified in Figure 9-4. These DREs will be monitored by a safety committee on a routine basis.

Note: The event must be recorded and reported as an SAE (instead of a DRE) if one of the following applies:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
- The event resulted in death.

9.6.7 Pregnancies and associated adverse events

Details of pregnancies in female partners of male patients (paternal) will be collected after the first-trial-related activity after obtaining informed consent and until EoT visit.

If a pregnancy is reported in female partners of male patients, the pregnancy should be documented in the medical record of the male patient and in case of abnormal outcome, the investigator should inform Novo Nordisk within 14 calendar days of learning of the abnormal outcome and should follow the procedures outlined in Figure 9-3 and Appendix 5.

Pregnancy outcome should be documented in the patient's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.

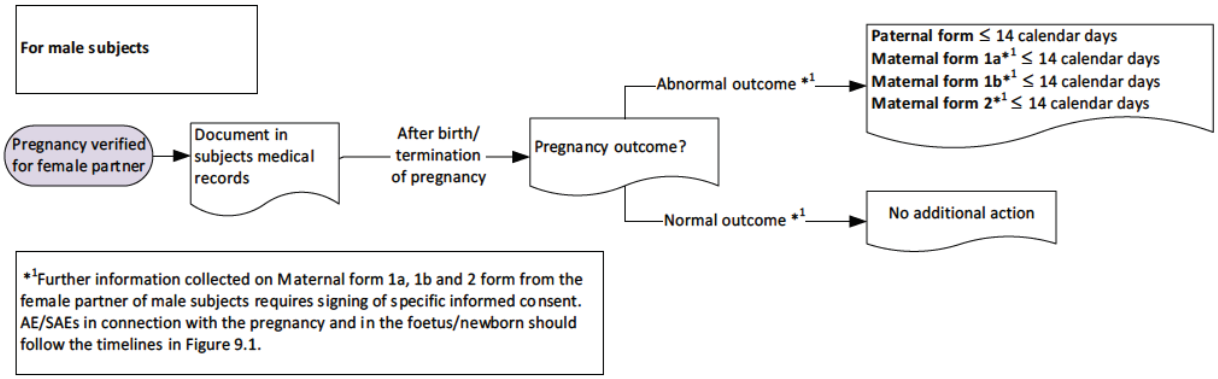


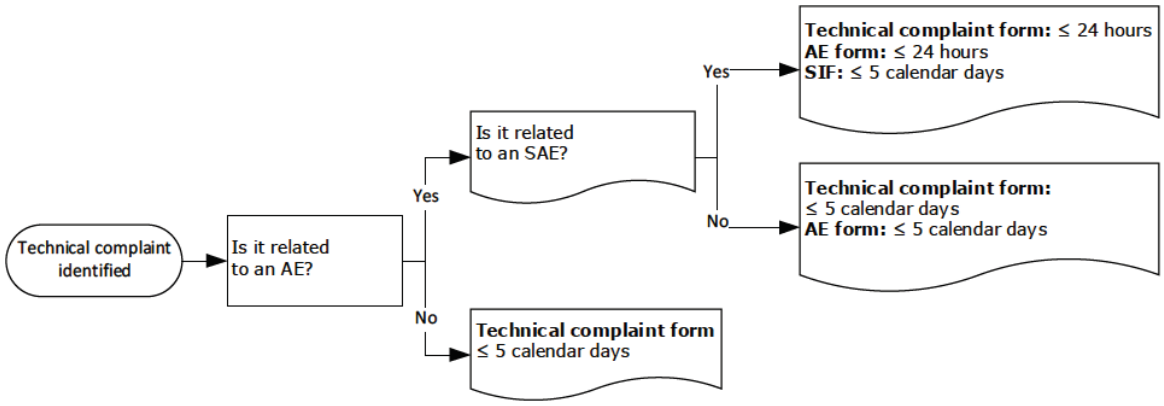
Figure 9-3 Decision tree for determining the forms to complete with associated timelines for pregnancy.

9.6.8 Medical device incidents (including malfunctions)

Section not applicable for this trial. Refer to technical complaints in Section 9.6.9.

9.6.9 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.
The definitions and reporting process for technical complaints can be found in Appendix 6.
Timelines for reporting technical complaints are listed in Figure 9-4.



AE: Adverse Event, SAE: Serious Adverse Event, SIF: Safety Information Form

Figure 9-4 Decision tree for determining the forms to complete with associated timelines for technical complaints.

9.7 Treatment of overdose

The maximum dose to be administered to a patient within 24 hours is 200 IU/kg BW. This dose is recommended to be divided and only considered under exceptional circumstances such as serious trauma or severe bleeding episodes.

If an overdose is suspected, further N8-GP administration should be stopped and the patient should receive treatment as appropriate according to the local practice and guidelines
Novo Nordisk does not recommend specific treatment for an overdose.

The overdose must be reported as a medication error. Refer to Section 9.6.1 for further details.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAE and laboratory abnormalities

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the patient.

For more information on overdose, also consult the current version of the N8-GP IB[5].

9.8 Safety assessments

Assessments at visits must be performed prior to any trial product administration unless otherwise specified.

Planned time points for all safety assessments are provided in the flowchart.

9.8.1 Body measurements

Body measurements (e.g. height and weight*)* will also be measured and recorded as specified in the flowchart in section 2.

- Body weight (registered with one decimal), wearing light clothing only and without shoes (kg or pounds)
- Height, without shoes (cm or inches)

9.8.2 Vital signs

Ear temperature or according to local standard practice, pulse rate (beats/min), as well as diastolic and systolic blood pressure (mm Hg) will be assessed according to flowchart section 2.

