Cover Page for Protocol and SAP

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16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

Protocol

Trial ID:NN7088-3908

pathfinder™6

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A

Trial phase: 3a

Protocol originator:

[redacted], International Trial Manager

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List of abbreviations

AE	adverse event
APCC	activated prothrombin complex concentrate
BP	blood pressure
BU	Bethesda Units
BW	body weight
CRF	case report form
CFR	code of federal regulations
CHMP	Committee for Medical Products for Human Use
CHO	chinese hamster ovary
CNS	central nervous system
CLAE	clinical laboratory adverse event
CRO	contract research organisation
CTA	clinical trial application
CTR	clinical trial report
CV	curriculum vitae
DU	dispensing unit
DUN	dispensing unit number
eCRF	electronic case report form
ED	exposure day (Definition: An exposure day (ED) is any day on which the patient has been exposed to trial product)
eDiary	electronic diary
EMA	European Medicines Agency
EOT	end of trial
eSIF	electronic safety information form
F8	factor VIII gene
FAS	full analysis set
FDA	Food and Drug Administration

FPFV	first patient first visit
FVII	coagulation factor VII
FVIII	coagulation factor VIII
FVIIIa	activated coagulation factor VIII
FX	coagulation factor X
FU	follow-up
GCP	Good Clinical Practice
HCP	host cell protein
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HTC	haemophilia treatment centre
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IgE	immunoglobulin E
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
IR_{30min}	incremental recovery 30 min
ITI	immune tolerance induction
IU	international unit
I.V.	intravenous
IV/WRS	interactive voice/web response system
LAR	legally acceptable representative
LOCF	last observed carried forward
M	months
MedDRA	medical dictionary for regulatory activities

MESI	medical event of special interest
N8-GP	turoctocog alfa pegol, glycopegylated recombinant coagulation factor FVIII
NIMP	non-investigational medicinal product
PDCO	Paediatric Committee (EMA)
Pd-aPCC	plasma-derived activated prothrombin complex concentrates
PdFVIII	plasma derived FVIII
Pd-PCC	plasma-derived prothrombin complex concentrates
PEG	polyethylene glycol
PI	principal investigator
PIP	paediatric investigation plan
PK	pharmacokinetics
PPX	prophylaxis
PT	prothrombin time
PTP	previously treated patients
PUP	previously untreated patients
rFVIIa	activated recombinant factor VII
rFVIII	recombinant coagulation factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SIF	safety information form
SDV	source data verification
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TMM	trial materials manual
UNS	unscheduled visit

UTN	universal trial number
V	visit
W	weeks

1 Summary

Objective(s) and endpoint(s):

Primary Objective

- To evaluate immunogenicity of N8-GP (turoctocog alfa pegol) in previously untreated patients (PUPs) with severe haemophilia A

Primary Endpoint

- Incidence of FVIII inhibitors

Secondary Objectives

- To evaluate safety other than immunogenicity of N8-GP (turoctocog alfa pegol) in PUPs with severe haemophilia A
- To evaluate efficacy of N8-GP (turoctocog alfa pegol) in PUPs with severe haemophilia A
  - in long-term prophylaxis treatment (bleeding preventive effect)
  - in the treatment of bleeding episodes

Key Secondary Endpoint

- Frequency of adverse events including serious adverse events and medical events of special interest.
- Incidence of confirmed high titre inhibitors (defined as inhibitor titre > 5BU).
- Number of breakthrough bleeding episodes during prophylaxis with N8-GP (annualised bleeding rate).
- Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “none”).

Time frames for evaluation of Objectives/Endpoints

All objectives/endpoints will be evaluated when the first 50 PUP have reached at least 50 exposure dates, when the first 100 PUP have reached 100 exposure dates, and at end of trial. End of trial will be up to 4 years after the patient has reached 100 exposure dates.

Trial design:

This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of PUPs (age below 6 years) with severe haemophilia A (factor VIII baseline level < 1%). There will only be one treatment arm and no comparator.

The European medical agency requires submission of safety and efficacy data from minimum 50 exposure days in at least 50 patients for approval of the indication in PUPs, with a post-approval commitment to follow- at least 100 patients for a minimum of 100 exposure days. When the first 50 patients have reached a minimum of 50 exposure days, the analysis and evaluation for the main trial report will be performed. All patients continue in the extension phase for the purpose of collecting data for a minimum of 100 exposure days in at least 100 patients.

Trial population:

Inclusion criteria

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male, age < 6 years at the time of signing informed consent
- Diagnosis of severe haemophilia A (factor VIII activity level < 1%) based on medical records or central laboratory results
- No prior use of purified clotting factor products (5 previous exposure to blood components is acceptable)

Exclusion criteria

- Any history of FVIII inhibitor (defined by medical records)
- Known or suspected hypersensitivity to trial product or related products
- Previous participation in this trial. Participation is defined as administration of trial product
- Receipt of any investigational medicinal product within 30 days before screening
- Congenital or acquired coagulation disorder other than haemophilia A. Any chronic disorder or severe disease which, in the opinion of the Investigator, might jeopardise patient's safety or compliance with the protocol.
- Patient's parent(s)/legally acceptable representative(s) mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation

Assessments:

Key Safety assessments

- Antibody assessment: binding antibodies towards trial product (N8-GP) and inhibitory antibodies (factor VIII inhibitors)
- Other adverse events

Key Efficacy assessments

- Breakthrough bleeding episodes (annualised bleeding rate)

- Haemostatic effect in treatment of bleeds
- Number of doses to treat a bleed

Trial product

The following trial product will be used in the trial:

- N8-GP (500 U/vial and 2000 U/vial)

N8-GP is supplied as a sterile, freeze-dried powder in a single use vial with a nominal content of 500 U/vial or 2000 U/vial to be reconstituted with 4.3 mL 0.9% Sodium Chloride solution for intravenous injection
N8-GP is used for prevention and treatment of bleeding episodes.

2 Flow chart

Table 2–1 Flow chart visits and assessments

Visit number	**0**[1]	**1**[1]	**2**	**3**	**4-6**	**7-8**	**9**	**10-13**	**14**[18]	**15-X**[19]	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**End of main**	**Dosing**	**End of extension**	**Dosing** (until EOT)	**End of Trial**
Time of visit (ED(s))[2]	**0**	**1**	**2**	**5**	**10, 15, 20**[3]	**30,40**	**50**	**60, 70, 80, 90**	**100**	**NA**	
Visit interval (ED(s))[2]		**0**	**0**	**3±1**	**5±2**	**10±2**	**10+2**	**10±2**	**10+2**	**24w±4w**	
PATIENT RELATED INFORMATION											
Informed consent	X										
Assent form, if applicable[4]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Informed Consent for Genotyping	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]					
Inclusion / Exclusion criteria	X										
Eligibility evaluation		X									
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X
Demography	X										
Concomitant illness & Medical history	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
ADVERSE EVENTS											
Adverse events[5]	X	X	X	X	X	X	X	X	X	X	X
CLINICAL ASSESSMENTS											
Body measurements[6]	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X		X		X
Vital signs[7]	X	X[7]					X		X		X
CENTRAL											

Visit number	**0**[1]	**1**[1]	**2**	**3**	**4-6**	**7-8**	**9**	**10-13**	**14**[18]	**15-X**[19]	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**End of main**	**Dosing**	**End of extension**	**Dosing** (until EOT)	**End of Trial**
Time of visit (ED(s))[2]	**0**	**1**	**2**	**5**	**10, 15, 20**[3]	**30,40**	**50**	**60, 70, 80, 90**	**100**	**NA**	
Visit interval (ED(s))[2]		**0**	**0**	**3±1**	**5±2**	**10±2**	**10+2**	**10±2**	**10+2**	**24w±4w**	
LABORATORY ASSESSMENTS											
FVIII activity – trough[9]	X[8]	X		X	X	X	X	X	X	X	X
FVIII activity – recovery (30 post-dose)		X		X	X	X	X	X	X	X	
N8-GP/FVIII binding antibodies[9]		X		X	X	X	X	X	X	X	X
PEG antibodies[9]		X					X		X		X
FVIII inhibitor test[9]		X		X	X	X	X	X	X	X	X
HIV 1 and 2 antibodies	(X)[10]										
CD4+ lymphocyte count and HIV viral load	(X)[10]										
Haematology	X	X[11]					X		X		X
Biochemistry	X	X[11]					X		X		X
F8 + *HLA* genotype testing	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]					
Allergic reaction testing	X										
TRIAL PRODUCT ADMINISTRATION											
N8-GP administration		X	X	X	X	X	X	X	X	X	
Change of regimen			X	X	X	X	X	X	X	X	
N8-GP dispensing for home treatment			X[13]	X	X	X	X	X	X	X[17]	
N8-GP accountability		X	X	X	X	X	X	X	X	X	X
TRAINING AND REMINDERS											
Trial card dispensing	X										

Visit number	**0**[1]	**1**[1]	**2**	**3**	**4-6**	**7-8**	**9**	**10-13**	**14**[18]	**15-X**[19]	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**Dosing**	**End of main**	**Dosing**	**End of extension**	**Dosing** (until EOT)	**End of Trial**
Time of visit (ED(s))[2]	**0**	**1**	**2**	**5**	**10, 15, 20**[3]	**30,40**	**50**	**60, 70, 80, 90**	**100**	**NA**	
Visit interval (ED(s))[2]		**0**	**0**	**3±1**	**5±2**	**10±2**	**10+2**	**10±2**	**10+2**	**24w±4w**	
Home treatment training		X	X	X	X	X	X	X	X	X	
eDiary training		X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	
Compliance check of eDiary data, protocol requirements and used drug			X	X	X	X	X	X	X	X	X
Contact with patient's parent/LAR		(X)[16]								(X)[16]	
IV/WRS[15]	X	X	X	X	X	X	X	X	X	X	X
End of trial form											X

Table 2–2 Flow chart explanatory descriptions

Footer	Description
1	V0 and V1 can be combined to one visit, if the patient fulfils the in- and exclusion criteria
2	When the patient has commenced prophylaxis, visits can for practical purposes be planned according to the predicted number of EDs based on the patient's prophylaxis regimen. A visit does not need to be re-scheduled even if the actual EDs between visits turn out higher or lower due to treatment of bleeding episodes during the home treatment period.
3	If not already on prophylaxis, all patients must initiate prophylaxis treatment no later than at V6. Pre-prophylaxis is only allowed for children below the age of 24 months or up to V6, whatever comes first. Visits at 10EDs±2EDs, 15EDs±2EDs, 20EDs±2EDs must be performed even the window allows 2 visits to be 2 EDs aside (eg ED12 and ED13)
4	Any patient above the age of 3 years should sign a child assent form, if capable, and if required by local requirements. This can be performed on a separate day. As this is a long term trial the investigator should check the progressing maturation of the child and his ability to assent throughout the trial.
5	After Informed consent has been obtained all Adverse Events must reported in the eCRF
6	The frequency of body weight measurements should follow local practice, but should at least be measured every 10 weeks in children ≥3 years of age and within a timeframe of 6 weeks in children <3 years of age. Please refer to Section 8.3.1
7	Vital signs should be measured prior to dosing at all screening, V1, V9, V14 and EOT. In addition vital signs should also be measured 30±10minutes after the first injection with N8-GP at V1.
8	FVIII activity should only be measured at V0 if diagnosis of haemophilia A (FVIII<1%) has not been documented in the patients' medical record. FVIII activity at V0 can either be measured at local or central laboratory depending on the urgency of receiving the result i.e. in case V0 and V1 are combined
9	Blood samples must be collected prior to dosing at dosing visits. Please check that the required washout period has been met for inhibitor testing, see section 8.1.1.3
10	HIV 1 and 2 antibodies are only to be assed, if status is unknown (i.e. previous test older than 6 months). Tests for CD4+ lymphocyte count and HIV viral load are only required for HIV positive patients. Sampling can be postponed to the earliest convenient visit to ensure that the allowed blood volume is not exceeded
11	In case V1 is more than a month after V0, Haematology and Biochemistry need to be retaken at V1 prior to dosing, see Section 8.4.2.4 and 8.4.2.5
12	*F8* and *HLA* genotype sample is only allowed upon patient's parent(s)/LAR(s) signing the consent for genotyping and should only be done if not already documented in patient's medical record. The sample can be collected at any visit between V0 and V9, taking the limitation of the allowed blood sampling volume into account
13	Home treatment can be postponed until the patient's parent(s)/LAR(s) are comfortable with reconstitution procedure and administration of N8-GP
14	eDiary training prior to initiating home treatment to ensure that the patient's parent(s)/LAR(s) are comfortable entering data in the eDiary. Retrain in the use of the eDiary as applicable at V2-VX to ensure entry of correct eDiary data
15	IV/WRS to be used for screening, visit registration, trial drug dispensing, drug accountability and completion. Refer to Section 10 for more information
16	When site visits are more than 3 months apart the Investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week to ensure patients well-being. For details please refer to Section 8.8.4. Primarily expected to be applicable for patients treated according to pre-prophylaxis (V1-V6) and whom visit the trial site less frequent than every 3 months. In addition all visits from V15-VX will be scheduled every 24 weeks ±4 weeks
17	At every dosing visit from V15-VX, drug will be dispensed to cover up to 3 months of treatment. Depending on patient's treatment regimen, an additional dispensing visit might be needed to cover treatment in the entire period between visits.
18	In case V14 will be the EOT visit, the procedures for the EOT visit should be followed
19	V15 to VX will be performed every 24 EDs ± 4EDs until the End of Trial

3 Background information and rationale for the trial

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

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

3.1 Background information

3.1.1 Haemophilia A

Haemophilia A is a recessive X-linked congenital bleeding disorder, resulting from deficiency of the essential blood coagulation factor VIII (FVIII) and characterised by increased bleeding tendency. Haemophilia is classified as "severe (<1%)", "moderate (1-5%)" or "mild (>5%)" according to the plasma activity of the affected clotting factor.

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 FVIII products approximately 3 times a week. However, with currently marketed FVIII products, the clinical practice for prophylaxis is associated with substantial unmet medical needs, primarily linked to cumbersome, frequent and painful i.v. administration of the haemostatic agent. Consequently adherence to prophylaxis is in general suboptimal, and non-compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with FVIII products.

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 (PUPs) with severe haemophilia A following exposure to FVIII products.[3,4] Availability of a recombinant human FVIII (rFVIII) product with reduced immunogenicity has been the priority request by the haemophilia community for many years. The immunogenicity of N8-GP will be monitored in the clinical setting and further investigated in nonclinical models to explore preliminary findings of reduced binding and uptake of N8-GP in human antigen presenting cells.

3.1.2 N8-GP

N8-GP is a glycopegylated recombinant coagulation FVIII hereafter referred to as N8-GP and represents a new rFVIII with a longer terminal half-life (t½) than currently available rFVIII

products. Clinical areas of interest include prevention (prophylaxis) and treatment of bleeding episodes in patients with haemophilia A without inhibitors, as well as the prevention of bleeding in surgery undertaken in these patients.

The N8-GP product is based on turoctocog alfa, which is a state of the art serum-free truncated rFVIII containing 21 amino acids of the wild type B-domain. N8-GP is a rFVIII molecule where a single 40-kDa polyethylene glycol (PEG) is specifically attached to a unique O-glycan in the truncated B-domain of turoctocog alfa, manufactured using three enzymes all produced by recombinant technology. When activated by thrombin, the B-domain containing the pegylation is cleaved off, thus generating active FVIII (FVIIIa) which is similar in structure to native activated FVIII - a key feature of the compound. N8-GP is a recombinant product, not based on human blood components, and hence the risk of transmission of viral and other blood-borne diseases has been eliminated. No animal-derived components besides the cell line (Chinese Hamster Ovary (CHO) cells) are used during the manufacturing process.

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

3.1.3 N8-GP clinical data

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

In the first human dose trial (NN7088-3776), a single dose of N8-GP (25, 50 or 75 U/Kg) was administered to 26 adult previously treated patients (PTPs) 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 commercially available FVIII products (patient's previous product including rFVIII and plasma derived FVIII (pdFVIII)).[6]

Three clinical trials investigating the safety and efficacy of N8-GP are on-going. The pivotal trial (pathfinder™2) in adolescents and adults aims to document the safety and efficacy of a prophylactic regimen with 50 U/Kg body weight (bw) of N8-GP given every four days. The surgery trial (pathfinder™3) aims to document the safety and efficacy of N8-GP during major surgery. The pathfinder™5 trial evaluates PK, safety and efficacy of N8-GP in previously treated children (below 12 years of age).

An internal review of safety and efficacy data for 52 bleeding episodes reported by 10 patients in the pivotal pathfinder™2 trial (including adolescent and adult PTPs) was performed in order to initiate N8-GP prophylaxis treatment in patients from the US participating in pathfinder™2, and to

allow the pathfinder™3 surgery trial to open globally. The cut-off-date was 12-Feb-2013. Among the patients included in the review N8-GP was well tolerated and no safety issues have been identified. In particular no FVIII inhibitors were detected and no treatment related serious adverse events (SAEs) were reported. The efficacy data showed that N8-GP effectively arrests bleeding episodes (96% of bleeds treated successfully) and thereby has the intended haemostatic potential. These results were confirmed in a subsequent review of safety and efficacy data from 20 adults and adolescents having at least 50 N8-GP exposure days (EDs)[1] in the pathfinder™2 trial, performed according to the EMA guideline[7], in order to allow the pathfinder™5 trial in paediatric PTPs below 12 years to be initiated (first patient first visit (FPFV) 20-Feb-2013). In conclusion, currently available clinical data indicate that N8−GP effectively arrests bleeds and has shown the intended haemostatic potential. In addition, no safety issues have been reported. Recently one case of low-titre FVIII inhibitor formation after multiple exposure to N8-GP has been reported in the ongoing phase 3 trial NN7088-3859 in adolescent and adult PTPs (as per 28-Jul-2013 this trial included 182 patients being treated with N8-GP). The FVIII inhibitor formation was reported for an 18-years-old patient receiving N8-GP every 4th day for prophylaxis. After 94 exposures to N8-GP a FVIII inhibitor test was positive for the first time, with an observed titre of 1.3 BU. The result was confirmed in the follow-up test 14 days later (1.9 BU). Hence, the protocol definition for the presence of a FVIII inhibitor was met.

In accordance with the EMA guideline[7], N8-GP exposure of PUPs may be initiated when treatment data from 20 paediatric PTPs with at least 50 N8-GP EDs are available from the pathfinder™5 trial, including data from a minimum of 10 patients below 6 years, and pharmacokinetic investigations in children (below 12 years) are completed.

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

3.2 Rationale for the trial

N8-GP represents a new recombinant FVIII product with a prolonged half-life developed to decrease the burden of treatment and thereby increase treatment compliance for patients with haemophilia A, potentially leading to better clinical outcomes.

The N8-GP clinical programme is designed to generate data on the pharmacokinetic (PK), safety and efficacy profile of N8-GP in all age groups.

Given the prolonged half-life of N8-GP it is expected that bleeding prophylaxis, treatment of acute bleeding episodes, and control and prevention of bleeding in the surgical setting may be achieved

[1] An exposure day (ED) is any day on which the patient has been exposed to trial product. This will be used for reporting purposes.

with a reduced frequency and number of injections as compared to current treatment options. This may increase treatment compliance, and thereby potentially leading to better clinical outcomes for patients with haemophilia A.

The rationale for performing the pathfinder™6 trial is to evaluate the safety (including immunogenicity) and efficacy of N8-GP in the treatment of PUPs with severe haemophilia A in accordance with EMA requirements.[7] For Europe, EMA requires a separate investigation in the PUP population as part of the development programme to be initiated before market authorisation.[7] The approval of the indication in PUPs will be based on a clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs connected with a post-approval commitment to follow up at least 100 PUPs for a minimum of 100 EDs. The 50 patients will continue to reach at least 100 EDs, and additional 50 patients will be included also to reach at least 100 EDs.

Given the prolonged half-life of N8-GP it is expected that bleeding prophylaxis, treatment of acute bleeds, and control and prevention of bleeding in the surgical setting may be achieved with a reduced frequency and number of injections as compared to current treatment options. This may increase treatment compliance, and thereby potentially leading to better clinical outcomes for patients with haemophilia A.

Finally, as the HIV and hepatitis C epidemics in patients with haemophilia have subsided, 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 PUPs with severe haemophilia A following exposure to FVIII products.[3,4]

3.3 Risk and benefits

Children are among those who might benefit from prophylaxis with N8-GP. Current products available for the treatment of haemophilia A have short half-life of approximately12 hours demanding frequent dosing for prophylaxis of bleeding episodes, with 3 - 4 weekly injections. The prolonged half-life of N8-GP offers an expected advantage of twice weekly or potentially even less frequent injections, which reduces the burden of treatment while maintaining effective haemostasis. Likewise it may promote adherence to therapy due to less frequent injections.

The recombinant FVIII part of N8-GP has an amino acid sequence almost identical to human FVIII and to the currently marketed rFVIII products and is produced by the CHO cell-line AAMP5, a mammalian cell line shown to be free of known infectious agents.

There is a risk for development of antibodies against N8-GP and/or FVIII that could decrease the effectiveness of future treatment with FVIII products. However, this risk is not expected to be higher than with other FVIII products.

The benefits of N8-GP in PUPs include reduced frequency of injections compared with existing FVIII treatments due to the long half-life of N8-GP. Lack of compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with factor treatments.[8] Less frequent dosing is anticipated to result in a higher compliance. Furthermore, less frequent dosing regimens are believed to cause less interruption of daily life, which might improve the quality of life of the patients and their families.

N8-GP is manufactured in a serum-free process and the risk of transmission of viruses, prions and other known blood-borne diseases have been eliminated. Monoclonal antibodies used for purification of the product further reduce the risk of allergic reactions.

The primary concern in PUPs is the risk of development of inhibitory antibodies to FVIII (inhibitors). Potential development of inhibitors will be monitored by a Nijmegen modified Bethesda assay (which has a high sensitivity for low concentrations of inhibitors), and testing for presence of N8-GP binding antibodies will be performed shortly after each visit. A patient is diagnosed with inhibitor formation if the patient has been tested positive for inhibitors at two consecutive tests from the central laboratory. If antibodies are identified, these will be further characterised on an exploratory basis and there will be close follow-up and case-by-case evaluations.

As with other proteins, allergic type hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, may occur. As the N8-GP product contains trace amount of hamster cell proteins antibodies to these may occur. Parent(s)/legally acceptable representatives (LAR)(s) to patients enrolled in the present trial will be informed of the signs of immediate type hypersensitivity reactions including hives, pruritus, generalised urticaria, angioedema, hypotension (e.g. dizziness or syncope), shock and acute respiratory distress (e.g. tightness of the chest, wheezing).