Vital sign assessment should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones).

Blood pressure and pulse measurements will be assessed sitting or lying down (the same posture should preferably be used throughout the visits) with a completely automated device. Manual techniques will be used only if an automated device is not available.

All measurements should, if possible, be performed using the same method and position throughout the trial for each individual patient.

9.8.3 Urinalysis

The following parameters will be evaluated based on a urine sample collected according to flowchart section 2

- pH
- Proteins
- Glucose
- Erythrocytes
- Leukocytes
- Albumin/creatinine ratio (central laboratory)

The parameters will be analysed using a urine dip-stick provided by central laboratory and reported in the eCRF. For parameters not possible to analyse via dip-stick (albumin/creatinine ratio), the urine sample will be analysed by the central laboratory.

9.8.4 Biochemistry

Blood samples for analysis of biochemistry will be collected according to flowchart section 2. Biochemistry samples include assessments according to Appendix 2.

9.8.5 Haematology

Blood samples for analysis of haematology will be collected according to flowchart section 2. Only applicable during major surgery, haematology must be collected at the surgery day before the pre-operative loading dose of N8-GP and again after completion of surgery.

Haematology samples include assessments according to Appendix 2 and must be assessed prior to any RBC transfusion

9.8.6 Coagulation parameters

Blood samples for analysis of coagulation parameters will be collected according to flowchart section 2. Coagulation parameter samples include assessments according to Appendix 2

9.8.7 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the flowchart in Section 2.

For patients < 12 years of age: Blood samples for laboratory analysis will be drawn as outlined in the flowcharts. Local guidelines on blood sampling volumes for children must be followed, and the blood sampling volume must comply with recommendations in Directive 2001/20/EC [19] i.e. the recommended blood sampling volume for the patient should not exceed 1% of the total blood volume at one occasion or 3% within 28 days.

9.8.7.1 FVIII activity

Blood samples for FVIII activity will be collected pre-dosing (trough level)[2] and 30 min post-dosing (recovery level)[3] according to flowchart section 2. Note that samples taken post dose must not be taken from the same vein as used for administration of N8-GP.

Plasma FVIII activity will be measured with a chromogenic assay. The analysis will be performed at a laboratory selected by Novo Nordisk.

Chromogenic assay
The chromogenic assay is a two-stage activity assay. In the first stage of the assay, patient plasma (containing an unknown amount of functional FVIII) is preincubated with a reaction mixture consisting of thrombin or prothrombin, FIXa, FX, calcium, and phospholipid. This instantly produces FVIIIa which together with FIXa activates FX. FXa production is proportional to the amount of functional FVIII present in the sample. The second stage of the assay measures FXa through cleavage of an FXa specific peptide nitroanilide substrate. P-nitroaniline is produced, giving a colour that can be measured photometrically by absorbance at 405 nm. The intensity of the produced colour is directly proportional to the FVIII activity present in the sample based on a standard curve generated from samples containing known FVIII activities.

Exploratory assays for measuring N8-GP activity
Other assays may also be applied for measuring activity of N8-GP.

9.8.8 Immunogenicity assessments

9.8.8.1 Evaluation of FVIII inhibitors and antibodies

Blood samples will be analysed for antibodies according to the flowchart see section 2:

- FVIII inhibitors

[2] The trough level is defined as the lowest level of FVIII measure immediately prior to doing and reported as IU/mL
[3] Recovery level is the FVIII level 30 min after trial product administration relative to the dose administered and will be reported as (IU/mL)/(U/kg)

- Anti N8-GP antibodies
- Anti PEG antibodies

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

If FVIII inhibitor development is suspected e.g. an increased number of spontaneous bleeding episodes, bleeding episodes difficult to treat, or FVIII recovery and FVIII trough levels below expected values are observed, additional inhibitor tests can be taken at Unscheduled Visits. A wash-out of approximately 3 days is required prior to blood sampling. All FVIII inhibitor tests must be analysed by the Central Laboratory. Please refer to Appendix 2 for the required blood samples for suspicion of inhibitors.
If the Investigator decides to send a sample for inhibitor testing to a local laboratory, the Investigator must also send a duplicate sample for inhibitor testing to the central laboratory. The data from the Central Laboratory will then be used in the official analysis. Any single positive inhibitor test must be reported as an AESI, see Appendix 4.

A positive FVIII inhibitor test is defined as ≥0.6 BU. A patient is considered to have developed an inhibitor if two separate samples have been tested positive (≥0.6 BU) for inhibitors at the central laboratory preferably with no more than 2 weeks between the tests.

In the event that a patient has a single positive test for FVIII inhibitors (≥0.6 BU), the patient must attend an unscheduled visit as soon as possible or within 1 week after the result is available to take a confirmatory inhibitor test on a separately drawn sample. Please refer to Appendix 2 for the required blood samples for confirming inhibitors.

These samples should preferably be taken prior to any change of treatment and after approximately 3 days wash-out period. A longer wash out period can be applied if the approximately 3 days wash out is not sufficient to avoid drug interference in the FVIII inhibitor assay.

If the second (confirmatory) inhibitor test is negative the patient will be regarded as inhibitor negative and continue in the trial as per protocol.