PEGylation of proteins is a well-established technology which is used in the treatment of a variety of clinical disorders[9] and the nonclinical safety profiling of N8-GP has not identified any safety concerns in relation to humans in the dose range proposed for the present trial.

N8-GP is currently being investigated in previously treated patients. The first human dose trial (NN7088-3776) demonstrated that a single dose of N8-GP is generally well-tolerated, and that N8-GP has a prolonged half-life compared to commercially available FVIII products. No safety concerns have been raised based on review of data (cut-off date was 12-Feb-2013) from patients

enrolled in the pivotal safety and efficacy trial (NN7088-3859) and the risk/benefit ratio for N8-GP is therefore expected to be favourable.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary Objective

- To evaluate immunogenicity of N8-GP in previously untreated patients (PUPs) with severe haemophilia A

Secondary Objectives

- To evaluate safety other than immunogenicity of N8-GP in PUPs with severe haemophilia A
- To evaluate efficacy of N8-GP in PUPs with severe haemophilia A
  - in long-term prophylaxis treatment (bleeding preventive effect)
  - in the treatment of bleeding episodes

4.2 Endpoint(s)

4.2.1 Primary Endpoint

- Incidence of FVIII inhibitors

4.2.2 Secondary Endpoint

- Frequency of Adverse events (AEs) including serious AEs and Medical Events of Special Interest (MESI).*
- Incidence of confirmed high titre inhibitors (defined as inhibitor titre > 5BU)*
- Number of breakthrough bleeding episodes during prophylaxis with N8-GP (annualised bleeding rate).*
- Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “none”).*
- Consumption of N8-GP for prophylaxis (number of injections and U/Kg per month and per year)
- Consumption of N8-GP for treatment of bleeding episodes (number of injections and U/Kg required per bleeding episode)

- Total consumption of N8-GP per patient (prevention and treatment of bleeding episodes) per month and annualised value

*Key supportive secondary endpoint prospectively selected for posting on clinicaltrials.gov

5 Trial design

5.1 Type of trial

This is a multi-national, non-randomised, open label phase 3 trial investigating the safety (including immunogenicity) and efficacy of N8-GP in prophylaxis and treatment of bleeds in a paediatric population of PUPs (age below 6 years) with severe haemophilia A (FVIII baseline level < 1%). There will only be one treatment arm and no comparator.

The trial design is based on the guideline on clinical investigation of recombinant and human plasma-derived factor VIII products developed by Committee for Medicinal Products for human use (CHMP) in EU.[7]

The number of patients to be investigated in this trial follows the minimum EU guideline requirements for approval of the indication in PUPs, which will be based on a pre-authorisation clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs, connected with a post-approval commitment to follow-up at least 100 PUPs for a minimum of 100 EDs.[7]

According to the EMA Guideline treatment with N8-GP in the pathfinder™6 PUP trial may start when 20 patients participating in the paediatric PTP trial (pathfinder™5) are available (including data from a minimum of 10 paediatric patients below 6 years of age), and pharmacokinetic investigations in paediatric PTPs are completed.[7]

For the individual patient the trial consists of four parts; screening, main phase and extension phase and a prophylaxis period until end of trial Figure 5–1.

In the main phase of the trial patients will receive treatment with N8-GP until they reach a minimum of 50 N8-GP EDs each, or until they develop high-titre inhibitors. An ED is defined as any day during which the patient has been exposed to N8-GP, including doses given for treatment of bleeding episodes, prophylaxis, surgery and for the purpose of PK assessment. If N8-GP is administered more than once during the same day, this will still count as one ED. When at least 50 patients have reached a minimum of 50 EDs each in the main phase, the analysis and evaluation for the main trial report will be performed. EDs during immune tolerance induction therapy (ITI) will not count in the determination of when a patient has reached 50 EDs.

Patients will be followed in the extension phase until at least 100 patients have reached at least 100 EDs each. Results from all patients in all parts of the trial will be reported as supportive results when the last patient has completed or left the trial.

Patients who develop inhibitors during the trial may continue treatment with N8-GP and will follow an alternative treatment regimen and visit schedule, see Section 5.3.6. These patients will be considered as a separate cohort and will be evaluated accordingly.

If needed, the patients can undergo minor or major surgical procedures during the trial. Upon completion of the surgery the patient can continue prophylaxis treatment with N8-GP as before the surgery.

5.2 Rationale for trial design

The trial design follows current standards for similar trials, and the EMA "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products"[7].

The trial design will provide information on safety and efficacy of N8-GP in paediatric PUPs below 6 years of age with severe haemophilia A (FVIII activity level of <1%).

The purpose of the present trial is to evaluate immunogenicity of N8-GP and to document the safety and efficacy of N8-GP in long-term prophylaxis and treatment of bleeding episodes in paediatric PUPs.

The main phase of the trial will generate safety and efficacy, aiming for a minimum of 50 EDs per patient. This number of EDs is required by the EMA guideline[7] for evaluation of new FVIII products. The trial does not include a placebo control group, as it is considered unethical to administer an ineffective treatment to patients with haemophilia. An active control has not been included as extensive comparative data from recently registered rFVIII products are available in comparable global populations including patients from EU and US.[14, 15] Furthermore, the EMA guideline does not require a comparison to neither placebo nor an active comparator.

There will be no randomisation due to the single-arm nature of the trial.

A multinational design has been chosen to ensure a sufficient screening pool of patients with this rare disorder, to meet local regulatory requirements and to reflect the anticipated patient population.

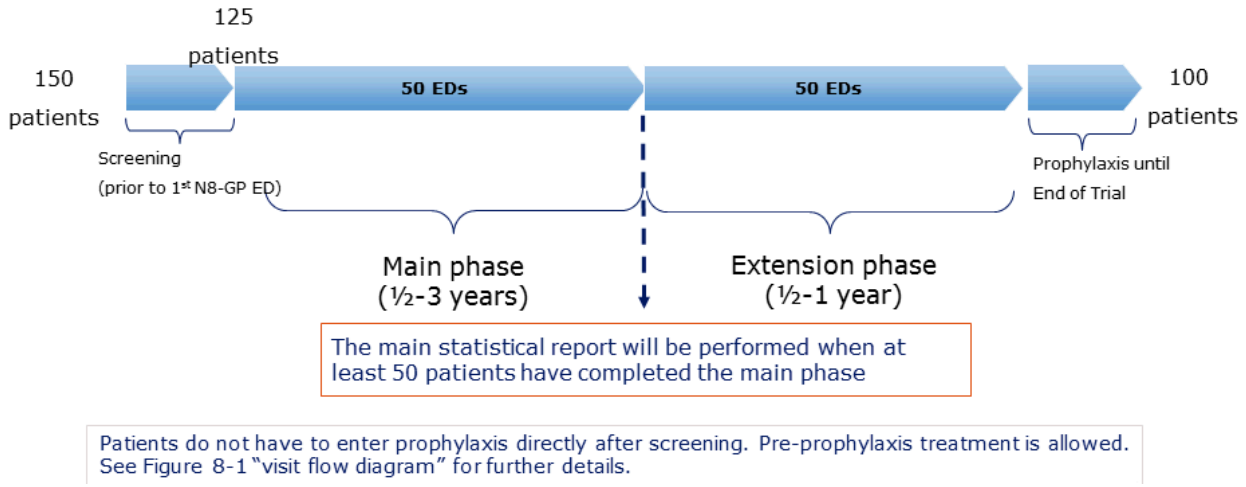

Figure 5–1 Patient flow chart

5.3 Treatment of patients

Trial visit schedule will be as shown in Figure 5–1.

According to common practise in haemophilia care, most children will initially receive on-demand (episodic) treatment for minor skin/mucosa bleedings episodes and after the first joint and/or muscle or severe bleed, switch to prophylaxis in order to prevent bleeds and musculoskeletal damage. This is usually done when the child is between 1 and 2 years of age.

The main phase of the trial is designed to reflect common practice in haemophilia treatment. Based on the decision made by the investigator and the child's parent(s)/LAR(s) patients can either begin directly with N8-GP prophylaxis (prior to any experienced bleeds) or with N8-GP on-demand treatment (pre-prophylaxis treatment), and subsequently switch to prophylaxis. It is decided by the investigator and patient's parent(s)/LAR(s) whether to start on prophylaxis or pre-prophylaxis.

For each patient at least the two initial doses of N8-GP will be administered in a hospital/clinic setting enabling observation for potential adverse reactions. The patient must be observed for at least 1 hour after dosing. Afterwards, home treatment with i.v. self-injection by the parent/caregiver/support person can be initiated if no safety concerns were raised after administration of the initial doses of N8-GP. The investigator should ensure that parent/caregiver/support person is sufficiently trained and confident with home treatment, including both prophylaxis and treatment of bleeding episodes. The patients can come to the clinic/trial site for their N8-GP injections until they are comfortable with home treatment.

The duration of a single patient's treatment in the main phase of the trial is until 50 N8-GP EDs is reached, or until development of high-titre inhibitors, but will be maximum 26 weeks if the recommended twice weekly dosing is used for prophylaxis.

The duration of N8-GP treatment in the extension phase is at least 50 EDs or up to a minimum total 100EDs (for both the main and extension phases) for each patient. Once a patient has achieved 100EDs, he may be offered the option to continue in the extension phase until either N8-GP is commercially available in the relevant country or until the marketing authorisation application for N8-GP is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the Last Patient Last Visit for the trial will be no later than 13 May 2019 whether or not the product is commercially available in the relevant country. Novo Nordisk will not provide any patient with trial medication after the end of the trial.

Treatment with FVIII products other than the investigational product, N8-GP, is not allowed. Previous exposure to FVIII products is not allowed in this trial. Previous exposure to maximum 5 plasma infusions, Pd-aPCC, and/or cryoprecipitate is allowed.

5.3.1 Pre-prophylaxis treatment

At the beginning of the main phase of the trial, slow start prophylaxis and on-demand treatment of bleeds with trial product (N8-GP) will be allowed at the discretion of the investigator and patient's parent(s)/LAR(s). The decision regarding pre-prophylaxis treatment will be made at visit 0 or 1.

The N8-GP dose for pre-prophylaxis treatment (except for bleeding episodes) is approximately 60 U/Kg body weight (bw) (within the dosing range of 50-75 U/Kg) to be administered as a single bolus dose intravenously (i.v.) less than once every 7 days (at the discretion of the investigator). Whole mL dosing is allowed from above 3 mL, explained in the trial material manual. For treatment of bleeding episodes see Table 5–1.

Switching from pre-prophylaxis treatment to prophylaxis should follow guideline in Section 5.3.3.

For regular safety monitoring (including blood sampling for inhibitor analysis) pre-prophylaxis treated patients must attend regular site visits (see Table 2–1).

5.3.2 Prophylaxis treatment

Prophylaxis with regular N8-GP administration must be initiated no later than at the patient's age of 24 months, or after 20 EDs in pre-prophylaxis, whatever comes first.

The N8-GP dose for prophylaxis treatment is approximately 60 U/Kg bw to be administered as a single bolus dose i.v. at each administration day, preferably in the morning. However, it is allowed

to dose within the dose range 50-75 U/Kg bw, enabling whole mL dosing. Whole mL dosing is allowed from above 3 mL.

During the main phase of the trial patients should receive prophylaxis with i.v. injections of N8-GP preferably twice weekly, with doses to be separated by at least 3 calendar days and no more than 4 calendar days. An increase in N8-GP dose frequency from twice weekly to every third day is permitted at the investigators discretion (should be based on patient's individual bleeding pattern).

Furthermore it is allowed to start prophylaxis in the main phase with a once-weekly dosing regimen, if considered sufficient for bleeding prevention by the investigator.

In the extension phase, all patients should continue the prophylaxis dosing regimen as prescribed at the end of the main phase. However, preferably after being 12 months on the same prophylaxis regimen (main phase and extension phase combined), the investigator is permitted to increase or decrease the N8-GP dosing interval within the range of every 3rd day to every 7th day (every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day (once weekly)) based on the patient's bleeding pattern.

The dose can be administered +1 day of the planned dosing date.

Furthermore, if considered relevant, the investigator is permitted to prescribe administration of extra N8-GP bleeding preventive doses before demanding physical activities (e.g. sports).The next regular prophylaxis dose should not be postponed due to an extra prophylaxis dose, but still be administered on the usual dosing day.

In the event of a concern about reduced treatment efficacy an unscheduled visit can be scheduled where a PK session may be performed to investigate the elimination (recovery, clearance and half-life) of N8-GP. Antibody tests should be taken if not done recently. The PK data may potentially be used to adjust the dose or dosing regimen.

5.3.3 Treatment of bleeding episodes

Patient's parent(s)/LAR(s) will be instructed by the trial site on how to treat a bleeding episode at home and record in the electronic diary (eDiary). Treatment requiring bleeding episodes should immediately (i.e., when the patient experiences the first clinical symptoms of a bleeding episode) be treated with N8-GP at doses of 20-75 U/Kg bw, depending on severity and location of the bleeding episode, see Table 5–1. For treatment of severe/life-threatening bleeding episodes administration of higher doses of N8-GP is permitted at the investigators discretion. For recommended dose levels see Table 5–1.

At least the first 2 treatment-requiring bleeding episodes should be treated in the presence of a qualified health care professional. If the patient cannot be brought quickly to the trial site, the trial site must be contacted for treatment instructions or transport. A severe bleeding episode should immediately be treated at home or at the local emergency room, and the trial site must be contacted for further instructions or transport. For severe bleeding episodes before the 2nd EDs the treatment must take place at the site.

In case of treatment requiring bleeding episodes prior to home treatment, these should immediately be treated at trial site. In case the bleeding episode occurs outside trial site opening hours, the bleeding episode should be treated according to local practice.

The need for a second dose of N8-GP should be evaluated within 8 hours of the initial dose. If two doses are not sufficient to treat the bleeding episode, and immediately in the case of a severe bleeding episode, the trial site must be contacted as soon as possible for further instructions and/or transport to the trial site for an unscheduled visit.

Total number of N8-GP doses and frequency of dosing for treatment of a bleeding episode is decided by the investigator based on the individual bleeding episode characteristics and haemostatic response to treatment, and/or based on local guideline or standard of practice. Dosing guidance may be provided at a scheduled or unscheduled visit at the clinic or by telephone contact to the trial site.

If a haemostatic response to treatment cannot be achieved (i.e. the bleed does not stop) within 48 hours after initiating treatment with N8-GP, another FVIII product may be selected at the discretion of the investigator, and the patient must be withdrawn from the trial.

If a bleeding episode occurs on a planned prophylaxis dosing day before administration of the prophylaxis dose, or if a bleeding episode extends into such a day, the bleeding episode must be treated with the full prophylaxis dose (this dose should be recorded as treatment of a bleeding episode) (does not apply for surgeries). The patient should at all times follow the original prophylaxis dosing scheme unless a dose has already been given to treat a bleeding episode during the same day.

Treatment of bleeding episodes with N8-GP will be included in the overall count of ED.

5.3.4 Treatment of suspected bleeding episodes

In case of an abdominal or head trauma where there is a risk of a severe traumatic bleeding episode it is allowed to initiate treatment before clinical 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

5.3.5 Surgery

Minor surgeries, dental extractions and placement of central venous access ports can be performed while participating in this trial by administering extra doses of N8-GP equivalent to the dose for a severe bleeding episode (see Table 5–1), or aligned to local standard of practice, or guidelines for treatment of patients with haemophilia A with FVIII in the perioperative period.

Major surgery will only be allowed after the individual patient has reached 50 N8-GP EDs, and upon completions of the pathfinder™3 surgery trial (NN7088-3860). The treatment regimen for major surgery will be based on results from the pathfinder™3 surgery trial (NN7088-3860) and PK data obtained in the pathfinder™5 trial (NN7088-3885) in paediatric PTPs. Novo Nordisk will communicate when major surgeries are allowed in this trial.

Definition of minor surgery

Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. For this trial, examples of minor surgery include:

- Implanting and removing ports in subcutaneous tissue
- Skin excisions
- Drainage of abscess
- Simple dental procedures
- Circumcision

Definition of major surgery

Major surgery is defined as any invasive operative procedure that require several days of FVIII 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
- When normal anatomy is operatively altered
- Major elective orthopaedic surgery

Treatment with N8-GP during surgery will be included in the overall count of N8-GP EDs. Upon completion of the surgical/invasive procedure the patient can continue prophylaxis treatment with N8-GP as before the surgery.

5.3.6 Treatment of patients with FVIII inhibitors

Approximately 20–30% of PUPs with severe haemophilia A develop inhibitors to infused FVIII rendering use of such replacement therapy ineffective. Patients who develop inhibitory antibodies remain at higher risk for morbidity and mortality associated with recurrent or uncontrolled bleeding events.

The majority of haemophilia patients with inhibitors develop high-titre (> 5 BU) inhibitors, and demonstrate an anamnestic rise in their inhibitor titre when re-exposed to FVIII. In these patients even frequent, high-dose FVIII substitution therapy becomes ineffective in controlling bleeding episodes as the infused coagulation factor products are neutralised by the inhibitor. Administration of FVIII bypassing agents (rFVII or activated prothrombin complex concentrates) becomes necessary for treatment of bleeding episodes.

Treatment of bleeding episodes with by-passing agents, i.e. rFVIIa or APCC according to local standard care, is allowed for patients who develop FVIII inhibitors within this trial. By-passing agents are not considered trial medication.

The ultimate goal of treatment in patients with high-titre inhibitors is to permanently eradicate the inhibitor by immune tolerance induction therapy (ITI), thereby making it possible for the patient to be treated routinely with FVIII replacement therapy. The therapeutic concept is based on long-term uninterrupted high exposure to FVIII in an effort to sufficiently tolerize the immune system. In that state, the clinical responsiveness to FVIII replacement therapy is restored.

Based on the available evidence, all patients with high-titre inhibitors (> 5 BU) should undergo ITI using the same type of product that the patient was using at the time of inhibitor development.[10] This approach is supported by an international expert panel[11] which concurred with treatment guidelines which recommend that ITI should be conducted with the same concentrate as the one against which antibodies were developed.[12,13] This should ensure successful tolerance induction and reduce the risk of further inhibitor development to new molecules. It may therefore be expected that N8-GP will be favourable over the use of commercially available FVIII products for ITI in patients who developed FVIII inhibitors within this trial.

Novo Nordisk plans that patients who develop inhibitors, within this trial, will be offered continued treatment with N8-GP, including ITI for a maximum of 24 months. ITI with N8-GP will not be initiated until Novo Nordisk has reviewed the clinical data available after completion of the N8-GP pivotal and surgery trial (pathfinder™2 and pathfinder™3), and of the paediatric PTP trial (pathfinder™5) data needed for opening the paediatric PUP trial according to EMA requirements.

It is expected to use a N8-GP dosing regimen for ITI similar to local standard care/guidelines applied for ITI with marketed FVIII products. For each individual patient, ITI regimens with N8-GP

would have to be reviewed by the investigator every month, and more formally reviewed every 3 months by Novo Nordisk.

Based on experience with marketed FVIII products, a successful ITI can be expected in about 60–80% of cases receiving ITI with N8-GP, leading to several important benefits for the patient, including:

- allowing regular FVIII replacement therapy in case of bleeding and surgery
- enabling prophylactic treatment with FVIII to prevent haemophilic arthropathy and life-threatening bleedings
- improving the patient`s quality of life (less morbidity etc.)

With current knowledge, the benefit/risk ratio for using N8-GP for ITI is expected to be favourable, and similar as being described in Section 3.3. Non-clinical and clinical data on N8-GP do not suggest any alteration to the established safety profile of current rFVIII products. It is evaluated as unlikely that clinical significant adverse events will occur in humans specifically as a result of N8-GP being used for ITI. However, close monitoring is strongly recommended when N8-GP will be used for ITI in this trial.

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

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

If needed and decided by the Investigator, the initiation of the ITI can be delayed but it has to start within 6 months from the time of diagnosis of inhibitor. Inhibitor patients that commence ITI with N8-GP will follow an alternative treatment regimen and visit schedule (see Section 8.1.11). If the inhibitor disappears during the ITI (see Section 8.4.2.2, the patient should resume prophylaxis treatment as recommended in Section 5.3.2. For patients still with positive inhibitors after 12 months ITI, continued trial participation will be evaluated by the investigator and sponsor based on the level of inhibitors, within the predefined specifications of withdrawal criteria 8, see Section 6.4. However, if the inhibitor persists after 24 months of ITI, the patient will be withdrawn from the trial.

For patients who develop low titre and/or clinically insignificant inhibitors (< 5 BU), the dose level and dosing frequency of N8-GP will be decided by the Investigator based on clinical evaluation.

Table 5–1 Intravenous N8-GP treatment

Indication	Dosage	Frequency
Pre-prophylaxis (pt. less than 24 months of age)	Approximately 60 U/Kg (50-75U/Kg)	On-demand or slow start prophylaxis (less than weekly dosing)
Prophylaxis – main phase	Approximately 60 U/Kg (50-75U/Kg)	Every 3rd day, twice weekly or every 7th day(±1 day)
Prophylaxis – extension phase	Approximately 60 U/Kg (50-75U/Kg)	Every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day(±1 day)
Mild/moderate bleeding episode	20-60 U/Kg	On-demand (breakthrough bleeding episodes)
Severe bleeding episode	40-75 U/Kg For treatment of severe/life-threatening bleeding episodes administration of higher doses of N8-GP is permitted at the investigator's discretion	On-demand
Minor surgery	40-75 U/Kg	In accordance with local standard of practice of the participating trial site
Major surgery, only allowed after 50 EDs	Recommended doses regimens will be provided when the N8-GP surgery trials completed	On-demand
Low titre inhibitor	Recommendation 60 U/Kg (50-75 U/Kg) for prevention and treatment of bleeding episodes	Dosing interval as needed
Maximum dose/day	200 U/Kg	Total maximum dose over 24 hours

5.3.7 Vaccinations

Vaccination are allowed before entering the trial but should preferably not take place until 3 months after the first N8-GP exposure, as vaccination activates the immune system of the patient, thereby potentially increasing the risk of inhibitor development.

5.4 Treatment after end of trial

After trial end the investigator will agree with the patient's parent(s)/LAR(s) upon the best available treatment for the patient.

When discontinuing trial product the patient should be switched to a suitable marketed product at the discretion of the investigator.

It is expected that N8-GP will be granted marketing authorisation and is commercially available when the patients complete this trial. However, this cannot be guaranteed.

5.5 Rationale for treatment

Lack of compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with coagulation factor treatment[8]. The increased half-life of N8-GP will allow for prophylaxis with fewer injections than currently available products and will most likely result in improving compliance.