If the second (confirmatory) inhibitor test is positive, the patient will be regarded as confirmed inhibitor positive and he must be discontinued if:

- FVIII inhibitor >5 BU or
- FVIII inhibitor ≥0.6 and ≤ 5 BU and treatment (prophylaxis or treatment of bleeding episodes) with N8-GP is clinically ineffective

If the second (confirmatory) inhibitor test is positive and the inhibitor level is ≤ 5 BU, the investigator should make a recommendation to Novo Nordisk on whether or not to continue the patient on trial product

If discontinued on trial product the patient should attend the EoT as soon as possible and preferably within 1 week after the confirmatory inhibitor result is available. A follow-up visit should be scheduled 1 month after the EoT and additional follow-up visits may be arranged at intervals as long as clinically warranted.

Patients who develop an inhibitor should be classified as:

- high responders (inhibitor titre > 5 BU),
- low responders (inhibitor titre ≤5 BU)
- transient inhibitor titre <0.6 BU on ≥ 2 consecutive measurements within 6 months without a change in treatment regimen

A confirmed positive inhibitor is considered to have disappeared if:

- the inhibitor titre is <0.6 BU on 2 consecutive inhibitor tests (performed at 2 consecutive visits)
- the FVIII recovery is ≥66% of expected values.

A patient with repeated positive inhibitor test results will count only once in the determination of the inhibitor incidence rate.

9.8.8.2 Antibody assays

FVIII inhibitors

Neutralising antibodies against FVIII (FVIII inhibitors) will be determined by the Nijmegen-modified FVIII Bethesda assay, which is based on a one-stage clotting assay for FVIII activity that measures aPTT in human citrated plasma. Samples will be heat pre-treated to minimise the effect of residual FVIII activity.

Anti-N8-GP antibodies

A radioimmunoassay using radiolabelled N8-GP will be used for measuring antibodies against N8-GP and validated according to guidelines. If the sample was found positive for anti-N8-GP binding antibodies a cross-reactivity test will be performed to identify if the antibodies could cross-react with endogenous FVIII. The level of antibodies will be determined by diluting samples to obtain a titre.

Anti-PEG antibodies

Antibodies against the PEG moiety will be analysed in a direct ELISA using a coating with 40kDa PEG. It is validated according to guidelines to measure anti-PEG antibodies. The screening assay enables the identification of either negative or putative positive samples. Any putative positive

samples are tested in a confirmatory assay to distinguish between true anti-PEG antibody positive and false positive samples. If the test is confirmed positive, a titre determination will be applied to establish the level of anti-PEG antibodies.

9.8.8.3 Antibody assessments in case of severe allergic reaction/anaphylaxis

If a patient experiences a severe allergic reaction/anaphylaxis, extra blood samples should be taken according to flowchart section 2 as soon as convenient, and no later than 2 months after the event.

The blood samples should be collected and send for analysis at the central laboratory according to Appendix 2.

Patients developing anaphylaxis should be carefully investigated and followed-up for inhibitor development. If it is judged necessary, the same analysis will be performed for all patients enrolled in the trial using available blood samples.

9.8.9 Local laboratory assessments – only during major surgeries

Blood samples for FVIII activity and haematology must be collected according to flowchart 2.1 for central lab analysis. The Investigator/Surgeon should perform local lab assessments at his/her discretion.to ensure optimal treatment with N8-GP during major surgery. Only central lab data will be reported.

9.8.9.1 FVIII activity

The Investigator/Surgeon should perform local laboratory assessments of FVIII activity during surgery and the post-operative days in order to be able to adjust the dose level of N8-GP to aim for the recommended FVIII plasma activity level, see Section 7.1.4.2.

Local assessments of FVIII activity can be performed with either chromogenic or one-stage clotting assays. Glycopegylation has been reported to influence the FVIII activity in aPTT based one-stage clotting assays. Therefore careful validation and qualification of specific assays and conditions are necessary for the assessment of FVIII activity in samples containing N8-GP. Interference is avoided when using an N8-GP reference standard as calibrator in the assay. A reference standard provided by Novo Nordisk must be used when running the assays. The reference standard will be provided by Novo Nordisk together with a description of how to handle, store and use it.

Dependent on the type of aPTT reagent used by the local laboratory an exemption from this requirement can be made. In such cases Novo Nordisk will need to approve the suggested assay on an individual basis. For approval of aPTT based assays the investigator must contact Novo Nordisk.

9.9 Pharmacokinetics

Only applicable in case of antibody development, see section 9.8.8.1

9.10 Pharmacodynamics

Not applicable for this trial

9.11 Genetics

Not applicable for this trial

9.12 Biomarkers

Collection of samples for biomarker research is part of this trial as part of the retention for biosamples in Appendix 7. The following samples are required and will be collected from all patients in this trial as specified in the flowchart, see section 2:
Patients < 12 years will only have blood samples taken, if maximum limit for blood sampling is not exceeded.

9.13 PRO questionnaires

The PRO questionnaires should be completed EoT according to the flowchart in section 2. The PRO questionnaire used throughout the trial should be based on the patient's age at screening. The PRO questionnaire measures treatment satisfaction (Hemo-Sat).

Table 9-8: PRO questionnaire to be completed by the patient and/or parent(s)/LAR

Age at screening	Questionnaire to be filled in
16 years or younger	Hemo-SAT Parents
17 years or older	Hemo-SAT adults

10 Statistical considerations

Novo Nordisk will be responsible for the statistical analyses.

10.1 Sample size determination

All patients participating in NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5) fulfilling the inclusion and exclusion criteria of this trial will be eligible to participate where continuous safety assessments will be made. Given that at least 150 patients participate in this trial, the background incidence rate could be up to 0.02 for a given adverse event that was not observed, i.e. the 95% upper bound on the rate of occurrence is 0.02.

10.2 Definition of analysis sets

In general, safety endpoints will be reported for Safety Analysis Set while efficacy endpoints will be reported for Full Analysis Set (FAS). These analysis sets are described below.

The patients or observations to be excluded, and the reasons for their exclusion must be documented before database lock. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Safety analysis set
All patients enrolled in the trial have previously been exposed to trial product and therefore all enrolled patients will be included in the Safety Analysis Set. The trial patients will be analysed according to the received treatment.

Full analysis set
All patients exposed to at least one dose of trial product in the current trial will be included in the Full Analysis Set. The trial patients will be analysed according to the received treatment.

Exceptional outlier plasma activities may be excluded when analysing pharmacokinetic-related endpoints based on the FAS. Default rules for exclusion are described in the paragraph on pre-dose FVIII activity level. Decision to exclude additional FVIII activity measurements from analysis based on the FAS may be made during a review prior to database lock according to ICH-E9, and it will be the joint responsibility of the clinical pharmacology scientist and the trial statistician to decide upon this. The observations to be excluded from the FAS and the reason for their exclusion will be documented and signed by the clinical pharmacology scientist and the trial statistician as part of the database lock minutes. This will also be described in the clinical trial report. The documentation will be stored together with the remaining trial documentation.

10.3 Statistical analyses

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

10.3.1 Primary endpoint

Number of adverse events reported
All reported AEs will be considered treatment emergent adverse events since all patients had been treated with N8-GP in other pathfinder trials prior to participation in this trial. All AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) will be summarised by frequency of events and frequency of patients with any event. Furthermore, all AEs will be summarised by severity and causal relation to trial product. In addition, listings will be provided displaying all AEs, SAEs and AESIs.

10.3.2 Secondary endpoints

For all endpoints based on bleeding episode data, only bleeding episodes treated with N8-GP will be included.

Multiple bleeding locations occurring from the same event (e.g. due to a bicycle accident) or at the same time point will be counted as one bleeding episode.

A re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after completed treatment. If a bleeding episode occurs in the same location later than 72 hours after completed treatment it is considered a new bleeding episode.

10.3.2.1 Supportive secondary endpoints

Incidence of FVIII inhibitors ≥0.6 BU
The number of inhibitor patients will be reported and all inhibitor data will be presented.

Number of bleeding episodes on prophylaxis
The ABR of treatment requiring bleeding episodes will be estimated by a Poisson regression model with logarithmic prophylaxis duration as offset and allowing for over-dispersion. Over-dispersion will be estimated as Pearson's chi-square statistic divided by the degrees of freedom. The estimated ABR will be presented together with a two-sided 95% confidence interval. For sub-groups with no bleeds or less than 5 patients, the 95% confidence interval will not be presented. A sensitivity analysis based on a negative binomial regression model with number of bleeding episodes requiring treatment as the outcome variable and adjusting for exposure time will also be performed.

The analysis of ABR will be repeated as a sensitivity analysis to investigate the potential impact of early withdrawals by imputing number of bleeding episodes for withdrawals. For patients withdrawing prematurely, the number of bleeding episodes counting in the analysis will be imputed up to what they could be expected to have had if they had completed the trial. If e.g. a patient withdraws after 12 months with 5 bleeding episodes, but the patient should have been in the trial for 24 months, then this patient will in the sensitivity analysis count as having had 10 bleeding episodes in 24 months. This is similar to LOCF and will prevent a downwards bias in ABR caused patients with many bleeding episodes withdrawing early. If a patient changes from once weekly to one of the more frequent dosing frequencies, then when doing the sensitivity calculation for once weekly, bleeds during time on the more frequent dosing is calculated using LOCF based on the previous period on every seven day dosing. This is also the case if a patient changes from every seven day dosing more than once, i.e. for each period on more frequent dosing the bleeds for every seven day dosing is imputed based on the previous consecutive period on every seven day dosing.

ABR for each treatment regimen (once weekly, twice weekly, and three times weekly) will be estimated by age group (0-5 years, 6-11 years, 12-17 years and 18- years).

ABR will also be estimated by doing the following further sub-groupings:

- Cause of bleed (spontaneous and traumatic)
- Location of bleed. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Country. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Race. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Ethnicity. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Month in trial. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Time since last dose (0-24 hours, 24-48 hours, 48–72 hours and >72 hours). No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).

Number of spontaneous bleeding episodes on prophylaxis
Included in the above description of ABR by cause of bleed.

Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None

Haemostatic effect will for each treatment regimen (once weekly, twice weekly, and three times weekly) be summarised by age group (0-5 years, 6-11 years, 12-17 years and ≥18 years). Haemostatic effect will be summarised according to:

- Response expressed as excellent, good, moderate, none.
- Success or failure, where success will be defined as a response of good or excellent and failure will be defined as moderate, none or missing
- Success or failure after exclusion of bleeds with missing evaluation of haemostatic response, i.e. success will be defined as a response of good or excellent and failure will be defined as moderate or none information.

Furthermore, success rates will be estimated with 95% confidence intervals using logistic regression accounting for repeated measures within patient assuming compound symmetry working correlation. Age group will be included as a factor and modelling done separately for each treatment regimen. This estimation will be done both including missing haemostatic evaluations as failures and excluding missing evaluations.

Summaries will also be done for the following further sub-groupings:

- Cause of bleed (spontaneous and traumatic). Estimation of success rates and 95% confidence intervals using above described modelling will also be performed (both including missing as failures and excluding missing).
- Location of bleed.
- Severity.
- Country.
- Race
- Ethnicity

Number of N8-GP injections required per bleeding episode
This endpoint will be summarised and listed.