The dose level is based on PK data from the phase 1 PK trial (NN7088-3776) which showed that the $t_{½}$ of N8-GP was prolonged by approximately 1.6-fold compared to the patient's previous FVIII product. In the pivotal trial, pathfinder™2 (NN7088-3859), a fixed dose of 50 U/Kg bw is administered i.v. every fourth day. Due to an anticipated higher clearance of FVIII in children, compared with adults [14] a slightly higher and more frequent dose schedule has been chosen for this trial. With the longer plasma half-life of N8 GP it is expected that 2 administrations of N8-GP per week will provide the same prophylactic effect as 3 or 4 weekly injections with currently marketed FVIII products.

Please refer to the IB and any updates here of for further pre-clinical and clinical data.[5]

The rationale for introducing the dose level of 60U/Kg is, primarily to explore and utilise the full potential of the molecule, by reducing the burden of treatment due to less frequent dosing. Please refer to the IB and any updates hereof for further non-clinical and clinical data.

The rationale behind the once weekly dosing is to enable slow start prophylaxis as often done in clinical practice. This every 7 day dosing may continue if considered sufficient.

The reason for providing the possibility of ITI of patients who develops high-titre inhibitors is to permanently eradicate the inhibitor, thereby making it possible for the patient to be treated routinely with FVIII replacement therapy. Based on the available evidence patients should undergo ITI using the same type of product that the patient was using at the time of inhibitor development. This approach is supported by an international expert panel which concurred with treatment guidelines which recommend that ITI therapy should be conducted with the same concentrate as the one against which antibodies were developed. This should ensure successful tolerance induction and reduce the risk of further inhibitor development to new molecules.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 150

Number of patients planned to be started on trial product: 125

Number of patients expected to complete the trial: 100

6.2 Inclusion criteria

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male, age < 6 years of age at the time of signing informed consent
3. Diagnosis of severe haemophilia A (FVIII activity level < 1%) based on medical records or central laboratory results
4. No prior use of purified clotting factor products (5 previous exposures to blood components is acceptable)

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

6.3 Exclusion criteria

1. Any history of FVIII inhibitor (defined by medical records)
2. Known or suspected hypersensitivity to trial product or related products
3. Previous participation in this trial. Participation is defined as first dose administered of trial product
4. Receipt of any investigational medicinal product within 30 days before screening
5. Congenital or acquired coagulation disorder other than haemophilia A
6. Any chronic disorder or severe disease which, in the opinion of the Investigator, might jeopardise patient’s safety or compliance with the protocol.
7. Patient’s parent(s)/LAR(s) mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation

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

6.4 Withdrawal criteria

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

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

The patient must be withdrawn if the following applies:

1. Dosed in the trial, but not fulfilling the inclusion and/or exclusion criteria
2. Anaphylactic reaction to the trial product, for definition see Section 11.1
3. Major surgery before 50 EDs, see Section 5.3.4
4. Significant thromboembolic event, see Section 11.1
5. Incapacity or unwillingness to follow trial procedures
6. Use of coagulations factors other than N8-GP or anti-coagulants unless in relation to ITI
7. ITI treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (BU ≥ 0.6/mL)
8. FVIII inhibitor titre decline from peak level is less than 20% after 12 months of ITI treatment
9. FVIII inhibitor is positive (BU ≥ 0.6/mL) after 24 months of ITI treatment.
10. After completed ITI treatment (maximum 24 months), prophylaxis treatment as described in the protocol is not resumed/started.

If a patient experiences treatment failure where haemostatic response is rated as none according to Section 8.6, the investigator should consider if it is in the patient's best interest to continue in the trial.

All data collected prior to withdrawal may be used in the trial analyses if considered relevant by Novo Nordisk.

6.5 Patient replacement

Withdrawn patients may be replaced to ensure that 100 patients complete the trial with at least 100 EDs. Assuming a drop-out rate of 20%, it is estimated that 125 patients must be started on N8-GP to obtain the 100 completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate.

6.6 Rationale for trial population

The selection of the trial population is based on the specific requirements found in the final guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products[7] from the CHMP and in the paediatric investigational plan (PIP) in agreement with the Paediatric Committee (PDCO).

Children are among those who benefit significantly from prophylaxis. Less frequent injections with N8-GP as compared to other treatment options are likely to improve compliance, avoid interruptions of daily life and thereby increase the quality of life of the patients.

6.6.1 Rationale for inclusion criteria

- Criterion no. 1 is included in accordance with International Conference on Harmonisation/Good Clinical Practice (ICH-GCP).[1,2]
- Criterion no. 2 is included due to Novo Nordisk has decided to use an age cut-off of 6 years.
- Criteria no. 3, 4 are included to select the patient group based on the CHMP guideline[7].

6.6.2 Rationale for exclusion criteria

- Criterion no.1 is included to exclude patients with FVIII inhibitors since inhibitor development is the primary safety endpoint of the trial.
- Criteria 2 and 6 are to prevent unnecessary exposure of potentially fragile patient to a new compound.
- Criterion no. 3 is included to ensure that a patient only counts once in the data analyses and to ensure the patient is a PUP.
- Criterion no. 4 is included to minimise any effect of external compounds on the patient's coagulation and immune system.
- Criterion no. 5 is chosen to exclude patients with endogenous abnormalities of the coagulation system, other than haemophilia A.
- Criterion no 7 is included to ensure enrolment of patients likely to be compliant with the protocol, and to preclude enrolment of particularly vulnerable patients.

6.6.3 Rationale for withdrawal criteria

- Criteria nos. 1-6 are included to protect the patient's safety and reliability of the data.
- Criteria nos. 7-10 are included to ensure appropriate treatment of inhibitor patients.

7 Milestones

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

Planned FPFV: 01-May-2014

Planned LPFV: 02 -Apr-2018

End of trial is defined as LPLV: 13-May-2019

The duration of the trial for each individual country will vary. However, the end of trial will be no later than 13 May 2019.

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

Planned completion of clinical trial report (CTR): November 2019.

The duration of N8-GP treatment in the trial is a minimum total 100EDs for a particular patient. Once a patient has achieved 100EDs, they may be offered the option to continue in the trial until either N8-GP is commercially available in the relevant country or until the marketing authorisation application for N8-GP is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the LPLV for the trial will be no later than 30 June 2018 whether or not the product is commercially available in the relevant country.

The following exceptions will be made:

- Patients with inhibitor will be allowed to receive ITI treatment for up to 24 months.

Recruitment
The screening rate will be followed closely via the interactive voice/web response system (IV/WRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further consent will be sought from additional families and the IV/WRS, will be closed for further screening, unless additional screening is needed due to patient replacement.

Trial registration
Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[15], the Food and Drug Administration Amendment Act (FDAAA)[16], European Commission Regulation for EudraCT[17] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at

these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

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

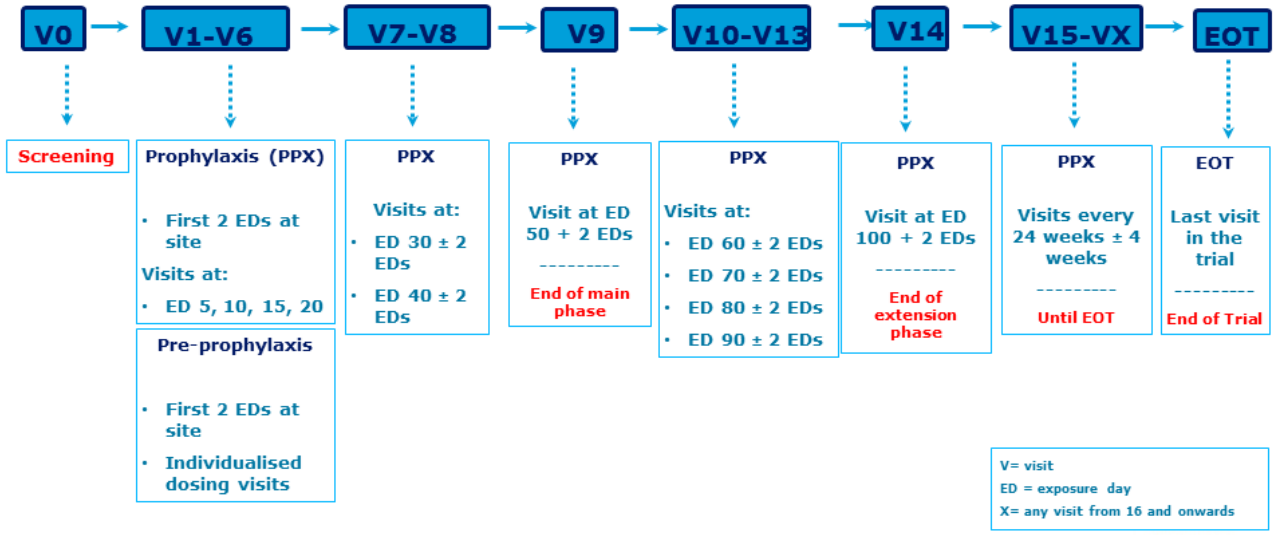

Figure 8–1 Visit flow diagram

Screening and enrolment log

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

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

It must be stated in the medical records that the patient is participating in the trial, including the patient number.

Informed consent procedure

The patient's parent(s)/LAR(s) will be provided with full written and verbal information about the trial prior to conduct of any trial-related procedures/activities, in accordance with GCP and local requirements, see Section 17.1.

A child assent form will be provided to patients above 3 years of age according to local requirements. This can be performed on a separate day. As this is a long term trial the investigator should check the progressing maturation of the child and its ability to assent throughout the trial.

Informed consent for obtaining genotyping must be collected, if applicable.

Screening failures
Screening failures are defined as patients for whom the parent(s)/LAR(s) have signed the Informed Consent Form, but fail to comply with the inclusion and/or exclusion criteria or if the consent is withdrawn prior to dosing.

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial. Serious and non-serious adverse events (AE) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to Section 11.3. A screening failure session must be made in the IV/WRS. The case book must be signed.

Re-screening is not allowed after the first dose of trial product – see exclusion criterion no. 3 in Section 6.3.

For withdrawn patients
Withdrawn patients are defined as patients who meet the withdrawal criteria after dosing, see Section 6.4

If a patient is withdrawn from the trial, the investigator must aim to perform the End of trial visit, as soon as possible.

The end of trial form must be completed, and final drug accountability must be performed even if the patient is not able to come to the trial site. A withdrawal session must be made in the IV/IWRS and case book must be signed in the eCRF.

All data collected in the period the patient participated in the trial must be documented.

Although a patient or patient's parent(s)/LAR(s) is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Where the reasons are obtained, the primary reason(s) for discontinuation must be specified on the end of trial form in the eCRF e.g.:

- Adverse events
- Protocol violation
- Lack of efficacy
- Lost to follow up

- Withdrawal by patient or parent(s)/LAR(s)
- Technical problems
- Other

End of trial
The end of trial (EOT) form should be filled in at the End of trial visit or the last visit of the patient. If a patient is withdrawn prior to completion of the trial, all attempts must be made to schedule the end of trial visit for the patient.

In general
Review of eDiary reports, laboratory reports etc. must be documented either on the front page of the documents and/or in the patient's medical record.

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

8.1.1 Visit 0 – screening visit

The patient's parent(s)/LAR(s) must give signed and dated informed consent prior to any trial related activities. All patients will be provided with a copy on the patient information and a copy of the signed and dated Informed Consent Form.

For all patients with a signed Informed Consent/Assent form, the patient will be assigned a unique 6 digits patient number, which will follow the patient throughout the trial.

A screening period (interval between Visit 0 (V0) and V1) is allowed until the first dose of N8-GP is required.

The screening visit (V0) can be combined with the first treatment of N8-GP (V1), hereby allowing patients to be enrolled in the trial and treated for their first bleeding episode immediately after having confirmed inclusion and exclusion criteria.

All results necessary for evaluating the inclusion and exclusion criteria must be available before determining whether or not the patient can continue in the trial and whether it will be possible to receive the first dose of N8-GP at the same day.

If the screenings results do not become available during the screening visit, and if the next visit is not planned, the patient and parent(s)/LAR(s) must be informed when eligibility has been evaluated by investigator.

Assessments for V0 are listed in Table 2–1.

Reminders

- Dispense trial card, see Section 8.8.1
- A Screening call in the IV/WRS, see Section 10
- Discuss treatment regimen: prophylaxis versus pre-prophylaxis
- In case V1 is not planned or performed within 3 month from visit 0 the investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week, see Sections 8.8.4 and 8.1.9.
- During the screening period the patient cannot be treated with commercially available FVIII products

8.1.1.1 Pre-prophylaxis treatment

Pre-prophylaxis is optional and is the period before start of regular prophylaxis.

During pre-prophylaxis the following dosing regimen applies:

- approximately 60 U/Kg N8-GP within the range of 50-75 U/Kg bw, see Section 5.3
- individualised prophylactic dosing intervals but less frequent than every 7th day(once weekly)
- on-demand treatment of bleeding episodes

See further Section 5.3.1.

Dosing visits during the pre-prophylaxis period can be performed at any time until ED 20 being either part of visits in Table 2–1 or being registered as an unscheduled visit if the dose is not part of Table 2-1. Visits during the pre-prophylaxis period without dosing should be performed as unscheduled visits, see Section 8.1.9.

The site must make sure that the patient's parent(s)/LAR(s) are contacted at least at least every 12 weeks ± 1week if no planned visits, Section 8.8.4.

Visits 1-6 are when the patient needs treatment of a bleeding episode and/or planned individually per patient at the investigator and patient's parent(s)/LAR(s) discretion.

8.1.1.2 Prophylaxis treatment

A patient may change from pre-prophylaxis to prophylaxis at any time during the pre-prophylaxis period or must be initiated when the patient has reached 20 EDs, or has turned 24 months of age, whatever comes first.

The dosing frequency during main phase is individualised within the following interval: twice weekly, every 3rd day or every 7th day. Changes to the regimen should be recorded in the IV/WRS. If changes occur between visits, it should be recorded in an unscheduled visit, see Section 8.1.9.

For patients that enter the prophylaxis treatment after a period of pre-prophylaxis the next visit in the sequence will be determined by the numbers of EDs.

8.1.1.3 Wash-out prior to visits

A washout period is required prior to visits including inhibitor testing. The required wash-out period is at least 72 hours.

In case the wash-out period has not been fulfilled the scheduled visit should be re-scheduled unless the visit is due to a bleeding episode treated at site during the pre-prophylaxis period or prior to initiating home treatment.

8.1.2 Visit 1 – first dosing with N8-GP

V1 will take place after the screening visit (V0) whenever the first treatment of N8-GP is administered, if not already combined with V0.

In case of subjective signs of illness and/or fever within 48 hours prior to the first injection of N8-GP the dose should be postponed, if possible.

The patient will continue treatment on either:

- **Pre-prophylaxis treatment**. See Sections 5.3.1 and 8.1.1.1.
- **Prophylaxis treatment.** See Sections 5.3.1 and 8.1.1.2.

Assessments for V1 are listed in Table 2–1. In case V0 and V1 have been combined into one visit, assessments should only be performed once.

Reminders

- Next visit should be scheduled if applicable, see Sections 8.1.1.1 and 8.1.1.2.
- In case V2 is not planned or performed within 3 month from visit 1 the Investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week. See Sections 8.8.4 and 8.1.9
- Drug accountability of trial product at V1 must be recorded in the IV/WRS, see Section 10
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing via IV/WRS, see Section 10.

8.1.3 Visit 2, 3, 4-6 – main phase

The 2 first N8-GP injections must take place at trial site (V1+V2). Hereafter the injections can be administered at the trial site or outside the trial site.

If the treatment is given at site the doses should be registered in the eCRF. If not given at site, the dose should be registered in the eDiary.

Visits at ED: 2, 5 ± 1 ED, 10 ± 2 EDs, 15 ± 2 EDs, 20 ± 2 EDs.

The visits should be scheduled taking into account the patient's regular dosing day(s) in the week.

Assessments for V2-V6 are listed in Table 2–1.

Reminders

- In case next visit is not planned or performed within 3 month from the previous visit the investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week. See Sections 8.8.4 and 8.1.9
- All visits must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing and home treatment from visit 2 must be performed via IV/WRS, see Section 10
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10
- Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire during the next home treatment period
- eDiary dispensing at V2 or when treatment outside trial site is initiated, see Section 8.8.3.1
- eDiary training, see Section 8.8.3

8.1.4 Visit 7-8 – main phase

From V6 all patients (including patients previously on pre-prophylaxis) will be on prophylaxis treatment with N8-GP on twice weekly, every 3rd day or every 7th day. Between the visits the patient will receive N8-GP treatment at home if comfortable with home administrations or at the site, see Section 8.1.12.

Visits at EDs: 30 ± 2 EDs, and 40 ± 2 EDs.

The visit should be scheduled taking into account the patient's dosing day.

Assessments for V7-V8 are listed in Table 2–1.

Reminders

- An appointment for the next visit should be made
- All visits must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing/home treatment must be performed via IV/WRS, see Section 10
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10

- Home treatment training, if the trial site suspects that the patient's parent(s)/LAR(s) is not fully confident with administration and how to deal with safety related signs and symptoms, see Sections 8.5 and 8.6
- eDiary training, see Section 8.8.3
- eDiary compliance review, see Section 12.3.

8.1.5 Visit 9 – end of main phase

Visit 9 should take place at either ED 50, ED 51 or ED 52.

Assessments for V9 are listed in Table 2–1.

Reminders
- An appointment for the next visit should be made
- Next visits must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing/home treatment must be performed via IV/WRS, see Section 10
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10
- Home treatment, if the trial site suspects that the patient's parent(s)/LAR(s) is not fully confident with administration and how to deal with safety related signs and symptoms, see Sections 8.5 and 8.6
- eDiary training, see Section 8.8.3 and 12.3
- eDiary compliance review, see Section 12.3

8.1.6 Visit 10-13 – extension phase

The patient will continue prophylaxis throughout the extension phase, with 60 U/Kg in the regimen of every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day. See Table 5–1. Changes to the regimen should be recorded in the eCRF. If changes occur between visits, it should be recorded in an unscheduled visit, see Section 8.1.9.

Visit at EDs: 60 ± 2 EDs, 70 ± 2 EDs, 80 ± 2 EDs, and 90 ± 2 EDs.

The visits should be scheduled taking into account the patient's dosing day.

The duration of the extension phase is between 6 months and 1 year depending on the dosing frequency, for a patient to achieve a total of 100 EDs.

Assessments for V10-V13 are listed in Table 2–1.

Reminders
- An appointment for the next visit should be made

- Next visits must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing/home treatment must be performed via IV/WRS, see Section 10
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10
- Home treatment, see Sections 8.1.12 and 8.8.2.
- eDiary training, see Section 8.8.3
- eDiary compliance review, see Section 12.3

8.1.7 Visit 14 - end of extension phase

Visit 14 should take place at either ED 100, ED 101 or at ED 102.

Assessments for V14 are listed in Table 2–1.

Reminders

- An appointment for the next visit should be made
- Next visit must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1
- Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing/home treatment must be performed via IV/WRS, see Section 10
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10
- eDiary compliance review, see Section 12.3

8.1.8 Visit 15-X until end of trial

If N8-GP is not commercially available in a patient's country at the time of visit 14, the trial period may be extended with visits that are scheduled 24 weeks ± 4 weeks. These additional visits are referred to as visit 15 to visit X, where X can be any visit from 16 and onwards. This option for the patient to continue in the extension phase of the trial may be offered until either N8-GP becomes commercially available in the relevant country, or until the marketing authorisation application is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason, the End of Trial visit must be scheduled within 1 month provided always that the Last Patient Last Visit for the prophylaxis period until end of trial will be no later than 13 May 2019 whether or not the product is commercially available in the relevant country at this time.

At every dosing visit from V15-VX, drug will be dispensed to cover up to 3 months of treatment. Depending on patient's treatment regimen, additional dispensing visits might need to be scheduled to cover treatment in the period between visits.

Assessments for V15-VX are listed in Table 2–1.

8.1.9 End of trial visit

The EOT visit can take place at any time after completion of 100EDs or if the patient is withdrawn from the trial.

Assessments for the EOT are listed in Table 2–1

Reminders
- Drug accountability of trial product must be recorded in the IV/WRS, see Section 10
- eDiary compliance review, see Section 12.3
- eDiary LogPad collection, see Section 8.8.3.1
- Complete EOT form

8.1.10 Unscheduled visit

Unscheduled visits of trial related character can be performed at any time during the trial and the purpose must be documented.

The following forms can be found in the unscheduled visit in the eCRF:
- Central lab
- Bleeding episodes
- Dosing of N8-GP
- Surgery
- PK session
- Change of regimen

8.1.11 ITI Visit

N8-GP treatment may continue in case of low titre FVIII inhibitor (≤5BU) confirmed by central laboratory, that does not result in clinically ineffective treatment with N8-GP. Patients may follow the visit flow either as described in Table 2–1, or visits at the discretion of the investigator.

In case of high titre FVIII inhibitor (>5BU) confirmed by central laboratory the investigator must decide how to proceed with treatment. Novo Nordisk will communicate when ITI is allowed in this trial, see Section 5.3.6.

If ITI is initiated, the patient will follow a visit schedule prescribed by the investigator and according to local standard of practice. Monthly visits are recommended, and the below listed assessments are recommended to be performed:

- Adverse Events
- Concomitant medication
- Sampling for inhibitor test
- Sampling for FVIII activity test
- Bleeding episode evaluation
- Review of eDiary
- Body measurements, see Section 8.3.1

Treatment of bleeding episodes with bypassing agents is allowed at the discretion of the investigator according to local practice, see Section 11.2.

Reminder
- Follow up on any AEs according to Section 11.2

For patients returning to regular prophylaxis N8-GP treatment, the visit schedule is taken up from V9 end of main phase Table 2–1, even when the corresponding total ED does not match.

8.1.12 Home treatment

Home treatment with N8-GP can commence any time after the first 2 EDs and the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process, see Section 5.3.

8.1.12.1 Prophylactic home treatment

After 2 doses home treatment can be initiated with prophylaxis doses of approximately 60 U/Kg (50-75U/Kg). The regimen should follow Table 5–1, and adjusted as needed during the trial.

Bleeding episodes must be treated as described in Section 8.6.

The following procedures must be performed during home treatment between visits:
- N8-GP administrations according to regimen prescribed by investigator.
- Contact to the investigator/medically qualified person in case of severe bleeding episodes
- Completion of the patient eDiary, including details of all bleeding episodes and N8-GP administrations (see Section 8.6)

8.1.12.2 Home treatment of bleeding episodes

Bleeding episodes must be treated as soon as identified according to Table 5–1 and Section 8.6.

Patient's parents(s)/LAR(s) will be instructed by the investigator on how to treat their child for a bleeding episode at home and how to record this in the eDiary.

The following procedures must be performed

- N8-GP administration for treatment of treatment requiring bleeding episodes, see Section 8.6
- Completion of the patient eDiary, including details of all bleeding episodes and N8-GP administrations (see Section 8.6).