Pre-dose FVIII activity levels on N8-GP prophylaxis
The following rules will be implemented for FVIII pre-dose and post-dose activity to ensure data representing steady-state on a given treatment regimen:

- FVIII activity data prior to the 4th prophylaxis dose will be excluded for each switch in treatment regimen
- FVIII activity data will be excluded if post-dose activity is ≤ pre-dose FVIII activity
- FVIII activity data will be excluded if post-dose sample is taken more than 90 minutes after dosing
- FVIII activity results will be excluded for plasma samples defrosted during transit.

The pre-dose FVIII activity levels will be modelled to get an estimate of the pre-dose level for N8-GP at steady-state. The model will be a mixed model on the logarithmic plasma activity levels with age as a factor and patient as a random effect. Separate modelling will be performed for each treatment regimen. Plasma concentrations below lower limit of quantification (LLOQ) will be set to half the value of the LLOQ. The estimated pre-dose FVIII level will be presented together with the 95% confidence intervals.

A sensitivity analysis will be performed including all activity results except activities measured in relation to the first 4 prophylaxis doses after switch of treatment regimen.

Pre-dose activity will furthermore be summarised by visit and treatment regimen.

Change in joint health status from start to end of trial
Target joint status is assessed at inclusion in trial. For intervals of 12 months, the number of baseline target joints with 0, 1, 2,… number of bleeds is presented.

Haemostatic response during major surgical interventions
The endpoint of assessment of haemostatic effect during major surgical intervention (excellent, good, moderate or none) will be summarised and listed.

Change from baseline till end of trial in treatment satisfaction (Hemo-SAT)
Data will be scored according to established scoring algorithms (where applicable) and changes from first assessment (at screening/V1) to last assessment (at EoT visit) will be summarised and listed using descriptive statistics. Further analysis will be performed separately by Novo Nordisk Health Economics Department.

10.3.3 Exploratory endpoint

Incidence of anti-N8-GP binding antibodies
Number of positive/negative samples will be summarised by visit and listed.

Incidence of anti-PEG binding antibodies
Number of positive/negative samples will be summarised by visit and listed. Furthermore, plots will be created of incremental recovery according to PEG antibody status at baseline and during the trial. Rules for exclusion of FVIII activity measurements are as defined in the paragraph on: “Pre-dose FVIII activity levels on N8-GP prophylaxis”.

10.3.4 Interim analyses

Interim analysis may be performed, if deemed appropriate.

10.4 Pharmacokinetic and/or pharmacodynamic modelling

Data from the trial may be used for exploratory pharmacokinetic and/or pharmacodynamic analysis as needed.

10.5 Additional efficacy related tables/figures/listings

Post-dose activity measurements will be modelled and presented in the same forms as pre-dose activity measurements, see section on "Pre-dose FVIII activity levels on N8-GP prophylaxis".

Incremental recovery is defined as post-dose FVIII activity minus pre-dose FVIII activity and divided by the administered dose. Incremental recovery will be summarised by visit and listed.

10.6 Additional safety related tables/figures/listings

All safety parameters not addressed above such as laboratory parameters, vital signs and physical examinations will be summarised by visit.

Laboratory reference ranges and abnormal laboratory values will be listed.

Furthermore, the following safety related output will be created.

Frequency of adverse events that are reported within the system organ classes nervous system, psychiatric, hepatic and renal disorders
Will be summarised and listed.

Changes in laboratory assessments, including hepatic and renal function parameters
Individual profiles of laboratory parameters will be created by age group as plots of parameter values vs. time since first dose in trial.

Estimated glomerular filtration rate (eGFR) in ml/min per 1.73 m^2 will be calculated e.g. using following formula:

For ≥ 18 years of age: Constant * s-cr $^{-1.154}$ * age$^{-0.203}$ * [1.212 if black or African American] *[0.742 if female], where constant=175*(88.4$^{1.154}$) [17]
For <18 years of age: Constant* height (cm)/s-cr, where constant=0.413*88.4 [18]

eGFR will also be plotted vs. baseline value.

11 References

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ABR	Annualised Bleeding Rate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APCC	Activated Prothrombin Complex Concentrates
BU	Bethesda Units
BW	Body Weight
CHO	Chinese Hamster Ovary
CLAE	Clinical Laboratory Adverse Event
CRF	Case Report Form
CRP	C-reactive protein
CTR	Clinical Trial Report
DCF	Data Clarification Form
DFU	Direction for Use
DRE	Disease Related Event
DUN	Dispensing Unit Number
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoT	End of Trial
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FFP	Fresh Frozen Plasma
FPFV	First Patient First Visit
FIX	Coagulation Factor IX
FVIII	Coagulation Factor VIII
FU	Follow-Up

GCP	Good Clinical Practice
Hemo-SAT	Haemophilia Satisfaction Survey
HCP	Host Cell Protein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
i.v.	Intravenous
IWRS	Interactive Web Response System
LAR	Legally Acceptable Representative
LPLV	Last Patient Last Visit
MIDF	Monitor-Initiated Discrepancy Form
N8-GP	Turoctocog Alfa Pegol
NIMP	Non-Investigational Medical Product
PCD	Primary Completion Date
pd-aPCC	Plasma-Derived Activated Prothrombin Complex Concentrates
pd-PCC	Plasma-Derived Prothrombin Complex Concentrates
PEG	Polyethylene Glycol
PRO	Patient Reported Outcome
rFVIIa	Activated Recombinant Factor VII
rFVIII	Recombinant Factor VIII
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMM	Trial Materials Manual

V1, V2...	Visit 1, Visit 2 etc
WFH	World Federation of Haemophilia

Appendix 2 Clinical laboratory tests

The tests detailed in Table 12-1 will be performed by the central laboratory.