8.2 Patient related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial at the first visit (V0). All concomitant illnesses should be reported including disease under investigation.

Medical history is a medical event that the patient has experienced in the past, which should be obtained during the screening procedure including haemophilia treatment history. In the event that a diagnosis is unknown, the description of symptoms will be recorded. All significant symptoms and/or illnesses since birth should be recorded.

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

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

8.2.1.1 Details on haemophilia

All available information on haemophilia, prior to screening should be recorded including diagnostic FVIII activity level, if known. If possible, information about relatives with haemophilia A and inhibitors should be obtained.

8.2.1.2 Allergies

Any allergies, including any drug sensitivities should be recorded.

8.2.2 Concomitant medication

A **concomitant medication** is any medication including vaccination, other than the investigational medicinal product (N8-GP), which is taken during the trial until EOT.

Details of any concomitant medication must be recorded at the first visit (V0). Changes in concomitant medication must be recorded at each visit as they occur.

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

If a change in medication is due to an AE, then this must be recorded and reported according to Section 11.2. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.3 Treatment of bleeding episodes in inhibitor patients

Bleeding episodes in inhibitor patients that do not respond sufficiently to N8-GP treatment may be treated with by-passing agents according to local practice.

8.2.4 Prohibited medication

Treatment with other FVIII concentrates are not allowed during the course of the trial.
If possible, use of Tranexamic acid should be avoided.
Heparin sealing of central venous access ports and cannulae is allowed.

8.2.5 Demography

Demographic data will be collected as allowed per local law:

- Date of birth, year or age
- Ethnicity
- Race

8.3 Clinical assessments

Clinical assessments should preferably be performed prior to blood sampling and prior to administration of N8-GP unless it is stated otherwise.

8.3.1 Body measurements

- Height at screening
- Body weight, wearing light clothing only (Kg)

Body weight should be measured in connection with regularly visit where trial drug is dispensed. For practical purposes when dispensing trial drug the weight from an earlier measurement (or visit) can be used if the measurement was performed within the previous 10 weeks (in children <3 years of age, within 6 weeks). If new body weight is not needed to be measured at a visit, the body weight from last weighing should be used.

8.3.2 Physical examination

The physical examinations will be performed according to local procedure and should include:

- General appearance
- Head, ears, eyes, nose, throat and neck

- Lymph node palpation
- Abdomen
- Skin
- Respiratory system
- Musculoskeletal system
- Central and peripheral nervous systems

8.3.3 Vital signs

When dosing at the trial site (V1), vital signs should be recorded pre-dose and post-dosing of N8-GP. Hereafter vital signs will only be measured pre-dose and according to Table 2–1.

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

Vitals signs include assessment of:
- Body temperature (C/F)
- Blood pressure (BP) (mm Hg)
- Pulse (beats/min)

If not possible to perform some or all of the above measurements, it is allowed to evaluate the child for normal appearance checking for signs and symptoms of acute or chronic disease.

If a change in clinical assessments after V0 is due to an AE, then this must be recorded and reported according to Section 11.2.

8.4 Laboratory assessments

Blood samples for laboratory analysis of safety, and efficacy parameters will be drawn as outlined in Table 2–1. Approximate total volumes of blood to be taken from each patient see Section 8.4.3.

The sample taken 30 minutes (±10 minutes) post-dose must not be taken from the same vein as used for administration of N8-GP.

Laboratory results being out of normal range must be categorised as “out of normal range, not clinically significant” or “out of normal range, clinically significant”. A laboratory result evaluated as “out of normal range, clinically significant” must be recorded as an AE, or if present at V0 it should be recorded as concomitant illness.

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 eCRF or the trial database, but abnormal values must be reported to the investigator.

The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

8.4.1 Local laboratory assessments

Local laboratory results are considered as source data and must be signed, dated and categorised by the investigator.

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

8.4.1.1 FVIII activity

FVIII activity will be analysed at the predefined time point as at a central laboratory selected by Novo Nordisk but the investigator can at any time during the trial assess FVIII activity at his/her discretion.

If V0 and V1 are combined, as one combined screening visit, and if FVIII activity <1% has not been documented in the patient medical records, it should be analysed locally and documented in the patient medical records. In this case the local laboratory should use their standard FVIII activity assay with the assay calibrator routinely used for FVIII activity analysis.

A N8-GP reference standard must be used as assay calibrator in the FVIII activity assay after the patient has been dosed with N8-GP. The reference standard will be provided by Novo Nordisk together with a description of how to the reference standard should be handled, stored and used.

8.4.2 Central laboratory assessments

Central laboratory will throughout the protocol cover both the central laboratory as well as specialised laboratory analysing samples for all sites. The central laboratory will analyse and report all laboratory data to Novo Nordisk electronically in a manner that anonymity of patients will be maintained. The central laboratory results will be reported to the investigator.

The quality control of the central laboratory test results will be performed according to the regulations and specifications set by the authorities at the location of the central laboratory used for this trial.

A detailed description of procedures for sampling, handling, shipment of laboratory samples and all materials such as test tubes and labels will be provided in the laboratory manual by the central laboratory. The central laboratory manual and the central laboratory results will include the reference ranges.

8.4.2.1 FVIII activity

The analysis of plasma FVIII activity will be performed at a laboratory selected by Novo Nordisk or at a Novo Nordisk laboratory. The procedures for analyses will follow the recommendations provided by Novo Nordisk. A description of the method will be included in the final report of this trial.

FVIII activity should be measured according to Table 2–1.

FVIII activity will be measured by the use of two different assays developed and validated for N8-GP:

- FVIII chromogenic assay
- FVIII one-stage clotting assay

In each assay both an N8-GP reference standard and a human plasma standard calibrated against the WHO international FVIII standard are used as assay calibrators.

FVIII chromogenic assay

The FVIII chromogenic assay measures the activity of the compound with a two-stage method. The FVIII activity is determined by measuring the FVIIIa/FIXa-mediated activation of coagulation factor X (FX) activation (first stage) and the subsequent cleavage of a chromogenic activated coagulation factor X (FXa) substrate (second stage).

The FVIII one-stage clotting assay

The FVIII one stage assay is a modified activated partial thromboplastin time (aPTT) assay. The one-stage assay measures the activity of the compound in a specific process (clot formation).

8.4.2.2 Antibody assessments

The analysis will be performed at a laboratory selected by Novo Nordisk or at a Novo Nordisk laboratory. The procedures for analyses will follow the recommendations provided by Novo Nordisk. A description of the method will be included in the final report of this trial.

Plasma samples will be collected for assessment of:

- N8-GP/FVIII binding antibodies

- PEG antibodies
- FVIII inhibitor

Antibody assessment should be measured according to Table 2–1.

N8-GP/FVIII binding antibodies

Screening for antibodies is based on assays that are validated according to international recognised guidelines.[18-20] Samples measured above the assay cut-point will be subject to a confirmation test. Samples positive in the confirmatory test will be characterised for specificity to N8-GP, rFVIII and PEG. Isotyping of the anti-drug antibodies will possibly also be performed.

If a patient develops N8-GP binding antibodies and the recovery value at that visit is less than 60% of recovery values after the first N8-GP administrations and FVIII level at time of inhibitor sampling (pre-dose) is more than 0.020 U/mL, Novo Nordisk will ask the Investigator to call the patient for an unscheduled visit for collection of a new sample for assessment of inhibitors and binding antibodies which should will be taken after a 7 days wash out period.

A patient that tests negative for inhibitors following a 7 days wash out will confirm a negative inhibitor test and the patient will continue in the trial.

This algorithm will not apply for those who enter the trial with positive test for N8-GP binding antibodies and will not be triggered more than twice for an individual patient, unless increases in antibody levels are observed. Furthermore, a 7 days wash out period will only be applied if the 72 hours wash out is not sufficient to avoid drug interference in the inhibitor assay.

Samples will be analysed regularly for N8-GP binding antibodies, results will be reported to investigators at the end of trial and will be included in the CTR.

PEG antibodies

Screening for PEG antibodies is based on assays that are validated according to international recognised guidelines.[18-20] Samples measured above the assay cut-point will be subject to a confirmation test.

Samples will be analysed for PEG binding antibodies at the end of trial.

FVIII inhibitors

Assessment for FVIII inhibitors will be carried out using a heat modified Nijmegen FVIII Bethesda assay analysed at the central laboratory. The assay is validated according to international recognised guidelines.[18, 21] The assay is based on measurement of the FVIII activity (inhibitory activity) in plasma samples mixed with a fixed amount of normal plasma pool in buffer. Inhibitors will be

considered: 0.6 BU ≤ low titre inhibitor ≤ 5 BU, high titre inhibitors are defined as > 5 BU. Inhibitors will be recognised by comparison to a clinical cut-point of ≥ 0.6 BU.

If FVIII inhibitor development is suspected during the course of the trial due to for instance increased number of bleeding episodes, bleeding episodes difficult to treat, recovery and trough levels below expected values or a positive local inhibitor test, the patient must attend an unscheduled visit as soon as possible and a plasma sample must be shipped to the central laboratory for inhibitor analysis.

Any sampling for the inhibitor test must be performed at least 4 days after last administration of N8-GP to allow for wash-out of the drug.

If the result of the inhibitor test is positive, a second confirmatory inhibitor test should be performed by the central laboratory. The confirmatory samples should be collected as soon as possible, but no sooner than 4 days after the last dose of N8-GP. Assessments of FVIII activity (recovery) and binding antibodies must be performed. If considered relevant a lupus anticoagulant test can be performed.

A positive confirmed inhibitor is considered to have disappeared if the inhibitor titre is < 0.6 BU on 2 consecutive inhibitor tests (performed with 1 month intervals) and the FVIII recovery is ≥ 66% of expected values. A patient with repeated positive test result will count only once in the determination of the inhibitor incidence rate.

If an investigator decides to perform inhibitor testing locally, he/she must send a duplicate sample for inhibitor testing at the central laboratory. The results from the central laboratory will be used in the analysis of trial data. A positive inhibitor test must always be reported as a MESI irrespective of the test being performed locally or at the central laboratory (refer to Section 11.2).

PK assessment (optional)

In the event of a concern about reduced treatment efficacy in a patient with or without confirmed positive test for binding antibodies towards N8-GP/ or inhibitors an unscheduled visit can be scheduled where a PK session may be performed with a dose of 60 U/Kg to investigate the elimination (recovery, clearance and half-life) of N8-GP. The PK data may potentially be used to adjust the dose or dosing regimen.

The following time-points for blood sampling for the PK profile are suggested: pre-dose, 30 minutes (± 10 min), 1h (± 10 min), 24h (± 8 hours), 48h (± 8 hours), and 96h (± 8 hours).

8.4.2.3 HIV testing and CD4+ lymphocyte count

All patients will be assessed for HIV at visit 0, if status is unknown, or HIV negative results in medical record are older than 6 months. Sampling can be postponed to the earliest convenient visit to ensure that the allowed blood volume is not exceeded.

Tests for CD4+ lymphocyte count and HIV viral load are only required for HIV positive patients. HIV positive patients should have CD4+ lymphocytes >200/µL and the viral load <400,000 copies/mL. If the patient is not immunocompetent according to the above mentioned criteria relevant anti-HIV treatment should be initiated.

Results can be transferred from the medical records if obtained within the last 6 months.

- HIV 1 and 2 antibodies
- CD4+ lymphocyte count
- HIV viral load

HIV and CD4+ assessments should be measured according to Table 2–1.

8.4.2.4 Haematology

- Haemoglobin (mmol/L)
- Haematocrit (%)
- Leucocytes ($x10^9$/L)
- Thrombocytes ($x10^9$/L)

If test results for the above mentioned haematology parameters are available from within one month prior to V0, they can be used for the V0 haematology assessment, if older, a new sample must be drawn and assessed at the central laboratory.

Haematology should be measured according to Table 2–1.

8.4.2.5 Biochemistry

- Creatinine (µmol/L)
- Alanine aminotransferase (ALT) (IU/L)
- C-reactive protein (CRP) (mg/L)

If test results for the above mentioned biochemistry parameters are available from within one month prior to V0, they can be used for the V0 biochemistry assessment, if older, a new sample must be drawn and assessed at the central laboratory.

Biochemistry should be measured according to Table 2–1.

8.4.2.6 *F8* and *HLA* genotype testing

At Visit 0, all patient's parent(s)/LAR(s) will be asked about documentation of previous Factor VIII gene (*F8)* and *Human Leucocyte Antigen (HLA)* genotype tests. If not available or if it needs to be re-tested, based on the investigators discretion, *F8* and *HLA* genotype testing will be offered if allowed according to local law. The *F8* and *HLA* genotype analysis will be performed at a laboratory selected by Novo Nordisk, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than *F8* and *HLA*. Samples will be disposed appropriately after the test and all test results are kept confidential.

Investigator and/or patient's parent(s)/LAR(s) have the right to refuse to provide patient's *F8* and *HLA* genotype documentation or to refuse genotyping. This will not prevent the patient from participating in the trial.

F8 and *HLA* genotype can be measured any time from visit 0 to visit 8.

F8 and *HLA* genotype can be measured according to Table 2–1.

Applicable for Japan only: If documentation of the patient´s genotype already exists, the patient is offered to provide his data for the trial. If no previous data exists and genotyping consent is obtained, FVIII and HLA genotype analysis is performed at the laboratory in Bonn, Germany, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than *F8* and *HLA*. Samples will be disposed appropriately after the test and all test results are kept confidential.

Applicable for Israel only: No genotype testing or genotype information will be collected.

8.4.2.7 Allergic reaction testing

Allergic reaction testing will only be performed in patients developing severe allergic reactions related to N8-GP treatment as judged by the Investigator. The baseline sample will be analysed for assessment of the allergic reaction.

If a severe allergic reaction related to treatment occurs, blood samples should be taken at an unscheduled visit as soon as convenient, and not later than 2 months after the event. The allergic reaction assessments will be performed at a laboratory selected by Novo Nordisk or at a Novo Nordisk laboratory.

Test to be performed:

- N8-GP IgE antibodies

- FVIII IgE antibodies
- FVIII inhibitors
- N8-GP/rFVIII binding antibodies

Optional tests at the discretion of the investigator:
- HCP IgE antibodies
- Murine IgG antibodies

If relevant, baseline levels for optional test can be set using samples from other patients enrolled in the trial.

Patients developing severe allergic reaction should be carefully investigated and followed up for inhibitor development.

8.4.3 Blood sampling in infants and children

The blood sampling volume for the patient must not exceed 1% of the total blood volume at one occasion or 3% within in 28 days. This is in accordance with European regulatory guidelines (Directive 2001/20/EC)[22].

The total volume of blood to be collected for each patient per visit will not exceed 10 mL.

Detailed instructions will be provided to the trial sites regarding blood sampling volumes and prioritisation of the samples. If trial sites as part of routine assessments perform additional blood draws, they must ensure that the blood sampling volume will not exceed the above requirements.

It is recommended not to attempt venepuncture more than 3 times for the purpose of obtaining sufficient blood sampling. Documentation must be available in medical record.

Port-a-caths and other central venous access devices should preferably not be used for blood sampling due to a risk of dilution or contamination with drugs (e.g. heparin). Should it be necessary to use such a device, it should preferably have been locked with saline prior to use.

8.4.4 Storage of samples

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

All remaining blood samples stored at the central laboratory will be destroyed after finalisation of the CTR, except for samples for antibody assessment and biospecimens, see Section 23.2.

Antibody samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

8.5 N8-GP administration

N8-GP will be administered while the patient is in a comfortable position according to Table 5–1.

During ED 1-2 with treatment at the trial site (V1 -V2):
The first 2 N8-GP doses should be administered at trial site by, or under direct supervision of an attending physician.

Trial injection kits (butterflies etc) will be provided by Novo Nordisk. Choice of butterfly or cannula for N8-GP injections is at the discretion of the investigator

The actual time of completion of the injection will be recorded and corresponds to trial time point = 0.

During ED 3-100 with treatment at trial site and at home (after V2):

Home treatment with administration of N8-GP can start after 2 EDs if the patient or the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process. If not the drug administration can take place at site.

- Home treatment may be given by the patient's parent(s)/LAR(s) or a home nurse, as applicable.
- The injection should be performed as an i.v. bolus injection (approximately 2 min for an injection). The date and the actual time of completion of the injection must be recorded in the patient's eDiary.
- All treatment requiring bleeding episodes should be treated and registered independently of the on-going prophylaxis treatment regimen.
- If a bleeding episode occurs earlier at the same day as the planned prophylaxis, the dose should be registered for the bleeding episode and not as prophylaxis and the planned prophylaxis dose later the same day should be omitted. The dose for the treatment of bleeding episode on a prophylaxis day should be approximately 60 U/Kg, and then the prophylaxis dose should not be taken.
- When a prophylaxis dose has been taken and a bleeding episode occurs later the same day, the bleeding episode should be treated and registered independently of the prophylaxis dose.

8.6 Bleeding episodes

All bleeding episodes and treatments with N8-GP must be recorded in the eCRF by the investigator or in the eDiary by the patient's parent(s)/LAR(s).

8.6.1 Assessments of bleeding episodes and treatment response

The severity of bleeding episodes is defined as

- Mild/moderate: Bleeding episodes that are uncomplicated joint bleeding episodes, muscular bleeding episodes without compartment syndrome, mucosal- or subcutaneous bleeding episodes. These bleeding episodes can be treated at home after V2 and details of the bleeding episodes should be entered in the eDiary by the patient's parent(s)/LAR(s).

- Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeding episodes must be categorised as severe. Muscle bleeding episodes with compartment syndrome and/or bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe (it is the investigators decision if haemoglobin measurements should be performed). The investigator must be contacted in case of a severe bleeding episode.

In case of treatment requiring bleeding episode outside the trial site opening hours prior to 2 EDs the patient must be treated according to local procedures.

Bleeding Episode – information to be collected

Information about bleeding episodes prior to the 2 ED (V2) should always be recorded in eCRF. In case the patient is treated outside the trial site the trial site should be informed in case of a bleeding episode and the details hereof. After 2 EDs bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see Section 12.3.

- Date and time the bleeding episode started
- Date and time the bleeding episode stopped
- Cause of the bleeding episode
  - i.e. spontaneous, traumatic or due to surgery
- Anatomical location of bleeding episodes
- Treatment of bleeding episodes
  - Amount, and time of each dose of N8-GP
- Haemostatic response assessed by the 4-point scale defined in Table 8–1

Table 8–1 4-point scale

Classification	Description
Excellent	Abrupt pain relief and/or clear 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 a single injection, but possibly requiring more than

Classification	Description
	one injection for complete resolution
Moderate	Probable or slight beneficial effect within approximately 8 hours after the first injection, but usually requiring more than one injection
None	No improvement, or worsening of symptoms

Re-bleed

Classification of re-bleed will be performed at the time of the statistical analysis, according to the following criteria:

- A re-bleed is defined as a new bleed within 72 hours after stopping of a previous bleed at the same or a subset of the same anatomical locations

If a bleeding episode occurs in the same location later than 72 hours after stopping the treatment it is considered as a new bleeding episode.

8.7 Surgery

Preventive N8-GP treatment before minor surgery including placement or removal of central venous access port can be performed within this trial at the investigator's discretion according to local guidelines. A dose of 40-75 U/Kg N8-GP prior to minor surgery is recommended to prevent perioperative bleeding episodes, see Table 5–1. Major surgeries are only allowed after 50 EDs and when the result from the pathfinder™3 (NN7088-3860) is available, see Section 5.3.4.

Preventive N8-GP treatment prior to surgery should be captured in eCRF or in the eDiary.

8.7.1 Minor surgery

Definition of minor surgery, see Section 5.3.4.
For minor surgery the following should be recorded:

- Date, time and volume of preventive dose before surgery
- Type of surgery
- Indication for surgery
- Date of surgery
- Start time of surgery

8.7.2 Major surgery

Definition of major surgery, see Section 5.3.4.
FVIII inhibitor sample should be taken prior to surgery and analysed at the central laboratory.

For major surgery the following should be recorded in the eCRF:

- Date, time and volume of preventive dose before surgery
- Type of surgery
- Indication for surgery
- Date of surgery
- Start and stop time of surgery
- Clinical evaluation of haemostatic response, see Table 8–1
- Clinical narrative of the procedure

Injections with N8-GP administered after surgery has been completed should be reported either in the eCRF (injections administered at site) or in the eDiary (injections administered at home), see Section 12.3

8.8 Training and reminders

8.8.1 Trial card dispensing

At V0 the patient's parent(s)/LAR(s) will receive a trial card stating that the patient is participating in a clinical trial. Telephone numbers and contact persons at the trial site will be listed.

8.8.2 Home treatment training

Home treatment training with administration of N8-GP can start after administrations of the first dose at the trial site (see Section 8.1.12), and should continue until the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process.

A home treatment guide for the reconstitution and administration process will be available as hands-out for the patient's parent(s)/LAR(s). Training in reconstitution and administration must be performed until parent(s)/LAR(s) feel comfortable in handling the treatment. The training must be documented in the medical records.

All patient's parent(s)/LAR(s) must be carefully instructed in recognising and dealing with signs and symptoms of an anaphylactic reaction. This includes knowledge of which medical facility to contact in this situation.

If the patient does not follow the planned dosing schedule, the investigator must retrain the patient's parent(s)/LAR(s).

8.8.3 Electronic diary (eDiary)

Pre-prophylaxis treatment, prophylaxis treatment and bleeding episodes should be recorded in the eCRF for the first 2 EDs. When the first 2 EDs have been administered, the data will be captured either in eCRF or eDiary according to Section 12.3.

Parent(s)/LAR(s) should be trained in using the eDiary before or when they receive the eDiary. If needed the training must be repeated until the parent(s)/LAR(s) use the eDiary as intended.

It will be the responsibility of the investigator to assess the eDiary data throughout the conduct of the trial and to ensure entry compliance.

During the home treatment period the patient's parent(s)/LAR(s) must ensure that all pre-prophylaxis and prophylactic home treatment, bleeding episodes, treatment of bleeding episodes as well as haemostatic evaluation of the treatment of bleeding episodes are captured in the eDiary.

8.8.3.1 eDiary dispensing and collection

The eDiary will be dispensed to the patient's parent(s)/LAR(s) at V2.

For details regarding patient's eDiary, please refer to Section 12.3.

For patients completing the trial or in case of withdrawal, the eDiary will be collected at the EOT visit.

8.8.4 Contact between the investigator/medically qualified person and the patient

The investigator and/or medically qualified person must establish contact with the patient's parent(s)/LAR(s) at least every 12 weeks ± 1 week, if site visits are more than 3 months apart, either by visits at the trial site or other contact e.g. telephone calls. All contact must be captured in eCRF.

The patient and patient's parent(s)/LAR(s) should be notified that they will be contacted according to the protocol.