Table 12-1 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Haemoglobin • Leucocytes • Thrombocytes
Biochemistry	• Alanine Aminotransferase (ALT) • Bilirubin • Creatinine • Urea • C-reactive protein (CRP)
Coagulation parameters	• Lupus anticoagulant • von Willebrand factor
FVIII activity	• Pre-dose FVIII activity level (trough) • Post-dose FVIII activity level (recovery)
Antibodies	• FVIII inhibitors • Anti N8-GP antibodies • Anti PEG antibodies
Antibodies (in case of severe allergic reactions)	• FVIII activity • FVIII inhibitors • anti-N8-GP antibodies • anti-PEG antibodies • anti-CHO-HCP antibodies • Tryptase (in case of systemic reactions) • IgE against N8-GP and optional against CHO-HCP
Confirmatory/suspision of inhibitor Inhibitor follow-up visit	• FVIII inhibitors • Anti N8-GP antibody • Anti PEG antibodies • FVIII activity • Lupus anticoagulant .
Urinalysis	• Albumin/creatinine ratio
Human biosamples for retention	• further characterisation if needed (Appendix 7)

Local laboratory results are only required in the event of major surgery where the central laboratory results are not available in time for treatment evaluation. If a local sample is required, a sample for central laboratory analysis must be obtained at the same time.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.

The investigator must review all laboratory results for concomitant illnesses and AEs.
Laboratory samples will be destroyed no later than at end of trial or no later than at finalisation of the clinical trial report.
Human biosamples for retention will be stored as described in Appendix 7.

Appendix 3 Trial governance considerations

1) Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[21] and applicable ICH Good Clinical Practice (GCP) Guideline [22]
- Applicable laws and regulations
- The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial patients.
- Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - Providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - Ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

The investigator or his/her representative will explain the nature of the trial to the patient and/or the patient's LAR and answer all questions regarding the trial. The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.
Patients must be informed that their participation is voluntary. Patients or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines [22], Declaration of Helsinki [21] and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.

Patients and/or their LAR must be re-consented to the most current version of the informed consent form(s) during their participation in the trial. A copy of the informed consent form(s) must be provided to the patient or the patient's LAR.
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.

Long-term storage of human samples
If allowed according to local law patient will be asked to sign a consent that addresses long-term storage of human samples and/or the use of samples for optional exploratory research. The objectives of the exploratory research must be explained to each patient.

4) Information to patients during trial

All written information prepared by Novo Nordisk to patients must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations. The patient may receive, for example, a "thank you for your participation in this trial" letter.

5) Data protection

Patients will be assigned a 6-digit unique identifier, a patient number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

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

The patient must be informed that his personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the patient.

The patient must be informed that his medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee
Novo Nordisk has constituted an internal N8-GP safety committee to perform on-going safety surveillance.

The Safety Committee works according to a written guideline. The Safety Committee is responsible for reviewing any safety concern, signal or alert and determining actions to be taken according to the guidelines for the Safety Committee.

Data monitoring committee
As this is an open label and non-randomised trial no data monitoring committee will be established for this trial. An internal Novo Nordisk Safety Committee has been established with the overall responsibility of overseeing the safety of the patients enrolled in the trial.

7) Publication policy

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 investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information

obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial. One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

Communication of results
Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. 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. 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.

Authorship
Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors [24].

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned 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.

Site-specific publication(s) by investigator(s)
For a multicentre 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. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

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.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[25], the Food and Drug Administration Amendment Act (FDAAA)[26], European Commission Requirements[27, 28, 29] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial corresponding to visit EoT. If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed visit EoT. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)
Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
All patient data relating to the trial will be recorded on eCRFs and paper CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Novo Nordisk will provide a system for the eCRFs. This system and support services to the system will be provided by an external supplier. The activities of this vendor will be under the direction and supervision of Novo Nordisk.

The investigator or delegated person has to ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- PRO questionnaires
- Paper Diary

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- AE forms
- Pregnancy forms
- Safety information forms
- Technical complaint forms

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

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

Corrections to eCRFs

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

If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.

Corrections in paper CRFs

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

If a CRF accountability page is not implemented, then an alternative CRF accountability system should be set up ensuring a central and easy overview of unused or missing pages at patient level.

Case report form flow
The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes. Queries to data in the eCRF must be answered in the system preferably within 3 days and during interim or DBL preferably daily.

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

Paper Diary
Novo Nordisk will provide the patient and/or LAR with a paper diary for recording of details of their home treatment, bleeding episodes and treatment of bleeding episodes.

Patients will be instructed in the use of the diary by the investigator or delegated person before recording any data.

The diaries will be returned by the patient at every visit.

Investigator review of Diary data
It is the responsibility of the Investigator or delegated staff to review and enter the diary data reported by the patient. As a minimum it must be verified that the diary data is complete, consistent and according to the requirements defined in this protocol. This also includes the number of doses reported in the diary reviewed against the number of vials accounted for actually used by the patient.

Upon review the Investigator or delegated staff must document that the review has taken place and any actions required e.g. retraining of the patient and/or change to the data. Changes can only be done if the patient confirms the correctness of the data.