The communication will focus on the well-being of the patient, including enquiry to all AEs, and any medical treatment (including treatment of bleeding episodes) since the last contact. The investigator/medically qualified person should not suggest specific AEs to patient's parent(s)/LAR(s), but should inquire e.g. "how is your child doing?" and "has your child had any medical problems since the last contact?", and "have you remembered to enter all treatment in the eDiary?".

The expiry date of the drug that the patient has received should be checked by the site staff before the patient's next visit to determine if an extra dispensing is relevant and to inform the patient of which unused vials to return to the site.

All attempts to contact the patient's parent(s)/LAR(s) must be documented in a source document. If a successful contact cannot be made after 3 documented attempts, no further attempts are required. If the patient's parent(s)/LAR(s) have withdrawn consent, this must be documented.

At each contact the investigator will at a minimum capture/evaluate

- Assessment of bleeding episodes
- Adverse events
- Concomitant Medication
- eDiary compliance
- N8-GP administration compliance

8.8.5 Interactive voice/web response system

Please refer to Section 10 regarding the IV/WRS.

For details on how to use the IV/WRS, please refer to the trial specific IV/WRS user documents provided to the trial site.

8.9 Patient compliance

Throughout the trial the investigator will remind the patient's parent(s)/LAR(s) 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's parent(s)/LAR(s) of the importance of following the instructions given including taking the trial products as described.

Assessment of patient compliance with protocol procedures for determination of continuation of the trial will be done by the investigator's discretion.

Failure to comply with scheduled visits and N8-GP administration may result in withdrawal in accordance with the protocol withdrawal criteria, see Section 6.4.

Treatment with FVIII concentrates, other than N8-GP, during the trial is not allowed and violation of this may lead to withdrawal due to non-compliance (please refer to Section 8.2.4). Regarding by-passing agents, see Section 8.2.3.

Compliance with N8-GP treatment must be addressed at each visit. Compliance check includes a cross check between number of injections recorded in eDiary, expected number of doses and the used/returned vials.

9 Trial supplies

Trial supplies comprise trial product and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Material Manual (TMM) and Handling instruction.

Trial product must not be dispensed to any person not included in the trial (excluding patient's parent(s)/LAR(s)).

Auxiliary supplies comprise supplies other than trial product, e.g. needles and syringes.

9.1 Trial product

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

Table 9–1 Trial Product

Trial product	Strength	Dosage form	Route of administration
N8-GP (turoctocog alfa pegol)	• 500 U/vial, 53µg/vial • 2000 U/vial, 211µg/vial	Freeze-dried Powder for solution for injection	i.v. injection

N8-GP is supplied as a sterile freeze-dried powder for solution for injection in single use vials with a nominal content of 2000 U/vial or 500 U/vial to be reconstituted with 4.3 mL 0.9% Sodium Chloride Solution. After reconstitution each vial contains 500 U/mL or 125 U/mL N8-GP, respectively. The reconstituted solution is colourless and clear to almost-clear with a pH of 6.9. The reconstituted solution must not be diluted further. Trial product must not be used if it does not appear colourless and clear to almost-clear.

After reconstitution the appropriate volume of the vials will be drawn into a syringe. The content of several vials may be combined in one syringe. N8-GP may not be added to or mixed with any other material.

Administration of the appropriate volume of N8-GP will be given as i.v. bolus injection over approximately 2 minutes (from start to completion of injection).

The investigator must explain to the patient's parent(s)/LAR(s) the injection process of N8-GP at home.

The maximum dose to be administered to a patient within 24 hours is 200 U/Kg, with a maximum individual dose of 75 U/Kg. These doses are only relevant in case of trauma, severe bleedings or surgery.

Novo Nordisk will not supply any Non Investigational Medical Products (NIMPs).

9.2 Packing, labelling and dispensing

Labelling of the trial product will be in accordance with Annex 13[23], local regulations and trial requirements. Novo Nordisk A/S will be responsible for labelling and packaging of the trial product. Third party vendors may be employed.

N8-GP and Sodium Chloride will be provided in boxes. The boxes will be provided with labels containing the following information: product name, expiry date, storage conditions. Each trial product box will have a unique Dispensing Unit Number (DUN) for identification and traceability.

The details of the packaging and labelling of the trial product will be provided in the TMM supplied by Clinical Supplies Coordination, Novo Nordisk.

The IV/WRS will allocate the trial product in uniquely numbered DUs to the patient at each dispensing visit. The DUs will be dispensed in accordance with the patient's body weight. Trial product will be dispensed at dispensing or assessments visits, as appropriate.

The investigator must document that direction for use is given to the patient's parent(s)/LAR(s) orally and/or in writing at each dispensing visit according to the Handling instruction.

9.3 Storage

Table 9–2 Storage

Storage must be done according to the table below	**Storage conditions(not-in-use)**	**In-use conditions**
N8-GP (turoctocog alfa pegol)	• 2-8˚C • Protect from light	• 4 hours below 30˚C • Do not freeze • Avoid direct sunlight
0.9 % Sodium Chloride Solution	• 2-30°C • Protect from light	N/A

The trial product N8-GP powder and Sodium Chloride Solution must be stored in a secure place at trial site. For N8-GP under refrigeration at 2-8°C, and for Sodium Chloride Solvent at 2-30°C, both protected against light and are hereby stable until the expiry date given. It is recommended to use the reconstituted N8-GP immediately following reconstitution. If not used immediately, the reconstituted product can be stored in the vial for up to 4 hours below 30°C. Exposure to direct sunlight as well as freezing must be avoided after reconstitution. As for other parenteral preparations, the product should be inspected visually for particulate matter and discoloration prior to administration and discarded if either is present.

The trial site must carefully instruct the patients' parent(s)/LAR(s) in how to store the trial product. No temperature monitoring is required after the trial product is taken home by the patient.

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

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

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

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator. The investigator or delegated person, eg, a trial nurse will perform drug accountability in the IV/WRS Drug Accountability Module.

Once a patient is dosed, all trial drug product vials (dispensed, used, partly used or unused, returned and lost/damaged) must be recorded in the IV/WRS Drug Accountability Module.

Drug accountability is not required for Sodium Chloride Solution used for reconstitutions.

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

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

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of product must be documented.

For Japan only: Responsibility for storage and drug accountability of the trial drug product at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug product at the trial sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug product in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary supply

Auxiliary supplies are equipment such as needles, syringes, butterflies, sterile swabs, vial adaptor etc. These will be provided by Novo Nordisk.

10 Interactive voice/web response system (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time via internet or via telephone. Access to the IV/WRS must be restricted to and controlled by authorised persons.

IV/WRS is used for:

- Screening
- Screening failure
- Medication arrival
- Dispensing
- Withdrawal
- Completion
- Drug accountability
- Data change

IV/WRS call can be done the day before the actual visit.

IV/WRS user guides will be provided to each trial site.

11 Adverse events and technical complaints

11.1 Definitions

Adverse event:
An **adverse event** (AE) is any untoward medical occurrence in a patient administered a product, and which does not necessarily have a causal relationship with this treatment.

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

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

The following should not be reported as AEs:
- Bleeding episodes and other symptoms (eg synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. In case of life-threatening bleeding episode, it should always be reported as a SAE. All bleeding episodes and other findings related to underlying disease will be in Section 8.
- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.

The following three definitions are used when assessing an AE:
- **Severity assessment**
  - **Mild** - no or transient symptoms, no interference with the patient's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the patient's daily activities.
  - **Severe** - considerable interference with the patient's daily activities; unacceptable.

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

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome of an AE**
  - **Recovered/resolved** - The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient's parent(s)/LAR(s) signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the patient is lost to follow-up.

Serious adverse event:

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].
- Suspicion of transmission of infectious agents via the trial product and formation of inhibitory antibodies must always be considered an SAE.
- FVIII inhibitory antibodies (confirmed by two consecutive tests see Section 8.4.2.2) must always be considered a SAE

a. The term "life threatening" in the definition of SAE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

b. The term "hospitalisation" is used when a patient:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

c. A substantial disruption of a patient's ability to conduct normal life functions (eg following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

d. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

Non-serious adverse event

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

Medical event of special interest

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

1. Medication errors concerning trial product:
   - Administration of wrong drug
   - Wrong route of administration
   - Administration of an overdose with the intention to cause harm (eg suicide attempt)
   - Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although not necessarily did happen

2. Inhibitor formation against FVIII. Blood samples for measurement of FVIII inhibitors will be analysed at a central laboratory selected by Novo Nordisk. If an investigator obtains information of a positive central laboratory result or any indication of inhibitor formation by clinical signs or local laboratory results, this should be reported as a MESI prior to confirmation by two central laboratory results.

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

4. Anaphylactic reaction as defined by Sampson et al 2006[24] (see below).

5. Allergic reaction including, but not limited to, any acute immunoglobulin E (IgE) mediated reaction of delayed type hypersensitivity (clinical signs may include various types of skin rashes) that does not meet the definition of anaphylaxis as described by Sampson et al 2006[24]

Definition of an acute, evolving, or recent myocardial infarction:

Either one of the following two criteria satisfies the diagnosis for an acute, evolving or recent myocardial infarction:

1. Typical rise and gradual fall in troponin T or more rapid rise and fall in creatine kinase, muscle and brain or biochemical markers of myocardial necrosis with at least one of the following:
    - Ischaemic symptoms
    - Subsequent development of pathologic Q waves on the ECG
    - ECG changes indicative of ischaemia (ST segment elevation or depression)
    - Coronary artery intervention (eg angioplasty)
2. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria a and b below are fulfilled):
    - Increase in troponin T above the "diagnostic" limit: i.e. > 0.03 µg/L
    - Patients with:
        - ST-segment elevation: New ST-segment elevation at the J point in two or more contiguous leads with the cut-off points >= 0.2mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)
        - No ST-segment elevation: ST-segment depression and or T-wave inversion in two or more contiguous leads >= 0.1 mV

Definition of pulmonary embolism:
Obstruction of a pulmonary artery or one of its branches, most frequently by detached fragments of thrombus from a leg or pelvic vein, diagnosed by at least one of the following:

- Positive findings in ventilation/perfusion scan
- Positive findings in a spiral(helical) computed tomography or angiography
- Positive findings in a magnetic resonance imaging
- Positive findings in a pulmonary angiography

Definition of cerebral thrombosis/infarction:
Acute neurological injury that persists for at least 24 hours and occurs as a result of either a thrombosis or embolic process, diagnosed by at least one of the following:

- Computerised tomography
- Magnetic resonance scan
- Magnetic resonance angiogram
- Cerebral angiography

Deep vein thrombosis:
Venous thrombosis demonstrated by compression ultrasound, duplex ultrasound, or colour Doppler imaging.

Definition of other clinically significant thromboembolic events:
Sign or suspicion of clinically significant thromboembolic event, eg:

- visceral arterial embolus/thrombus,
- extremity arterial embolus/thrombus or
- portal venous thrombosis.

Superficial thrombophlebitis is not considered a clinically significant thromboembolic event unless evaluated so by the investigator.

Peripheral artery occlusion:
Clinical signs of acute arterial occlusion verified by either ankle-brachial index test, Doppler or ultrasound (Duplex) imaging, computed tomographic angiography, magnetic resonance angiography, or conventional angiography.

Clinical criteria for diagnosing anaphylaxis (Sampson et al. 2006[24]): Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
    b. Adults: systolic BP of less than 90 mm Hg or greater than

*30% decrease from that person's baseline

Technical complaint

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

Examples of technical complaints:

- The physical or chemical appearance of trial product (eg discoloration, particles or contamination)
- The packaging material (eg leakage, cracks, rubber membrane issues or errors in labelling text)

11.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient's parent(s)/LAR(s) has signed the informed

consent until the end of trial visit. The events must be recorded in the applicable CRF forms in a timely manner. See timelines below and Figure 11–1.

AEs between consent and first dosing should only be reported if associated with trial related activities.

During each contact with the trial site staff (trial site visits and telephone contacts), the patient and/or patient's parent(s)/LAR(s) must be asked about AEs and technical complaints, e.g. "Have you experienced any problems since the last contact?"

All AEs, either observed by the investigator or reported by the patient, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: investigator's brochure,[5] N8-GP, current version and any updates thereto.

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

For each SAE and MESI an electronic Safety Information Form (eSIF) should be completed in addition to the AE form in the eCRF, see Figure 11–1. If several symptoms or diagnoses occur as part of the same clinical picture, one eSIF may be used to describe all the SAEs. All concerned AE numbers must be included in the AE number field on the eSIF.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form. For MESIs of allergic aetiology, the hypersensitivity questionnaire must be completed.

The AE form for a non-serious AE should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:
The investigator must complete the following forms in the eCRF within the specified timelines:

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

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

- **Non-serious AE fulfilling the MESI criteria**: The AE form and the safety information form within 14 calendar days of the investigator's first knowledge of the event.

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

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

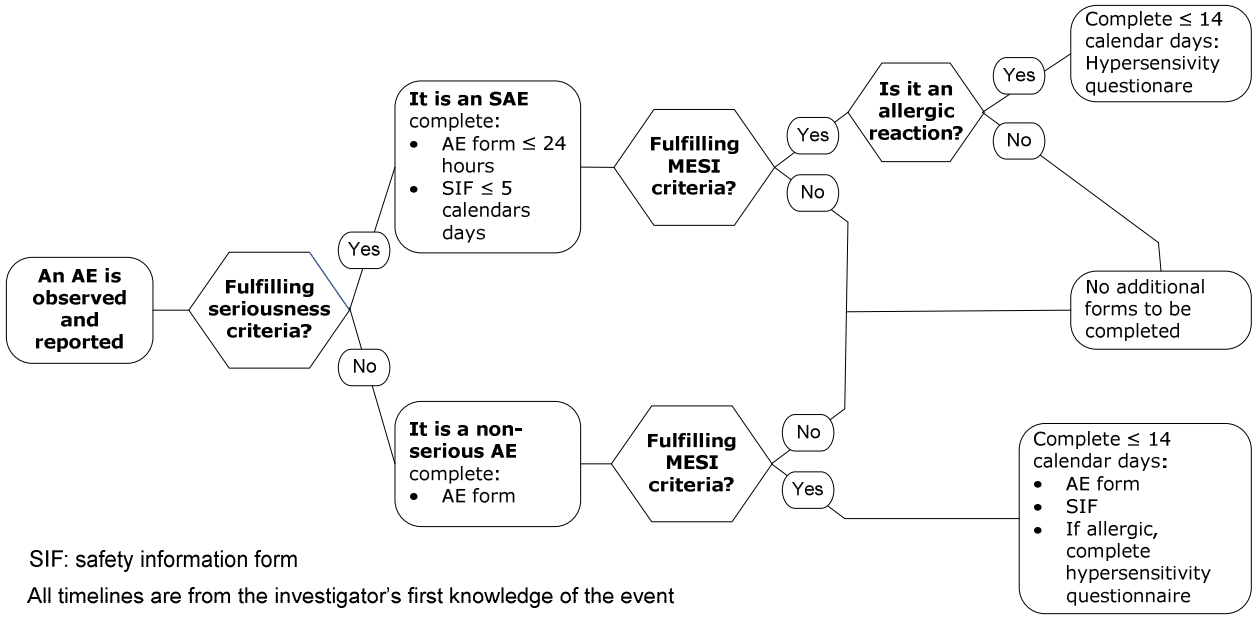

Figure 11–1 Initial reporting of AEs

Reporting of trial product-related SUSARs by the sponsor:

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

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the

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

11.3 Follow-up of adverse events

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

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

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (eg corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.
- **Non-serious AE fulfilling the MESI criteria:** Follow-up information on MESIs should only include new (eg corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

11.4 Technical complaints and technical complaint samples

11.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- N8-GP 500 U/vial
- N8-GP 2000 U/vial
- Sodium Chloride 0.9 % vial
- Novo Nordisk trial injection kit

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

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

The investigator must assess whether the technical complaint is related to any AE(s), SAE(s) and/or MESI(s).

Technical complaints must be reported on a separate technical complaint form for each product listed. If the technical complaint involves more than one batch, lot number or more than one DU, a technical complaint form for each batch, lot number or for each DU must be completed.

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

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

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

11.4.2 Collection, storage and shipment of technical complaint samples

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

The investigator must ensure that the technical complaint sample contains the batch, lot number and, if available, the dispensing unit number (DUN).

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

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product). The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage, see Section 9

11.5 Precautions and/or overdose

As with any protein injected i.v. hypersensitivity reactions may occur. The possible events include rash, pruritus, fever, nausea, headache, vomiting and changes in blood pressure. If any of these events are suspected, further N8-GP administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines.

If an overdose of N8-GP is suspected further N8-GP administration should be stopped prior to any further N8-GP administration and the patient should receive treatment as appropriate according to hospital practice and guidelines.

11.6 Committees related to safety

11.6.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance of N8-GP. The safety committee works according to a written guideline and will meet regularly to discuss and evaluate the overall safety for N8-GP for this trial and all other N8-GP trials. The Novo Nordisk safety committee can take action with regard to the patient safety for the trial based upon observations of the overall information for N8-GP. Pre-defined rules for setting the enrolment on hold is described in Section 11.6.2.

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

11.6.2 Rules for putting the enrolment on hold

A safety analysis will be performed to evaluate the development of inhibitor at the following predefined time point:

• after the first 25 patients have been to visit 6 (20-25 exposure days)

The expected rate of inhibitors is about 30% in PUPs with severe haemophilia A.[4] In case of confirmed FVIII inhibitor formation in 12 or more of all exposed patients, all cases of inhibitor formation will be evaluated by the N8-GP safety committee. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enrolled in the trial. The

evaluation will provide the basis for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial, and will be documented in the safety committee meeting minutes.

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

12 Case report forms

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be supplied by a vendor. The activities of this vendor will be under the direction and supervision of Novo Nordisk.

The investigator or delegated person should 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 (eg is not applicable), indicate this according to the date entry instructions.

The following will be provided as paper CRF:

1. Hypersensitivity questionnaire

In addition paper AE forms, safety information forms and Technical Complaint forms will be provided. These must be used when access to the eCRF is revoked.

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 or an 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 (eg 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 derived from source documentation is consistent with the source information. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF including related forms is reviewed, complete and correct.

12.1 Corrections to case report forms

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

If corrections are made by the investigator's authorised staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

Corrections to the data in paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

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

12.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data have been entered, it will be available to Novo Nordisk for data verification and validation purposes.

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

When the final CTR is available, the data will be archived by Novo Nordisk.

12.3 Electronic diary

Novo Nordisk will provide the patient's parent(s)/LAR(s) with an eDiary for electronic recording of details of their child's prophylaxis administration, bleeding episodes, surgery and treatment hereof, see Sections 8.1.12.1 and 8.6. The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

At visit 2, the patient's parent(s)/LAR(s) will receive the eDiary and they will be trained in the use hereof by the investigator or delegated person. After visit 2 (after 2 EDs) and onwards, data will be entered by the patient's parent(s)/LAR(s) in the eDiary device during home treatment.

During trial site visits, data will be recorded in the eCRF by the trial staff, and should not be entered by the patient's parent(s)/LAR(s) in the eDiary.

The eDiary will be returned by the patient's parent(s)/LAR(s) at the EOT visit.

All data entered will be transferred from the device to an electronic database, where it is kept as a certified copy of the source data. Data entered in the device will upon confirmation of a successful back-up be deleted from the device.

The eDiary will have built in edit checks and reminders, to ensure that all relevant questions are answered.

eDiary data transferred to the electronic database will be viewable to relevant trial site staff and Novo Nordisk personnel on a secure, password protected web portal.

It is the responsibility of the Investigator to review and thereby ensure the eDiary data quality. Following must be checked as minimum that the eDiary data is complete, consistent and according to the requirements defined in this protocol. Upon review the Investigator must document that the review has taken place and any actions required e.g. retraining of patients.
It must be confirmed by the patient's parent(s)/LAR(s) if missing eDiary data need to be entered and/or if the transferred eDiary data needs to be corrected. This is done by filling in and forwarding a Data Correction Request to the eDiary vendor. An audit trail will be maintained.

13 Monitoring procedures

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

The first monitoring visit will be performed as soon as possible after FPFV and no longer than 4 weeks after. The monitoring intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between monitoring visits must not exceed 12 weeks whilst patients are in the trial.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (eg by telephone).

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

All data must be verifiable in source documentation other than the eCRF, except for the following data that may be recorded directly in the eCRF and will then be considered source data:

- Ethnicity
- Race

The patient will only be identified by patient number and the monitor will verify and ensure that the eCRFs and eDiary are completed. Also it must be checked that the eDiary data review has been documented by investigator and that the needed action has been taken, if any

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

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

For screening failures: Data for the screening visit must be entered in the eCRF within preferably 3 days after data are available and the Screening Failure Form must be completed. Source data verification is not required except for informed consent, reason for screening failure and for data

relating to any AEs if applicable. All data entered in the eCRF will be transferred into the trial database.

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

All information captured during visits to the trial site will be collected in the eCRF. When home treatment is initiated all bleeding episodes and injections with N8-GP occurring outside the trial site should be entered in the eDiary by the patient's parents/LAR (see Section 8.8.3). The completed eDiary is considered source data.

14 Data management

Data management is always the responsibility of Novo Nordisk.

Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or an external Clinical Research Organisation (CRO).

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

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

The central and local laboratories will provide laboratory reports to the investigator for storage at the trial site. The laboratory report must be signed and dated by the investigator or delegated person and stored at the trial site as source data.

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

15 Computerised systems

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

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

Novo Nordisk will use the Global Haemophilia Network Investigator Portal to distribute and share trial-related documents and information with the participating sites.

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1,25] After trial completion, each trial site will be supplied with long-life CDs. These CDs will contain site-specific patient records including the patient's eDiaries and audit trail including any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 15 years or as required by local data retention laws for trial data.

16 Statistical considerations

Novo Nordisk will be responsible for the statistical analysis.

The main statistical reporting of the trial will be performed when 50 patients have completed main phase (minimum 25 weeks) with at least 50 EDs and completed visit 9. EDs during ITI treatment will not count in the determination of when a patient has reached 50 EDs. Data from patients not yet having completed the main phase and data from patients that have entered extension phase at this point will be included up to latest visit prior to this cut-off date. This report will cover all endpoints, and will form the basis for the paediatric indication. The data will be presented for the main phase and for the extension phase separately as well as combined.

Except for the confidence interval for inhibitor rate and for annualised bleeding rate, the evaluation of data will be based on descriptive statistics, i.e. summary tables, listings and figures.

An updated reporting of the trial with supportive data will be performed when 100 patients have had at least 100 EDs. Data from all patients will be included up to latest visit prior this cut-off date. The data will be presented for the main + extension phase and the extended prophylaxis period (beyond 100 EDs) separately as well as combined.