Monitoring
The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical

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

Trial monitors will perform on-going source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of patients are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.

Monitors will review the patient's medical records and other source data e.g. the diaries and PROs, to ensure consistency and/or identify omissions compared to the eCRF.

Protocol compliance
Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the trial database.

10) Source documents
All data entered in the eCRF must be verifiable in source documentation other than the eCRF.

The original of the completed diaries and PROs must not be removed from the trial site.

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the trial site.

Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
It must be possible to verify patient's medical history in source documents such as patient's medical record. Haemophilia details will be obtained from the baseline data recorded on the patient in previous trial (NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5))

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, eCRF and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific eCRFs and other patient data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic 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.

Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or 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.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of patients by the investigator

- discontinuation of further trial product development.

13) 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 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 that 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).

14) 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 local laws and guidelines, see Appendix 8.

15) Web-portal for document exchange

During the trial a web-portal will be used for document exchange between Novo Nordisk and the sites. The web-portal is not an archiving tool but could be used as a temporary archiving place during the trial as judged by the investigator.

Appendix 4 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial patient that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A CLAE: a clinical abnormal laboratory finding 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. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent..
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions other than haemophilia should be recorded as medical history/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.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** • Hospitalisation signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note: ▪ 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.
• **Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Important medical event:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
- The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
  - suspicion of transmission of infectious agents via the trial product.
  - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Description of AEs requiring additional data collection (via specific event form) and/or AESIs

AE requiring additional data collection

- Hypersensitivity

AESIs

An AESI is an event, which in the evaluation of safety, has a special focus due to requirements from regulatory authorities.

- Inhibitor development

Medication error:

A medication error concerning trial products is defined as:

- Administration of wrong drug.

Note: Use of wrong DUN is not considered a medication error unless it results in a confirmed administration of wrong drug.

- Wrong route of administration, e.g. intramuscular instead of i.v.
- Accidental administration of higher dose than intended, however, 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.

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the CRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- 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. For sign-off of SAE related forms refer to "SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication or Non-investigational medical product (NIMP): if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as NIMP or

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.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product*(s)* should be assessed as:

- 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.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the IB[5], for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the patient has not improved and the symptoms are unchanged or the outcome is not known.

- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the patient is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.
If a patient dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the CRF.

SAE reporting via electronic CRF

- Relevant forms (AE and safety information form) must be completed in the CRF.
- For reporting and sign-off timelines, see box below.
- If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the CRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below).
- The site will enter the SAE data into the CRF as soon as it becomes available, see 9.6.1.
- After the trial is completed at a given site, the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 9-2):
AE form within 24 hours.
Safety information form within 5 calendar days.
Both forms must be signed within 7 calendar days.

Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 5 Contraceptive guidance and collection of pregnancy information

Collection of pregnancy information

Male patients with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while male patient is participating in this trial.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Novo Nordisk within 14 calendar days of learning of the abnormal outcome of the partner's pregnancy. Information on the status of the mother and child will be included.
- Generally, follow-up will be 1 month following the delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Appendix 6 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition
• 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:

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

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the CRF within the timelines specified in Figure 9-3 . If the CRF is unavailable or when reporting a technical complaint that is not patient related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Appendix 7 Retention of human biosamples

Antibody samples will be retained for later analysis for further characterisation if required by health authorities or for safety reasons. These samples will be stored at a bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

Future characterisation may address issues such as unexpected safety events, refinement of the pharmacokinetic or anti-drug antibody assessments and to improve the understanding of the mechanism of action.

If allowed according to local law remaining blood samples may be retained for later analysis for further characterisation. As new biomarkers related to the disease or related diseases and/or safety, efficacy, or mechanism of action may evolve the analyses may also include biomarkers that are unknown at present or have not been included in the scientific hypothesis at initiation of the trial.

The samples will be stored at a Novo Nordisk designated central laboratory after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed. Samples might be transferred to other countries, if not prohibited by local regulations. The patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives.

Only Novo Nordisk staff and biorepository personnel (if applicable) will have access to the stored blood samples.

In the event that the collected biosamples, including remaining blood sample 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. In such case, a written summary of the findings, including listings of patient specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious hereditary diseases, other un-treatable diseases or any other abnormal findings could be part of the observations. Patients can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.

Appendix 8 Country-specific requirements

Only for Germany, Hungary, Netherlands, and Switzerland:

- Date of Birth can only be year of birth

Only for Canada:

- It is not allowed to collect race and ethnicity.

Only applicable for France:

- A specific indemnity statement is required: 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 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.

- It is not allowed to collect race and ethnicity.

Only applicable for Japan:

- Head of study site is responsible for drug accountability. The head of study sites should assign some or all of the responsibilities to a trial product storage manager.

- The N7088-4410 trial will be classified as a post-marketing clinical trial if obtaining marketing approval in Japan. Therefore, the term "chiken", which is a term for a clinical trial conducted for obtaining marketing approval, is replaced in the protocol and other related materials/documents with the term "seizouhanbaigorinshoushiken (i.e. post-marketing clinical trial)". If obtaining marketing approval in Japan, sponsor's assessment of expectedness is done according to the package insert of the commercial products in Japan. Additionally, the IB is also used for the assessment of expectedness for reporting to the Investigator and the head of a site.

Only applicable for Brazil:

- Resolution (Res. CNS 466/12): At the end of the trial, all participant subjects should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the trial.

- No patients from Brazil will participate in the optional retention of biosamples part of the trial, see Appendix 7.