All data,, will be reported separately in a final report when the trial is completed.

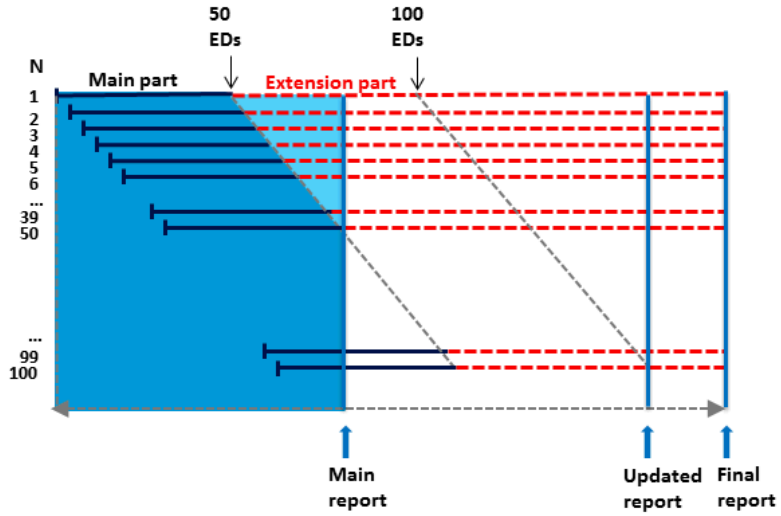

Figure 16–1 Individual patient flow and time periods for trial reporting

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

All bleeding endpoints will be evaluated based on bleeding episodes treated with N8-GP unless the bleeding was considered clinically insignificant (non-treatment requiring bleeding episode) and the associated treatment given was part of prophylaxis.

Patients initiating ITI treatment will for the statistical analyses be considered like withdrawals and data collected during ITI treatment period will be summarised and reported separately. Evaluation of these data will be considered exploratory only.

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. If created, the SAP will be finalised before the first database lock.

16.1 Sample size calculation

No formal sample size calculations have been performed. The sample size of 100 completers is based on EMA guideline[7].

16.2 Definition of analysis sets

Descriptions and analysis of efficacy data will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines.[26] The FAS includes all patients exposed to N8-GP. The safety analysis and descriptions will be based on the Safety Analysis Set (SAS). The SAS will consist of all patients exposed to N8-GP.

16.3 Primary endpoint

The primary endpoint is a safety endpoint defined as incidence of inhibitory antibodies against FVIII.

The rate of inhibitory antibodies will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the rate the numerator will include the patients with inhibitors, while the denominator will include all patients with a minimum of 10 exposure days plus any patient with less than 10 exposure days but with inhibitors.

16.4 Secondary endpoints

16.4.1 Confirmatory secondary endpoints

There are no confirmatory secondary endpoints in this trial

16.4.2 Supportive secondary endpoints

16.4.2.1 Number of bleeding episodes during prophylaxis

Annualised bleeding rate will be summarised and a 95% two sided confidence interval will be provided based on a negative binomial regression model with number of bleeding episodes requiring treatment with N8-GP as the outcome variable, and adjusting for exposure time. For comparison with previous trial, a sensitivity analysis based on a Poisson regression model allowing for over-dispersion will also be performed.

Since it must be expected that some patients will withdraw, it becomes essential to account for how such withdrawals may affect the analyses of the prophylaxis effect. The analyses above already account for possible different treatment durations by using treatment duration as an offset. This is a proper adjustment if withdrawal is not related to the observed bleeding frequency. However, since it is possible that patients will withdraw exactly because of the observed bleeding rate it is important to perform sensitivity analyses that may account for withdrawn patients possibly being qualitatively different from completing patients.

Specifically this will be done by performing sensitivity analyses for all prophylaxis analyses using a last observation carried forward (LOCF) approach for all patients with at least 1 month prophylaxis treatment duration by calculating the yearly bleeding episode rate for withdrawn patients and use that as an endpoint. As an example a patient with 6 bleeding episodes in 4 months will have an endpoint value of 18 corresponding to a maintained bleeding rate of 18 bleeding episodes per year. For patients withdrawing within 1 month this method is considered to give too uncertain LOCF values, hence imputation will not be attempted for such patients.

Annualised bleeding rate will also be summarised by type of bleeding episode.

16.4.2.2 Haemostatic effect

Description of the haemostatic effect of N8-GP when used for treatment of bleeding episodes will be summarised and listed according to the four point scale for haemostatic response (none, moderate, good and excellent).

A success rate will be calculated based on counting good or excellent as successes and none and moderate as failures, and based only on reported outcomes.

For the calculation of the success rate the numerator will include all treated bleeding episodes with a reported haemostatic response of good or excellent, while the denominator will include all treated bleeding episodes with a reported haemostatic response. A sensitivity analysis will also be conducted where the denominator also includes treated bleeding episodes with missing response (i.e., missing response is counted as a failure).

Haemostatic effect will be determined based on haemostatic response for bleeding episodes occurring both during pre-prophylaxis and prophylaxis period.

Haemostatic response will also be summarised by type of bleeding.

16.4.2.3 Incidence of high titre inhibitors

The rate of high titre inhibitors (defined as inhibitor titre > 5BU) will be reported similar to the primary endpoint

16.4.2.4 FVIII consumption

Total amount of N8-GP used, amount of N8-GP used for prophylaxis (U/Kg/month/year) and amount consumed per bleeding episode (number of injections and U/Kg bw/bleeding episode) will be summarised and listed.

16.4.2.5 Safety endpoints

Adverse events including SAEs and MESI

Treatment emergent AEs (TEAEs, defined as AEs occurring after dosing with trial product) and treatment emergent SAEs (TESAEs) will be summarised by frequency of events and frequency of patients with any event. Similar summaries cross-classified by severity and by causal relation to trial produce will also be made.

MESIs will be summarised similarly to AEs.

Furthermore, listings will be provided displaying all TEAEs and TESAEs including pertinent clinical information.

All additional safety parameters such as laboratory parameters and physical examinations will be summarised and listed.

16.4.2.6 Other assessments

Incremental recovery (IR_{30min}), FVIII activity at 30 minutes (C_{30min}) and trough level will be assessed at visit according to Table 2–1.

FVIII trough level is defined as the activity recorded immediately before N8-GP injection, and reported as (U/mL). IR_{30min} is defined as the peak activity recorded 30 minutes after the end of N8-GP injection, and reported as [U/mL]/[U/Kg]. It is calculated by subtracting the FVIII trough level from the FVIII activity recorded 30 minutes after ended N8-GP injection, and dividing the difference by the dose injected at time 0 expressed as U/Kg bw.

16.5 Interim reporting

All data from main phase of the trial will be analysed and reported when the first 50 patients have completed main phase with at least 50 EDs and completed visit 9. This report will cover all endpoints, and will form the basis for the paediatric indication. Data from patients that have entered extension phase at this point will be included up to latest visit prior this cut-off date. The data will be presented for separately for the main phase and extension as well as combined.

An updated report will be made when the first 100 patients have had at least 100 EDs. A final report with supportive data will be made when all patients have completed both parts of the trial.

16.6 Sequential safety analysis and safety monitoring

Novo Nordisk will constitute an internal safety committee to perform on-going safety surveillance. The trial will be subject to thresholds evaluated by the safety committee (see Section 11.6.1).

In addition a safety analysis will be performed to evaluate the development of inhibitor at the following predefined time point:

after the first 25 patients have been to visit 6 (20-25 exposure days)

The expected rate of inhibitors is about 30% in PUPs with severe haemophilia A[4]. In case of confirmed FVIII inhibitor formation in 12 or more of all exposed patients, all cases of inhibitor formation will be evaluated by the N8-GP safety committee. During these evaluations, ongoing treatment in the trial will continue, however new patients will not be enrolled in the trial. The evaluation will provide the basis for a decision on any actions required for the trial to allow for continuation of enrolment or decision to terminate the trial, and will be documented in the safety committee meeting minutes (see Section 11.6.2).

16.7 Reporting of *F*8 and *HLA* genotype

Information about underlying gene defects of *F*8 and *HLA* will be listed in the clinical trial report, except for Israel. No statistical analysis will be performed.

17 Ethics

Participation in this trial could be a possible benefit for the patient in terms of closer monitoring of the patient by the investigator, compared to standard care and possible avoidance of bleeding episodes. As with all investigational drugs, there is an anticipated risk of potential side effect[1].

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

17.1 Informed consent

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

Before any trial-related activity, the investigator must give the patient and/or the patient's parent(s)/LAR(s)) verbal and written information about the trial and the procedures involved in a form that the patient or the patient's parent(s)/LAR(s) can read and understand. This includes the use of an impartial witness where required. In this trial the notion of LAR is the legal representatives, as defined in Member States' national laws, who consent on behalf of the child.

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

The investigator must ensure the patient and/or patient's parent(s)/LAR(s) ample time to come to a decision whether or not to participate in the trial.

The requirement for obtaining informed consent from a patient's parent(s)/LAR(s) is that the patient is unable to provide informed consent, and the process has been approved by the relevant IRB/IEC.

A voluntary, signed and personally dated informed consent form must be obtained from the patient's parent(s)/LAR(s) before any trial-related activity. In this trial where informed consent and exposure to the N8-GP may occur on the same day, informed consent form must include a time field next to the data field.

Consent: As a child is unable to provide legally binding consent, informed consent must be sought from the patient's parent(s)/LAR on the child's behalf. The specific and written informed consent of the parent(s)/LAR must be sought prior to enrolling a child in the trial. Information about the trial should be given by an experienced investigator.

For children, from birth to the age of 3 years old, it is not possible to obtain assent and understanding of research is not expected[22].

Patients above the age of 3 years old should sign a child assent form, if capable, and if required by local requirements. This can be performed on a separate day; especially for long-term trials here the investigator should check the progressing maturation of the child and its ability for assent.

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

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

***F8* and *HLA* genotype testing/collection of previous genotype documentation (not applicable for Israel):**
Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient and/or the patient's parent(s)/LAR(s) must give their consent before the data can be collected for trial purpose. Prior to any trial-related activity, the investigator must provide the patient's parent(s)/LAR(s) with the possibility to abstain from the genetic testing/collection of previous documentation, but still be able to participate in the trial.

Only the *F8* and *HLA* genotype will be analysed by the central laboratory selected by Novo Nordisk and no other genomic analyses will be carried out. Samples will be appropriately disposed of, after the test. All test results are kept strictly confidential in sufficient consideration of individual information.

17.2 Data handling

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

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

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

17.3 Information to patient, parent(s)/LAR(s) during the trial

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

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

17.4 Premature termination of the trial and/or trial site

Novo Nordisk, the investigator, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but subject to the following procedure.

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

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

18 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

19 Audits and inspections

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

20 Critical documents

An Investigator Portal will be used as media for exchange and handling of investigator trial file documents between Novo Nordisk and the trial site and for electronic storage of these documents during trial conduct.

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

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

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by each investigator

FDA form 1572:

For US trial sites:

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

For trial sites outside the US:

- Intended for participating trial site outside of the US
- Not conducted under the IND

- All investigators outside of the US will not sign FDA form 1572

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

For local lab parameters the following will be collected:
- Laboratory normal ranges
- Laboratory certification/QA scheme/other documentation
- Laboratory methods

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

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

21 Responsibilities

All staff (Novo Nordisk, trial site, laboratory, CRO etc.) will conduct the trial in compliance with ICH GCP[1], applicable regulatory requirements and the Declaration of Helsinki[2].

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

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions. The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

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

The investigator is responsible for filing essential documents (ie those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator's trial file. The documents should be kept in a secure locked facility, so no unauthorized persons can get access to the data. The patient identification code list should be kept securely and separate from the personal data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator should 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 of investigator (eg if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

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

22 Reports and publications

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

A principal investigator will be designated as the signatory investigator with the responsibility to review and sign the main report based on data from when the first 50 PUPs have reached at least 50 EDs.

22.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

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

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the principal investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

22.1.1 Authorship

Authorship of publications should be determined in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria[27]).

Authorship credit should be based on:

- Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published.

22.1.2 Trial site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual trial site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission for publication of such primary policy will take place no later than 18 months after trial completion.

22.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.

23 Retention of clinical trial documentation and human biospecimens

23.1 Retention of clinical trial documentation

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

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

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Trial site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the Novo Nordisk provided data (eg the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy, as a copy of all data will be stored by Novo Nordisk.

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

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

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

23.2 Retention of human biospecimens

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

Antibody samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

All remaining blood samples will be stored until the trial has been evaluated by appropriate authorities or until the project terminates, but no longer than 15 years from end of trial. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of N8-GP may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral bio-repository with access to the samples. Samples might be transferred to other countries, if not prohibited by local regulations. The patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and bio-repository personnel (if applicable) will have access to the stored bio specimens.

24 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:
Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the patients.

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

Regulatory Authorities:
Regulatory authorities will receive the clinical trial application (CTA), protocol amendments, reports on SAEs, and the CTR according to national requirements.

25 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

Only applicable for Argentina: Novo Nordisk Pharma Argentina S.A. has contracted insurance (policy reference number 87828 and its respective updates) with the company Sancor Cooperativa de Seguros LTDA. Domiciled in Independencia 333, Sunchales, Santa Fé, Argentina. Telephone number: 0800-444-28500.

Only applicable for Australia: Medicines Australia Guidelines for Compensation for Injury Resulting From Participation in a Company-sponsored Clinical Trial. Version 160104B dated 16 January 2004.

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. I Nr. 48/2013

Only applicable for France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical 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".

Only applicaple for Netherlands: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit van 23 juni 2003, houdende regels inzake de verplichte verzekering bij medischwetenschappelijk onderzoek met mensen (Decree of 23 June 2003, containing rules for compulsory insurance in medical research involving human subjects (Medical Research (Human Subjects) Compulsory Insurance Decree)**.**

Only applicable for Poland: Novo Nordisk carries liability for the Study exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Study, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law'

26 .References

1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice, 01-May-1996, Geneva, Switzerland. 1996.

2 WMA. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2010.

3 Gouw SC, van der Bom JG, Marijke van den BH. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. Blood 2007; 109(11):4648-4654.

4 Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368(3):231-239.

5 Investigator's Brochure, N8-GP, 4th Edition. Novo Nordisk A/S. 2013.

6 Tiede A, Brand B, Fischer R, Kavakli K, Lentz SR, Matsushita T et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A. J Thromb Haemost 2013; 11(4):670-678.

7 EMA. Committee for medicinal products for human use (CHMP), Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products, EMA/CHMP/BPWP/144533/2009. 2011.

8 Geraghty S, Dunkley T, Harrington C, Lindvall K, Maahs J, Sek J. Practice patterns in haemophilia A therapy -- global progress towards optimal care. Haemophilia 2006; 12(1):75-81.

9 Ivens IA, Baumann A, McDonald TA, Humphries TJ, Michaels LA, Mathew P. PEGylated therapeutic proteins for haemophilia treatment: a review for haemophilia caregivers. Haemophilia 2013; 19(1):11-20.

10 Astermark J. Immune tolerance induction in patients with hemophilia A. Thromb Res 2011; 127 Suppl 1:S6-S9.

11 Benson G, Auerswald G, Elezovic I, Lambert T, Ljung R, Morfini M et al. Immune tolerance induction in patients with severe hemophilia with inhibitors: expert panel views and recommendations for clinical practice. Eur J Haematol 2012; 88(5):371-379.

12 Astermark J, Morado M, Rocino A, van den Berg HM, von DM, Gringeri A et al. Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors. Haemophilia 2006; 12(4):363-371.

13 DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. Haemophilia 2007; 13 Suppl 1:1-22.

14 Collins PW, Fischer K, Morfini M, Blanchette VS, Bjorkman S. Implications of coagulation factor VIII and IX pharmacokinetics in the prophylactic treatment of haemophilia. Haemophilia 2011; 17(1):2-10.

15 De AC, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004; 351(12):1250-1251.

16 Food and Drug Administration Amendments Act of 2007. 2007.

17 European Commission Regulation for EudraCT. 2011.

18 FDA. Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins. Draft Guidance. 2009. 31-1-2013.

19 Mire-Sluis AR, Barrett YC, Devanarayan V, Koren E, Liu H, Maia M et al. Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products. J Immunol Methods 2004; 289(1-2):1-16.

20 Shankar G, Devanarayan V, Amaravadi L, Barrett YC, Bowsher R, Finco-Kent D et al. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. J Pharm Biomed Anal 2008; 48(5):1267-1281.

21 Gupta S, Indelicato SR, Jethwa V, Kawabata T, Kelley M, Mire-Sluis AR et al. Recommendations for the design, optimization, and qualification of cell-based assays used for the detection of neutralizing antibody responses elicited to biological therapeutics. J Immunol Methods 2007; 321(1-2):1-18.

22 The ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population. EC Directive 2008.

23 The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterianry Use, Annex 13 Investigational Medicinal Products. 2010.

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

25 Food and Drug Administration. Food and Drug Administration: Code of Federal Regulations, 21 CFR Part 11, Electronic Records, Electronic Signatures. 2009.

26 ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat Med 1999; 18(15):1905-1942.

27 International Committee of Medical Journal Editors (ICMJE): Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication. Haematologica 2004; 89(3):264.

16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.

Log of Protocol Amendments

Trial ID:

Protocol amendment no	Date	Final, Version	Country(ies) and/or trial site(s) affected	Brief content
1	NA	NA	Portugal	Protocol amendment no 1 was dedicated to Portugal but never finalised. Due to SOP requirements the countries now have their own logs and this log will only cover global amendments
2	20-Mar-2015	2.0	All	(Final Version 1.0 never shared) Detailed information on Major surgery and ITI, extended trial timelines
3	01-Nov-2016	1.0	All	Amendment 3 includes a new secondary endpoint to assess the ITI treatment outcome and monitoring of antibody development against Host Cell Protein (HCP).
4	14-Jun-2018	1.0	Israel	Protocol Amendment 4 is for Israel seeking permission to obtain the F8 genotype.
5	13-Jun-2019	1.0	All	Interim analysis when approximately 45 patients have reached 50 exposure days, and administrative changes
6	21-jun-2019	1.0	Israel	Protocol amendment 6 for Israel for obtaining informed consent from withdrawn patients to provide genotype results

7	02-jul-2019	1.0	Japan	Protocol amendment 7 for Japan is due to the regulatory category of this clinical trial should be updated in accordance with Japanese regulations. This is mandatory before NNPL obtains marketing approval of N8-GP.
8	15-Jun-2020	1.0	All	- Close recruitment of trial NN7088-3908 with between 50 to 100 patients completing, (rather than the protocol agreed 100 patients completing), but maintain the protocol defined trial end date 13 November 2021. Anti-PEG IgG + additional IgM antibody analyses have been implemented.

Protocol Amendment

no 1.0
to Protocol, final version 1.0
dated 04 November 2013

Trial ID: NN7088-3908

An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previously untreated paediatric patients with severe haemophilia A

Trial phase: 3a

Applicable to: Portugal

Amendment originator:

Name: [redacted]

Department or business area: Medical Department

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1 Introduction including rationale for the protocol amendment

The purpose of this amendment is to include information that is missing in the Protocol Version 1.0, according to the Central Ethics Committee in Portugal, referring to the use of the pain control measures for venous punctures.

The amendment will be submitted to the Central Ethics Committee for Approval in Portugal.

According to local legislation, this amendment does not need to be submitted to Regulatory Authorities but only to the Ethics Committee in Portugal.

In this protocol amendment:

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

2 Changes

The following sentence will be added at the end of section **5.3 Treatment of Patients,** on final protocol.

Only applicable for Portugal:

For venous punctures, pain control measures are allowed according to local practice.

Protocol Amendment

no *2*
to Protocol, final version 1.0
dated 04 November 2013

Trial ID: NN7088-3908

pathfinder™6

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previous Untreated Patients with Haemophilia A

An open-label single arm multicentre non-controlled phase 3a trial investigating safety and efficacy of N8-GP in prophylaxis and treatment of bleeding episodes in previous untreated paediatric patients with severe haemophilia A

Trial phase: 3a

Applicable to *all countries*

Amendment originator:

[redacted], International Trial Manager

Department:Haemophilia, Clinical Operations 2

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1 Introduction including rationale for the protocol amendment

Rationale for amendment

Below list is the items that have been changed and the rationales for the amendment. The reason for the creating the amendment now is the availability of results from the pathfinder™2 (NN7088-3859), pathfinder™3 (NN7088-3860) and pathfinder™5 (NN7088-3885).

1. Major surgeries has been allowed after having completed the pathfinder™3 surgery trial. (section 5.3.5, 8.7)
    a. Recommendations for doses has been added (section 5.3.5, 8.7)
    b. Details on definition of data sampling has been updated and data collection from minor and major surgery aligned (section 5.3.5, 8.1.10, 8.7)
    c. Haemostatic response for surgery 4-point scale added (section 8.6.1, 8.7.1)
2. ITI recommendations and requirements have been updates after new data available from pathfinder™2 pivotal trial, pathfinder™3 surgery trial and pathfinder™5 paediatric trial to support the ITI recommendations. (section 5.3.6)
    a. Dose recommendations added (section 5.3.6, 8.1.11)
    b. Detailing of recommendations for low titre inhibitor patients added (section 5.3.6, 5.5, 6.4, 6.6.3)
    c. How to evaluate the ITI treatment before returning to prophylaxis added (section 5.3.6, 6.4, 6.6.3, 8.1.11, 8.4.2.2, 16)
    d. ITI doses will count as overall number of doses (section 5.1)
3. Prolonged recruitment period and prolonged trial. Prolongation is due to postponed submission of the application for market approval of N8-GP (section 5.3, 7, 8.1)
4. Updated text on when trial could start as needed data is available at this point (section 3.1.3, 5.1, 5.3, 8.7)
5. Addition of mandatory inhibitor test before treatment including addition of a withdrawal criterion if positive at visit 1 before first dosing. This has been added because of the risk of developing inhibitors after receipt of maximum 5 doses of blood components. (section 2, 6.2, 6.4, 8.1)
6. Precised when safety committee should meet instead of having an interval for the meeting (section 11.6.2, 16.6)
7. PK time points have been changed based on the need experienced from the first patients enrolled in the trial. (section 8.4.2.2)
8. Allergic reaction sampling updated with 2 new tests, as found relevant based on the experience form the first patients enrolled in the trial. (section 8.4.2.7)
9. All wash out periods before pre-dose blood sampling has been aligned to be 72 hours instead of either 72hour or 4 days. This changed in implemented because of new information from the pathfinder™5 paediatric trial. (section 8.4.2.2)

10. Analyses of binding antibodies and PEG antibodies have been changed to not only being analysed at the end of the trial to also being analysed when considered relevant, based on experience from first patients in the trial. (section 8.4.2.2)
11. Added a window for sampling of blood at visits to allow more flexibility for the patients and sites (section 8.1, 8.4)
12. Clarified inclusion criterion 4 to be covering only FVIII purified product and not all faction products (section 1, 5.3, 6.2)
13. Added cardio vascular to physical examination (section 8.3.2)
14. Elaborated on drug reconstitution and solvent supplies (section 9)
15. Added informed consent can be signed before first visit (section 8.1)
16. Clarified dosing regimen text and visit windows (5.3, 8.1,
17. Reminder of monitoring of expiry of solvent, injection kits, and reference standard based on experience from pathfinder™ and guardian™ programmes. (section 8.1, 8.8.4, 9.4)
18. Added information that the vein used for drug infusion can be used for blood sampling half an hour after the infusion to ease the problematic blood draw from infants (section 8.4)
19. Changed the form of writing visit windows in table 2-1 after feedback of being difficult to understand (section 2)
20. Elaborated figure 8-1 to be more precise for visits during the pre-prophylaxis period. (Section 8.1)
21. Added that if according to local law a caregiver can take over some of a parent(s)/LAR(s) task to allow more flexibility for patients (section 8.1)
22. Added reminders to the visit 15-X to help site following the trial requirements (section 8.1.3)
23. Requirement for site to be able to analyse FVIII activity and inhibitor samples locally to ensure immediate action if needed for the patient's safety. This has been added based from experience from the initiation of the trial (section 8.4.1.1)
24. Added extra samples to be taken together with the confirmatory inhibitor test to ensure a positive test is not a false positive and to ensure sufficient knowledge of the inhibitor (section 8.4.2.2)
25. Added that monitoring visit intervals can be prolonged when site only have patients attending visits every 24 weeks, but monitor needs to ensure contact to site at least every 12 weeks (section 13)
26. Added that the e-learning of the protocol is mandatory for Investigator if investigator has not attended the investigators meetings (section 21)
27. Deleted specific text for Japan upon request from Japan (section 23.1)
28. Added required text for Portugal upon amendment 1 (section 25)
29. Clarified table 2-1 elements (section 2)
30. Updated total blood sampling volume after having finalised lab set-up (section 8.4.3)
31. Clarified where to enter data in eCRF and eDiary (section 8.1, 8.2, 8.8)
32. Clarified location to align with rest of protocol (section 5.3)
33. Deleted repetitive text (section 3.2)

34. Added required elements from new protocol template. It was decided not to change to the new protocol template as this would change the protocol too much for sites convenience, but all relevant elements from the new protocol template has been added to the protocol. (section 3, 4, 5, 6, 8, 16, 17, 20, 21, 22, 23, 24)

Corrected abbreviation order, spelling, grammar and clarifications, text formatting, and incorrect section references.

In this protocol amendment:

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

2 Changes

General over whole protocol

- ~~IV/WRS~~ to *IWRS*
- ~~Bleed~~ to *Bleeding episode*
- Spelling corrections and grammatical corrections and corrected section references have not been listed below

List of Abbreviations

CRP	*C-reactive protein*
APTT	*activated partial thromboplastin time*

1 Summary

Trial population:
Inclusion criteria
…..

- No prior use of purified *factor VIII containing* clotting ~~factor~~ products (5 previous exposure *days* to blood components is acceptable)

2 Flow Chart

Table 2-1

Visit number	**0**[1]	**1**[1]	**2**	**3**	**4-6**	**7-8**	**9**	**10-13**	**14**[~~18~~]	**15-X**[19]	**EOT**
Time of visit (ED(s))[2]	**0**	**1**	**2**	**5**	**10, 15, 20**[3]	**30,40**	**50**	**60, 70, 80, 90**	**100**	**NA**	
Visit interval (ED(s))[2]		**0**	**0**	**~~3~~±1**	**~~5~~±2**	**~~10~~±2**	**~~10~~+2**	**~~10~~±2**	**~~10~~+2**	**24w±4w**	
Adverse events[5]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[7]	X	X[7]					X		X		X
FVIII activity – recovery (30 *min* post-dose)		X		X	X	X	X	X	X	X	
FVIII inhibitor test[9]		X[18]		X	X	X	X	X	X	X	X
HIV ~~1 and 2~~ antibodies	(X)[10]										
F8 + HLA genotype testing	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]					
eDiary training		~~X~~[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	

Compliance check of eDiary data, protocol requirements, ~~and~~ used drug *and bleeding episode evaluation*		X	X	X	X	X	X	X	X	X	X

Table 2-2

3	If not already on prophylaxis, all patients must initiate prophylaxis treatment no later than at V6 *or shortly after at ED 20*. Pre-prophylaxis is only allowed for children below the age of 24 months or up to V6, whatever comes first. Visits at 10EDs±2EDs, 15EDs±2EDs, 20EDs±2EDs must be performed even the window allows 2 visits to be 2 EDs aside (e,g, ED12 and ED13)
5	After Informed consent has been obtained all Adverse Events ~~if associated with trial related activities~~ must *be* reported in the eCRF
7	Vital signs should be measured prior to dosing at ~~all screening~~ V1, V9, *and at* V14 ~~and at EOT~~. In addition vital signs should also be measured 30±10minutes after the first injection with N8-GP at V1.
9	Blood samples must be collected prior to dosing at dosing visits. Please check that the required washout period has been met for inhibitor testing, see section 8.1.1.3 *Before any surgeries are performed an inhibitor test must be taken if this test is more than 30 days*
12	*F8* and *HLA* genotype sample is only allowed upon patient's parent(s)/LAR(s) signing the consent for genotyping and should only be done if not already documented in patient's medical record. The sample can be collected at any visit between V0 and V8~~9~~, taking the limitation of the allowed blood sampling volume into account. *Genotype is not applicable for Israel*.
18	~~In case V14 will be the EOT visit, the procedures for the EOT visit should be followed~~ *Inhibitor sample at visit 1 before dosing is mandatory*
19	V15 to VX will be performed every 24 *weeks* ~~EDs~~ ± 4 *weeks* ~~EDs~~ until the End of Trial

3 Background information and rationale for the trial

3.1.1 Haemophilia A

…..

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 (PUPs) with severe haemophilia A following exposure to FVIII products.[3,4] Availability of a recombinant human FVIII (rFVIII) product with reduced immunogenicity has been the priority request by the haemophilia community for many years. The immunogenicity of N8-GP will be monitored in the clinical setting and further investigated in nonclinical models to explore preliminary findings of reduced binding and uptake of N8-GP in human antigen presenting cells.

Immune tolerance induction (ITI) therapy is the first-choice approach in patients with high-responding FVIII inhibitors, and the only proven strategy for eradicating FVIII inhibitors. Based on clinical evidence and international consensus recommendations, most patients are attempted tolerised with the same product that was being used at the time of inhibitor development.

…

3.1.3 N8-GP clinical data

…

In accordance with the EMA guideline[7], N8-GP exposure of PUPs ~~may be~~ *was* initiated when treatment data from 20 paediatric PTPs with at least 50 N8-GP EDs ~~are~~ *was* available from the pathfinder™5 trial, including data from a minimum of 10 patients below 6 years, and pharmacokinetic investigations in children (below 12 years) ~~are~~ *were* completed.

….

3.2 Rationale for the trial

The rationale for performing the pathfinder™6 trial is to evaluate the safety (including immunogenicity) and efficacy of N8-GP in the treatment of PUPs with severe haemophilia A in accordance with EMA requirements.[7] For Europe, EMA requires a separate investigation in the PUP population as part of the development programme to be initiated before market authorisation.[7] The approval of the indication in PUPs will be based on a clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs connected with a post-approval commitment to follow up at least 100 PUPs for a minimum of 100 EDs. The 50 patients will continue to reach at least 100 EDs, and additional 50 patients will be included also to reach at least 100 EDs.

~~Given the prolonged half-life of N8-GP it is expected that bleeding prophylaxis, treatment of acute bleeding episodes, and control and prevention of bleeding in the surgical setting may be achieved with a reduced frequency and number of injections as compared to current treatment options. This may increase treatment compliance, and thereby potentially leading to better clinical outcomes for patients with haemophilia A.~~

3.3 Risk and benefits

.....
N8-GP is currently being investigated in previously treated patients. The first human dose trial (NN7088-3776) demonstrated that a single dose of N8-GP is generally well-tolerated, and that N8-GP has a prolonged half-life compared to commercially available FVIII products. No safety concerns have been raised based on review of data (cut-off date was ~~12-Feb-2013~~ *28-Jul-2014*) from patients enrolled in the pivotal safety and efficacy trial (NN7088-3859) and the risk/benefit ratio for N8-GP is therefore expected to be favourable.

4 Objective(s) and endpoint(s)

…

4.2.2 Secondary Endpoint

….

*Key supportive secondary endpoint prospectively selected for posting (*e.g.* ~~on~~ clinicaltrials.gov *and EudraCT*).

5 Trial design

5.1 Type of trial

...

According to the EMA Guideline treatment with N8-GP in the pathfinder™6 PUP trial *was able to* ~~may~~ start when 20 patients participating in the paediatric PTP trial (pathfinder™5) *were* ~~are~~ available (including data from a minimum of 10 paediatric patients below 6 years of age), and pharmacokinetic investigations in paediatric PTPs *were* ~~are~~ completed.

….

In the main phase of the trial patients will receive treatment with N8-GP until they reach a minimum of 50 N8-GP EDs each ~~or until they develop high titre inhibitor~~. An ED is defined as any day during which the patient has been exposed to N8-GP, including doses given for treatment of bleeding episodes, prophylaxis, surgery, and for the purpose of PK assessment. If N8-GP is administered more than once during the same day, this will still count as one ED. When at least 50 patients have reached a minimum of 50 EDs each in the main phase, the analysis and evaluation for the main trial report will be performed. EDs during immune tolerance induction therapy (ITI) will ~~not~~ count in the determination of when a patient has reached 50 EDs.

Patients will be followed in the extension phase until at least 100 patients have reached at least 100 EDs each. *EDs during immune tolerance induction therapy (ITI) will count in the determination of when a patient has reached 100 EDs*.

….

5.3 Treatment of patients

Trial *overview* ~~visit schedule~~ will be as shown in Figure 5-1.

….

For each patient at least the ~~two initial~~ doses of N8-GP *given on the first 2 EDs* will be administered in a *site* ~~hospital/clinic~~ setting enabling observation for potential adverse reactions. The patient must be observed for at least 1 hour after dosing. *If no safety concerns were raised after administration of these initial doses of N8-GP,* ~~Afterwards~~ home treatment with i.v. self-injection by the parent/caregiver/support person can be initiated. ~~If no safety concerns were raised after administration of the initial doses of N8-GP~~ The investigator should ensure that parent/caregiver/support person is sufficiently trained and confident with home treatment, including

both prophylaxis and treatment of bleeding episodes. The patients can come to the clinic/trial site for their N8-GP injections until they are comfortable with home treatment.

…

The duration of N8-GP treatment in the extension phase is at least 50 EDs or up to ~~a minimum~~ *at least a* total *of* 100 EDs (for both the main and extension phases) for each patient. Once a patient has achieved 100 EDs, he may be offered the option to continue in the extension phase until either N8-GP is commercially available in the relevant country or until the marketing authorisation application for N8-GP is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the Last Patient Last Visit for the trial will be no later than 13 *November 2021* ~~May 2019~~ whether or not the product is commercially available in the relevant country. Novo Nordisk will not provide any patient with trial medication after the end of the trial.

Treatment with FVIII products other than the investigational product, N8-GP, is not allowed. Previous exposure to FVIII products is not allowed in this trial. ~~Previous exposure to maximum 5 plasma infusions, Pd-aPCC, and/or cryoprecipitate is allowed.~~ *Maximum 5 previous blood product (e.g. plasma, cryoprecipitate, erythrocyte concentrate or platelets) infusions are allowed.*

5.3.1 Pre-prophylaxis treatment

….

The N8-GP dose for pre-prophylaxis treatment (except for bleeding episodes) is approximately 60 U/Kg body weight (bw) (within the dosing range of 50-75 U/Kg) to be administered as a single bolus dose intravenously (i.v.) *with more than one week between doses* ~~less than once every 7 days~~ (at the discretion of the investigator). Whole mL dosing is allowed from above 3 mL. *This is* explained *in further detail in* the trial materials manual. For treatment of bleeding episodes see Table 5-1.

…

5.3.2 Prophylaxis treatment

…

During the main phase of the trial patients should receive prophylaxis with i.v. injections of N8-GP preferably twice weekly, with doses to be separated by at least 3 calendar days and no more than 4 calendar days. *Based on the patient's individual bleeding pattern*, an increase in N8-GP dose frequency from twice weekly to every third day is permitted at the investigators discretion ~~(should be based on the patient's individual bleeding pattern)~~.

…

In the extension phase, all patients should continue the prophylaxis dosing regimen as prescribed at the end of the main phase. However, preferably after *having been* ~~being 12 months~~ on the same prophylaxis regimen *for 12 months* (main phase and extension phase combined), the investigator is permitted to increase or decrease the N8-GP dosing *frequency* ~~interval~~ within the range of every 3rd

day to every 7th day (every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day (once weekly)) based on the patient's bleeding pattern.

The dose can be administered ~~±~~1 day of the planned dosing date *(this window is related to the dosing regimen and not to the visit window)*.

…

In the event of a concern about reduced treatment efficacy an unscheduled visit can be scheduled where a PK session may be performed to investigate the ~~elimination (~~recovery, clearance and half-life~~)~~ of N8-GP. Antibody tests should be taken if not done recently. The PK data may potentially be used to adjust the ~~dose of~~ *dosing* regimen.

5.3.3 Treatment of bleeding episodes

Patient's parent(s)/LAR(s) will be instructed by the trial site on how to treat a bleeding episode at home and *how to* record *the bleeding episodes, the treatment and the response to treatment* in the electronic diary (eDiary). Treatment requiring bleeding episodes should *be treated* immediately (i.e., when the patient experiences the first clinical symptoms of a bleeding episode, *or when observed by parent(s)/LAR(s))* ~~be treated~~ with N8-GP at doses of 20-75 U/Kg bw, depending on severity and location of the bleeding episode, see Table 5-1.

For treatment of severe/life-threatening bleeding episodes administration of higher doses of N8-GP is permitted at the investigators discretion. For recommended dose levels see Table 5-1. *In cases of a severe bleeding episode the site must be contacted.*

~~At least the first 2 treatment-requiring bleeding episodes should be treated in the presence of a qualified health care professional. If the patient cannot be brought quickly to the trial site, the trial site must be contacted for treatment instructions or transport.~~ A severe bleeding episode should immediately be treated at home or at the local emergency room, and the trial site must be contacted for further instructions or transport. ~~For severe bleeding episodes before the 2nd EDs the treatment must take place at the site.~~

~~In case of~~ Treatment requiring bleeding episodes prior to *the start of the* home treatment ~~these~~ should immediately be treated at *the* trial site. In case the bleeding episode occurs outside trial site opening hours, the bleeding episode should be treated according to local practice.

5.3.4 Treatment of suspected bleeding episodes

In case of a ~~an abdominal or head~~ trauma where there is a risk of a severe traumatic bleeding episode it is allowed to initiate treatment before clinical symptoms arise. This is defined as preventive treatment of suspected severe traumatic bleeding episode *and will be recorded in EDC*

as other severe bleeding episodes. The recommended dose is equivalent to treatment of a severe bleeding episode

5.3.5 Surgery

Patients undergoing surgical procedures while participating in this trial can receive bleeding preventive treatments with N8-GP. Minor surgeries, dental extractions and placement of central venous access ports can be performed ~~while participating in the trial~~ by administering extra doses of N8-GP equivalent to the dose for a severe bleeding episode (see Table 5-1), or aligned to local standard of practice, or guidelines for treatment of patients with haemophilia A with FVIII in the perioperative period.

Major surgery will only be allowed after the individual patient has reached 50 N8-GP EDs. *The major surgery should be planned and conducted in accordance with recommendation in the WFH guidelines for management of haemophilia (ref 29) and local guidelines. Determination of dose and dose interval should include close monitoring of FVIII activity trough and peak levels considering the T½ of N8-GP and clinical evaluation of the haemostatic effect. It is up to the investigator to decide how long the post-surgery period should be and when the patient should resume regular prophylaxis or pre-prophylaxis treatment.* ~~and upon completions of the pathfinder™3 surgery trial (NN7088-3860). The treatment regimen for major surgery will be based on results from the pathfinder™3 surgery trial (NN7088-3860) and PK data obtained in the pathfinder™5 trial (NN7088-3885) in paediatric PTPs. Novo Nordisk will communicate when major surgeries are allowed in this trial.~~

….

Definition of major surgery

Major surgery is defined as any invasive operative procedure that requires ~~several days~~ *more than 3 days* of FVIII 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
- When normal anatomy is operatively altered
- Major elective orthopaedic surgery

Doses of N8-GP should be aimed at securing haemostasis and in accordance with recommendation in the WFH guidelines for management of haemophilia (ref 29) and/or local guidelines. In the recovery period the patient should be dosed with N8-GP according to local standard of practice and/or general guidelines for treatment of patients with haemophilia A. Determination of dose and dose interval should include close monitoring of FVIII activity trough and peak levels considering the T½ of N8-GP.

…

5.3.6 Treatment of patients with FVIII inhibitors

…

Patients who develop FVIII inhibitors during this trial may receive N8-GP and/or ~~Treatment of bleeding episodes with~~ by-passing agents, *e.g.* ~~i.e.~~ rFVIIa or APCC *for treatment of bleeding episodes* according to local standard care ~~is allowed for patients who develop FVIII inhibitors within this trial~~. *However, N8-GP dose levels used should not exceed 75 U/kg as a single dose and not exceed 200 U/kg as a maximum 24 hour dose. Treatment with FVIII concentrates other than N8-GP is not allowed.* By-passing agents are not considered trial medication.

The ultimate goal of treatment in patients with high-titre inhibitors is to permanently eradicate the inhibitor by ~~immune tolerance induction therapy (~~ITI~~)~~, thereby making it possible for the patient to be treated routinely with FVIII replacement therapy *again*. The therapeutic concept is based on long-term uninterrupted high exposure to FVIII in an effort to sufficiently tolerise the immune system. In that state, the clinical responsiveness to FVIII replacement therapy is restored.

….

~~Novo Nordisk plans that~~ Patients who develop inhibitors, within this trial, will be offered ~~continued~~ treatment with N8-GP, including ITI for a maximum of 24 months. ~~ITI with N8-GP will not be initiated until Novo Nordisk has reviewed the clinical data available after completion of the N8-GP pivotal and surgery trial (pathfinder™2 and pathfinder™3), and of the paediatric PTP trial (pathfinder™5) data needed for opening the paediatric PUP trial according to EMA requirements.~~

~~It is expected to use a N8-GP dosing regimen for ITI similar to local standard care/guidelines applied for ITI with marketed FVIII products. For each individual patient, ITI regimens with N8-GP would have to be reviewed by the investigator every month, and more formally reviewed every 3 months by Novo Nordisk.~~

If patients with (usually low titre) inhibitors respond well to treatment with N8-GP then the patient can continue the prophylaxis. These patients can still start ITI treatment within 6 months after the

confirmatory inhibitor test. If the inhibitor is still present (BU>/=0.6) at 6 months after the confirmatory test the patient must start ITI or withdraw from the trial.

Based on experience with marketed FVIII products, a successful ITI can be expected in about 60–80% of cases receiving ITI with N8-GP, leading to several important benefits for the patient, including:

……

5.3.6.1 ITI therapy with N8-GP

Patients who develop inhibitors, within the pathfinder™6 trial, will be offered continued ITI treatment with N8-GP for a maximum of 24 months. ITI therapy with FVIII concentrates other than N8-GP is not allowed within the trial. It may also be decided by the Investigator and/or parent/legal representative to withdraw the patients ~~who developed~~ *developing* FVIII inhibitors.

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

If needed and decided by the Investigator, the initiation of the ITI can be delayed but it has to start within 6 months from the time of diagnosis of inhibitor. Inhibitor patients that commence ITI with N8-GP will follow an alternative treatment regimen and visit schedule (see Section 8.1.11).). *For each individual patient, ITI regimen with N8-GP will need to be reviewed by the investigator every month, and formally reviewed every 3 months by Novo Nordisk.*

The used N8-GP dosing regimen is at the discretion of the investigator, but a N8-GP dosing regimen similar to the local standard of care applied for ITI with marketed FVIII products is recommended. However, daily N8-GP dose levels used for ITI should not exceed 75 U/kg as a single dose and not exceed 200 U/kg as a maximum 24 hour dose.

The FVIII inhibitor level will be evaluated continuously in all patients that receive N8-GP for ITI. If the inhibitor disappears during the ITI (see Section 8.4.2.2), the patient should resume prophylaxis treatment as recommended in Section 5.3.2. *Patients will be evaluated after 12 months and 24 months of ITI treatment, based on the level of inhibitors, within the predefined specifications of withdrawal, see Section 6.4. If inhibitors are still positive after 12 months, but the decline from peak titre level is ≥ 20%, ITI may continue for a maximum period of 24 month in total.*~~For patients still with positive inhibitors after 12 months ITI, continued trial participation will be evaluated by the investigator and sponsor based on the level of inhibitors, within the predefined specifications of withdrawal criteria 8, see Section 6.4~~. However, if the inhibitor persists after 24 months of ITI, the patient will be withdrawn from the trial.

Criteria for successful ITI therapy with N8-GP: *In line with international consensus, and based on the mean N8-GP half-life observed in adults (18.5h) and children < 6 years of age (15h), successful N8-GP ITI outcome is based on the achievement of three stringent efficacy criteria*

- *Undetectable inhibitor titre < 0.6 BU*
- *Normalized FVIII in vivo recovery, defined as ≥ 66% of expected incremental recovery*
- *N8-GP half-life ≥ 9 hours after a 72 h treatment-free washout period*

Once the inhibitor is confirmed to be negative, FVIII recovery should be measured after an injection of 60 U/kg of N8-GP without washout period. When FVIII recovery is shown to be ≥66% of the expected incremental recovery, based on PK data obtained in paediatric PTPs, a FVIII half-life study needs to be conducted after administration of 60 U/kg of N8-GP after a 72 hours treatment-free washout period. This half-life study should be repeated, if necessary based on investigators discretion, until the half-life is confirmed to be ≥ 9 hours. Blood samples for FVIII half-life evaluation should be taken pre-dose and 1h, 6h, 24 h, 48 h, and optional 72 h post-dose (see Section 8.4.2). If half-life is 9 hours the ITI should continue.

For patients who develop low titre and/or clinically insignificant inhibitors (≤ ~~<~~5 BU), the dose level and dosing frequency of N8-GP will be decided by the Investigator based on clinical evaluation.