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 1.0 Trial ID: NN7088-4410 UTN: U1111-1202-2780 EudraCT no.: 2017-003788-36	~~CONFIDENTIAL~~	Date: Version: Status: Page:	10 August 2018 2.0 Final 1 of 4

Novo Nordisk

Protocol Amendment

no 1.0

to Protocol, version 1.0 dated 13 December 2017

Trial ID:NN7088-4410

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Trial phase: 3b
Applicable to France

Protocol Amendment no 1.0 Trial ID: NN7088-4410 UTN: U1111-1202-2780 EudraCT no.: 2017-003788-36	~~CONFIDENTIAL~~	Date: Version: Status: Page:	10 August 2018 2.0 Final 2 of 4

Novo Nordisk

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1 Introduction including rationale for the protocol amendment

Following Clinical Trial Application review by the French Health authorities, one additional discontinuation criteria will be added to apply for sites in France. This relates discontinuation of trial treatment in case of a major thromboembolic event (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as per investigator.

In this protocol amendment:

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

2 Changes

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5.1 Overall design

(…)

The follow-up period is 1 month after EoT and is only applicable for patients who have developed an inhibitor or discontinued trial product due to lack of haemostatic effect of the trial product (discontinuation criteria no. 2), or anaphylaxis to the trial product (discontinuation criteria no. 4) *or experience a major thromboembolic event (discontinuation criteria no. 9)*.

8.1 Discontinuation of trial treatment

The patient must be discontinued from trial product, if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Lack of haemostatic effect of the trial product. The bleed is not controlled after 48 hours of appropriate turoctocog alfa pegol treatment
3. FVIII inhibitor (>5 BU) as confirmed by re-testing by Central Laboratory
4. Allergy/anaphylaxis to the trial product requiring systemic treatment
5. Treatment with other FVIII containing products other than trial product turoctocog alfa pegol or anti-coagulants (therapeutic doses)
6. Incapacity or unwillingness to follow the trial procedures
7. FVIII inhibitor (≥0.6 and ≤ 5 BU) as confirmed by re-testing by Central Laboratory that makes treatment (prophylaxis and/or treatment of bleeding episodes) with turoctocog alfa pegol clinically ineffective

8. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product.
9. *In the case of a major thromboembolic event (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as per investigator*

8.1.1 Rationale for discontinuation of trial treatment criteria

No 1-4 are included to protect the patient's safety.
No 5 and 8 are included not to confound the effects of the investigational product.
No 6 ~~and~~ 7*, and 9* are included to protect the patient's safety.

Protocol Amendment

no 2

to Protocol, version 1 dated 13 December 2017

Trial ID: 7088-4410

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Trial phase: 3b
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

Visits 2, 4, 6 and 8 may be conducted as phone visits for patients receiving trial drug at home as part of the 'Direct to Patient' (DTP) programme.

The choice of vial strength for each patient will be based on the body weight at the last scheduled visit conducted in trial 7088-3859 or 3885 prior to the initial shipment of trial product in trial 7088-4410. This to ensure availability of trial product at the start of trial.

Added that patients may be discontinued from the trial when commercial N8-GP becomes available in their respective country. Trial discontinuation will allow for patients to undertake commercial treatment instead of participating in a clinical trial.

Sentence in the haematology section deleted to clarify that only FVIII activity must be taken 30 min post dose, not haematology.

"Web-portal for document exchange" section added to appendix 3 – Trial governance considerations.

A few minor administrative changes performed.

In this protocol amendment:

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

2 Changes

Section 2 Flowchart

i.	For selected countries, and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries to the patient's home by courier service. The bodyweight and height may be re-used from the previous visit. *For these patients visit 2, 4, 6 and 8 may be conducted as a phone visit.*

Section 5.2.1 Trial period completion for a patient:

Trial period completion is defined as when the patient has completed the final scheduled visit ('end of trial' according to the flowchart).
'Date of trial completion' is the date the patient completed the final scheduled visit.

The patients may be completed from the trial when N8-GP becomes commercially available in their respective country. The completion should be performed as an EoT visit according to the flowchart independent of the visit window.

Section 7.5

For a patient weighing <80 kg at ~~screening/V1~~ *the last scheduled visit conducted in trial NN7088-3859 or 3885*, 2000 IU vials will be dispensed, and for a patient weighing ≥ 80 kg at ~~screening/V1~~ *the last scheduled visit conducted in trial NN7088-3859 or 3885*, 3000 IU vials will be dispensed. The patient will remain on the same N8-GP product strength throughout the trial.

Section 7.6 Shipment of trial product to patient's home

For selected countries, and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the patient's home by courier service. *For these patients visit 2, 4, 6 and 8 may be conducted as a phone visit.*

Section 8 Discontinuation/Withdrawal criteria

The patient may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made to have the patients, who discontinue trial product, attend EoT visit to collect the required data for the analysis of the primary (and confirmatory secondary) endpoint. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

For patients shifting to commercial products see section 5.2.1.

Section 9.8.5 Haematology

Blood samples for analysis of haematology will be collected according to flowchart section 2. Only applicable during major surgery, haematology must be collected at the surgery day before ~~and after~~ the pre-operative loading dose of N8-GP and again after completion of surgery. ~~The sample taken post-dose must not be taken from the same vein used for administration of N8-GP~~

Appendix 3 – Trial governance considerations

15) Web-portal for document exchange

During the trial a web-portal will be used for document exchange between Novo Nordisk and the sites. The web-portal is not an archiving tool but could be used as a temporary archiving place during the trial as judged by the investigator.