Table 5-1 Intravenous N8-GP treatment

Indication	Dosage	Frequency
Pre-prophylaxis (pt. less than 24 months of age)	Approximately 60 U/Kg (50-75U/Kg)	On-demand or slow start prophylaxis (~~less than weekly dosing~~ *more than one week between doses*)
Prophylaxis – main phase	Approximately 60 U/Kg (50-75U/Kg)	Every 3rd day, twice weekly or every 7th day(±1 day)
Prophylaxis – extension phase	Approximately 60 U/Kg (50-75U/Kg)	Every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day(±1 day)
Mild/moderate bleeding episode	20-60 U/Kg	On-demand (breakthrough bleeding episodes) *(site must be contacted if more than 2 doses needed)*
Severe bleeding episode	40-75 U/Kg For treatment of severe/life-threatening bleeding episodes administration of higher doses of N8-GP is permitted at the investigator's discretion *guided by repetitive measurements of trough and recovery*	On-demand *(site must be contacted)*
Minor surgery	40-75 U/Kg	In accordance with local standard of practice of the participating trial site
Major surgery, only allowed after 50 EDs	~~Recommended doses regimens will be provided when the N8-GP surgery trials completed~~ *In accordance with WHF guideline and local standard of practice of the participating trial site*	~~On demand~~ *In accordance with WHF guideline and local standard of practice of the participating trial site*
Low titre inhibitor	Recommendation 60 U/Kg (50-75 U/Kg) for prevention and treatment of bleeding episodes	Dosing interval as needed
High titre inhibitors	*ITI treatment according to local standard. Maximum of 75 U/Kg as single dose, maximum of 200 U/Kg over 24 hours*	
Maximum dose/day	200 U/Kg	Total maximum dose over 24 hours

…..

5.5 Rationale for treatment

…..

The reason for providing the possibility of ITI of patients who develops ~~high titre~~ inhibitors is to permanently eradicate the inhibitor, thereby making it possible for the patient to be treated routinely with FVIII replacement therapy…..

6 Trial population

….

6.2 Trial population

…

4 No prior use of purified *factor VIII containing* clotting ~~factor~~ products (5 previous exposure *days* to blood components *are* ~~is~~ acceptable)

….

6.4 Withdrawal criteria

…

- **The patient must be withdrawn if the following applies**:

1. Dosed in the trial, but not fulfilling the inclusion and/or exclusion criteria
2. Anaphylactic reaction to the trial product, for definition see Section 11.1

Major surgery before 50 EDs, see Section 5.3.4

Significant thromboembolic event, see Section 11.1

Incapacity or unwillingness to follow trial procedures

Use of coagulations factors other than N8-GP or anti-coagulants unless in relation to ITI

ITI treatment has not been started within 6 months from the date of confirmation of positive FVIII inhibitor (BU ≥ 0.6~~/ml~~) *unless the FVIII inhibitor has disappeared (BU<0.6) under continuous prophylactic treatment within the 6 months.*

FVIII inhibitor titre decline from peak level is less than 20% after 12 months of ITI treatment

FVIII inhibitor is positive (BU ≥ 0.6~~/ml~~) after 24 months of ITI treatment.

After completed ITI treatment (maximum 24 months), prophylaxis treatment as described in the protocol is not resumed/started

Positive inhibitor test result from visit 1 before first dosing (a positive sample does not have to be confirmed in a confirmatory test)

Participation in another clinical trial throughout the trial.

….

6.6.3 Rationale for withdrawal criteria

- Criteria nos. 1-6 are included to protect the patient's safety and reliability of the data.
- Criteria nos. 7-~~10~~*12* are included to ensure appropriate treatment of inhibitor patients.

7 Milestones

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

~~Planned~~ FPFV: *26-Jun-2014* ~~01 May 2014~~

Planned LPFV: *02 October 2020* ~~02 Apr 2018~~

End of trial is defined as LPLV: *13 November 2021* ~~13 May 2019~~

The duration of the trial for each individual country will vary. However, the end of trial will be no later than ~~13 May 2019~~ *13 November 2021*

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

Planned completion of clinical trial report (CTR): ~~November 2019~~ *14 May 2022*.

The duration of N8-GP treatment in the trial is a minimum total 100EDs for a particular patient. Once a patient has achieved 100EDs, they may be offered the option to continue in the trial until either N8-GP is commercially available in the relevant country or until the marketing authorisation application for N8-GP is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. In any event, the LPLV for the trial will be no later than *13 November 2021* ~~30 June 2018~~ whether or not the product is commercially available in the relevant country.

8 Mathods and assessments

…

Fig 8-1: added to pre-prophylaxis box – Visits at: ED 5,10,15,20

…

Screening and enrolment log

….

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

Each patient will be assigned a unique 6-digit number. It must be stated in the medical records that the patient is participating in the trial, including the patient number.

Informed consent procedure

….

Informed consent for obtaining genotyping must be collected, if applicable. *Genotype consent is not applicable for Israel.*

….

For withdrawn patients

…

The end of trial form must be completed, and final drug accountability must be performed even if the patient is not able to come to the trial site. A withdrawal session must be made in the IWRS and case book must be signed ~~in the eCRF~~.

…

In general

Review of eDiary reports, laboratory reports etc. must be documented either on the front page of the documents and/or in the patient's medical record.

If considered relevant a caregiver can take over the responsibilities from the parent(s)/LAR(s) of handling and administrating the trial drug, filling in the eDiary and attending visits at site. The caregiver must be trained equally as the parent(s)/LAR(s) in the relevant responsibilities. Site must follow the local law and local guidelines for decision of which task a caregiver can take responsibility for.

Site must document correspondence with patient's parent(s)/LAR(s) concerning returning or destruction of trial drug, solvent and injection kits that are to expire or has expired.

….

8.1.1 Visit 0 – screening visit

The patient's parent(s)/LAR(s) must give signed and dated informed consent prior to any trial related activities. *Signing of the informed consent can take place before visit 0, if allowed by local law.* All patients will be provided with a copy on the patient information and a copy of the signed and dated Informed Consent Form.

….

Pre-prophylaxis treatment

Pre-prophylaxis is optional and is the period before start of regular prophylaxis. *The pre-prophylaxis period ends when the patient has reached 20 EDs or has turned 24 months of age, whatever comes first, and the patient must begin prophylaxis regimen.*

During pre-prophylaxis the following dosing regimen applies:

- approximately 60 U/Kg N8-GP within the range of 50-75 U/Kg bw, see Section 5.3
- individualised prophylactic dosing intervals but less frequent than every 7th day(once weekly)
- on-demand treatment of bleeding episodes *or minor surgeries*

See further Section 5.3.2.

…

8.1.1.2 Prophylaxis treatment

Prophylaxis treatment can begin ~~A patient may change from pre-prophylaxis to prophylaxis~~ *at visit 1 or* at any time during the pre-prophylaxis period ~~or~~ *but* must be initiated when the patient has reached 20 EDs *on pre-prophylaxis* or has turned 24 months of age, whatever comes first.

The dosing frequency during main phase is individualised within the following interval: twice weekly, every 3rd day or every 7th day. Changes to the regimen should be recorded in the IWRS. If changes occur between visits, it should be recorded in an unscheduled visit, see Section 8.1.9.

~~For patient that enter the prophylaxis treatement after a period of pre-prophylaxis the next visit in the sequence will be determinated by the numbers of EDs.~~

…

8.1.2 Visit 1 – first dosing with N8-GP

V1 will take place after the screening visit (V0) whenever the first treatment of N8-GP is administered, if not already combined with V0.

Before the first dose of N8-GP is given as a minimum the inhibitor test must be taken and send to central laboratory for analysis.

…

Assessments for V1 are listed in Table 2-1. In case V0 and V1 have been combined into one visit, assessments should only be performed once, *but recorded at both visit in the eCRF*.

8.1.3 Visit 2, 3, 4-6 – main phase

The 2 first N8-GP *EDs* ~~injections~~ must take place at trial site (V1+V2). Hereafter the injections can be administered at the trial site or outside the trial site.

…

Visits at ED: 2 *(V2),* 5 ± 1 ED *(V3)*, 10 ± 2 EDs *(V4)*, 15 ± 2 EDs *(V5)*, 20 ± 2 EDs *(V6)*.

….

Reminders

….

- Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire *and avoid use of any expired solvent or injection kit* during the next home treatment period

…..

Visit 7-8 – main phase

From V6 *or shortly after at ED 20* all patients (including patients previously on pre-prophylaxis) will be on prophylaxis treatment with N8-GP on twice weekly, every 3rd day or every 7th day. Between the visits the patient will receive N8-GP treatment at home if comfortable with home administrations or at the site, see Section 8.1.12.

Visits at EDs: 30 ± 2 EDs *(V7)*, and 40 ± 2 EDs *(V8)*.

…

Reminders

….

- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- *Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire and avoid use of any expired solvent or injection kit during the next home treatment period*

…..

Visit 9 – end of main phase

Visit 9 should take place at either ED 50, ED 51 or ED 52.

Assessments for V9 are listed in Table 2-1.*In the extension phase the patient will continue prophylaxis with 60 U/Kg in the regimen of every 3rd day, twice weekly, every 4th day, every 5th day, every 6th day or every 7th day. See Table 5-1. Changes to the regimen should be recorded in the eCRF.*

Reminders

….

- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- *Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire and avoid use of any expired solvent or injection kit during the next home treatment period*
- Home treatment *training*, if the trial site suspects that the patient's parent(s)/LAR(s) is not fully confident with administration and how to deal with safety related signs and symptoms, see Sections 8.5 and 8.6

….

Visit 10-13 – extension phase

…

Visit at EDs: 60 ± 2 EDs *(V10)*, 70 ± 2 EDs *(V11)*, 80 ± 2 EDs *(V12)*, and 90 ± 2 EDs *(V13)*.

…

Reminders

…

- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- *Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire and avoid use of any expired solvent or injection kit during the next home treatment period*
- Home treatment *training*, see Sections 8.1.12 and 8.8.2.

…

Visit 14 - end of extension phase

….

Reminders

…

- Drug accountability of trial product must be recorded in the IWRS, see Section 10

- *Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire and avoid use of any expired solvent or injection kit during the next home treatment period*

….

Visit 15-X until end of trial

If N8-GP is not commercially available in a patient's country at the time of visit 14, the trial period may be extended with visits that are scheduled 24 weeks ± 4 weeks. These additional visits are referred to as visit 15 to visit X, where X can be any visit from 16 and onwards. This option for the patient to continue in the extension phase of the trial may be offered until either N8-GP becomes commercially available in the relevant country, or until the marketing authorisation application is rejected in the relevant country unless the N8-GP trial, part of the trial or a trial site is terminated by Novo Nordisk or a relevant authority for any reason. The End of Trial visit must be scheduled within 1 month ~~provided always that~~ *after it has been communicated to site to close the trial* ~~the last patietn last visit for the prophylaxis period until end of trial~~ *but* no later than 13 ~~May 2019~~ *November 2021* whether or not the product is commercially available in the relevant country at this time.

At every dosing visit from ~~V14~~*V15*-VX, drug will be dispensed to cover up to 3 months of treatment. Depending on patient's treatment regimen, additional dispensing visits might need to be scheduled to cover treatment in the period between visits.

Assessments for V15-VX are listed in Table 2-1.

Reminders

- *An appointment for the next visit should be made*
- *Next visit must be planned to allow for the required wash-out of 72 hours, see Section 8.8.3.1*
- *Recording of body weight, see Section 8.3.1, and dispensing of N8-GP for trial site dosing/home treatment must be performed via IWRS, see Section 10*
- *Drug accountability of trial product must be recorded in the IWRS, see Section 10*
- *Investigator must ensure that patient's parent(s)/LAR(s) return any trial medication that would expire and avoid use of any expired solvent or injection kit during the next home treatment period*
- *eDiary compliance review, see Section 12.3*

……

8.1.10 Unscheduled visit

…

The following forms can be found in the unscheduled visit in the eCRF:

- Central lab
- Bleeding episodes
- Dosing of N8-GP
- Surgery*
- PK session*
- Change of regimen

** Surgery and PK session can also be performed during a regular visit but are to be registered under unscheduled visits.*

8.1.11 ITI Visit

…

In case of high titre FVIII inhibitor (>5BU) confirmed by central laboratory the investigator must decide how to proceed with treatment~~. Novo Nordisk will communicate when ITI is allowed in this trial, see Section 5.3.6.~~ *ITI with N8-GP must be initiated within 6 months of the confirmatory inhibitor test. The used N8-GP dose and dosing regimen is at the discretion of the investigator but should not exceed 75 U/Kg for a single dose, and not exceed a total daily dose of 200 U/Kg. By-passing agents can be used to treat bleeding episodes.*

If ITI is initiated, the patient will follow a visit schedule prescribed by the investigator and according to local standard of practice. Monthly visits are recommended, and the below listed assessments are recommended to be performed:

….

- Bleeding episode evaluation *(only if treatment with N8-GP)*

…

<u>Reminder</u>

- Follow up on any AEs according to Section 11.2

After ITI treatment, when the inhibitor is confirmed to be negative, a FVIII recovery test should be performed to confirm the recovery. A dose of 60 U/Kg should be used. Before returning to regular prophylaxis treatment a PK session must be performed after a 72 hours treatment-free wash-out period, see Section 8.4.2.2 for PK session details.

For patients returning to regular prophylaxis N8-GP treatment, the visit schedule is taken up from *where the patient left the visits according to Table 2-1. The patient must not attend the same visit number twice.* ~~V9 end of main phase Table 2-1 even when the corresponding total ED does not match.~~

8.1.12.1 Prophylactic home treatment

…..

The following procedures must be performed during home treatment between visits:

- N8-GP administrations according to regimen prescribed by investigator
- *Check trial drug, solvent and injection kit for expiry date before use*
- Contact to the investigator/medically qualified person in case of severe bleeding episodes
- Completion of the patient eDiary, including details of all bleeding episodes and N8-GP administrations (see Section 8.6)

…..

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial at the first visit (V0) *or found as a result of a screening procedure.* All concomitant illnesses should be reported including disease under investigation.

….

8.2.2 Concomitant medication

A **concomitant medication** is any medication including vaccination, other than the investigational medicinal product (N8-GP), which is taken during the trial until EOT. *By-passing agents should also be listed as concomitant medication.*

….

8.3.1 Body measurements

- Height at screening
- Body weight, wearing light clothing only ~~(Kg)~~

…

8.3.2 Physical examination

The physical examinations will be performed according to local procedure and should include:
…..

- Central and peripheral nervous systems
- *Cardiovascular system*

….

8.4 Laboratory assessments

….

Laboratory results being out of normal range must be categorised as "out of normal range, not clinically significant" or "out of normal range, clinically significant". A laboratory result evaluated as "out of normal range, clinically significant" must be recorded as an AE, or if present at V0 it should be recorded as concomitant illness.

The central laboratories provide results to the trial site in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

….

8.4.1.1 FVIII activity

FVIII activity will be analysed at the predefined time point as at a central laboratory selected by Novo Nordisk but the investigator can at any time during the trial assess FVIII activity at his/her discretion.

Site must be able to analyse for FVIII activity and inhibitors locally to ensure immediate results if needed to evaluate the patient's safety.

If V0 and V1 are combined, as one combined screening visit, and if FVIII activity <1% has not been documented in the patient medical records, it should be analysed locally and documented in the patient medical records. In this case the local laboratory should use their standard FVIII activity assay with the assay calibrator routinely used for FVIII activity analysis.

~~A N8-GP reference standard must be used as assay calibrator in the FVIII activity assay after the patient has been dosed with N8-GP. The reference standard will be provided by Novo Nordisk together with a description of how to the reference standard should be handled handle, stored and used~~.

After the patient has been dosed with N8-GP, FVIII activity should be measured with an activated partial thromboplastin time (APTT) based one-stage clotting assay calibrated by a N8-GP reference standard. The reference standard will be provided by Novo Nordisk together with a description of how to handle, store and use. The site must ensure that the reference standard has not expired and request a new one when relevant.

Dependent on the type of APTT reagent used by the local lab 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 please contact Novo Nordisk.

If available, FVIII activity may be measured with a chromogenic assay. In such cases a N8-GP reference standard is not needed.

….

8.4.2.1 FVIII activity

…

FVIII activity should be measured according to Table 2-1.*Historical value of FVIII activity can be used for inclusion of the patient from any time since the child was born. In relation to visit if an activity samples has been taken within ±1 week (for EOT only – 1 week) from the visit and send to central lab, this can be used for the visit assessment if the requirements for 72 hours wash out is respected.*

…

FVIII activity will be measured by the use of two different assays developed and validated for N8-GP (*except for V0 that will only be analysed in one assay*):

FVIII chromogen assay
FVIII one-stage clotting assay

….

8.4.2.2 Antibody assessments

…

Antibody assessment should be measured according to Table 2-1. *Antibody samples taken within ±1 week from the visit (for EOT only – 1 week) and send to central lab can be used for the visit assessment if the requirements for 72 hours wash out.*

N8-GP/FVIII binding antibodies

……

Samples will be analysed regularly for N8-GP binding antibodies, results will be reported to investigators at the end of trial, *or whenever considered relevant*, and will be included in the CTR.

PEG antibodies

…

Samples will be analysed for PEG binding antibodies at the end of trial *or whenever considered relevant.*

FVIII inhibitors

…

Any sampling for the inhibitor test must be performed at least ~~4 days~~ *72 hours* after last administration of N8-GP to allow for wash-out of the drug, *unless that patient is known to have increased clearance of N8-GP due to the presence of FVIII inhibitors*.~~unless that patient is undergoing ITI treatment.~~

If the result of the inhibitor test is positive, a second confirmatory inhibitor test should be performed by the central laboratory *(except for visit 1 sample that will not need to be confirmed).* The confirmatory samples should be collected as soon as possible, but no sooner than *72 hours* ~~4 days~~ after the last dose of N8-GP. S*ampling for* assessments of FVIII activity (*trough and* recovery), ~~and~~ binding antibodies, *lupus anticoagulant and PEG antibodies* must be performed *at the same time.* ~~If considered relevant a lupus anticoagulant test can be performed.~~*If the result from the lupus anticoagulant, the binding antibodies and/or the PEG antibodies analyses are positive we recommend the analyses to be repeated regularly.*

….

PK assessment ~~(optional)~~

In the event of a concern about reduced treatment efficacy in a patient with or without confirmed positive test for binding antibodies towards N8-GP/ or inhibitors an unscheduled visit *is recommended to* ~~can~~ be scheduled where a PK session may be performed with a dose of 60 U/Kg to

investigate the ~~elimination (~~recovery, clearance and half-life~~)~~ of N8-GP. The PK data may potentially be used to adjust the ~~dose or~~ dosing regimen.

After having completed ITI treatment a PK session must be performed ensuring the N8-GP half-life to be ≥ 9 hours. A dose of 60 U/Kg should be given after a 72 hours treatment-free wash-out period.

The following time-points for blood sampling for the PK profile ~~are suggested~~: pre-dose, ~~30 min (± 10 min),~~ 1h (± ~~10~~*30* min), *6h (± 2 hours)*, 24h (± 8 hours), 48h (± 8 hours), and *optional 72h* ~~96h~~ (± 8 hours).

8.4.2.3 HIV testing and CD4+ lymphocyte count

….

Results can be transferred from the medical records if obtained within the last 6 months.

- HIV ~~1 and 2~~ antibodies *(positive/negative)*

….

8.4.2.4 Haematology

- Haemoglobin (~~mmol~~g/L)

….

If test results for the above mentioned haematology parameters are available from within one month prior to V0, they can be used for the V0 haematology assessment, if older, a new sample must be drawn and assessed at the central laboratory. *If V1 is more than a month apart from V0, Haematology should be retaken.*

Haematology should be measured according to Table 2-1.*For visit 9, 14 and EOT Haematology sample taken within ±1 month (V9 and V14) and -1 month (EOT) and send to central lab can be used for the visit assessment*.

8.4.2.5 Biochemistry

….

If test results for the above mentioned biochemistry parameters are available from within one month prior to V0, they can be used for the V0 biochemistry assessment, if older, a new sample must be drawn and assessed at the central laboratory. *If V1 is more than a month apart from V0, Biochemistry should be retaken.*

Biochemistry should be measured according to Table 2-1.*For visit 9, 14 and EOT Biochemistry sample taken within ±1 month (V9 and V14) and -1 month (EOT) and send to central lab can be used for the visit assessment*.

8.4.2.6 F8 and HLA genotype testing (not applicable for Israel)

…..

F8 and *HLA* genotype can be measured any time from visit 0 to visit 8.

~~*F8* and *HLA* genotype can be measured according to Table 2-1.~~

….

8.4.2.7 Allergic reaction testing

Allergic reaction testing will only be performed in patients developing severe allergic reactions related to N8-GP treatment as judged by the Investigator. ~~The~~ Baseline sample will *only* be analysed for assessment *in case* of ~~the~~ allergic reactions.

If a severe allergic reaction related to treatment occurs, blood samples should be taken at an unscheduled visit as soon as convenient, *but* ~~and~~ not later than 2 months after the event. The allergic reaction assessments will be performed at a laboratory selected by Novo Nordisk or at a Novo Nordisk laboratory.

Test to be performed:

- N8-GP IgE antibodies
- FVIII IgE antibodies
- FVIII inhibitors
- N8-GP/FVIII binding antibodies

Optional tests at the discretion of the investigator:

- HCP IgE antibodies
- *HCP IgG antibodies*
- *PEG antibodies*
- Murine IgG antibodies

…

8.4.3 Blood sampling in infants and children

…..

The total volume of blood to be collected for each patient per visit will not exceed *12.5* ~~10~~ mL.

…

It is recommended not to attempt venepuncture more than 3 times for the purpose of obtaining sufficient blood sampling. Documentation must be available in medical record. *The vein used for drug injection should not be used for blood sampling until more than 30 minutes have passed after the injection. The same device use for drug injection may not be used for blood draw post-dose.*

….

8.4.4 Storage of samples

….

All remaining blood samples stored at the central laboratory will be destroyed after finalisation of the CTR, except for samples for antibody assessment and *other* biospecimens, see Section 23.2.

Antibody samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). *The retained antibody samples may be used for further characterisation for antibody responses towards drug if required by health authorities or for safety reasons, see Section 23.2.*

8.5 N8-GP administration

N8-GP will be administered while the patient is in a comfortable position according to Table 5-1.

During ED 1-2 with treatment at the trial site (V1 -V2):
The first 2 N8-GP doses should be administered at trial site.

Trial injection kits (butterflies etc) will be provided by Novo Nordisk. Choice ~~of~~ *between* butterfly or cannula for N8-GP injections is at the discretion of the investigator

The actual time of completion of the injection will be recorded and corresponds to trial time point = 0.

During ED 3-100 *and/or until EOT* with treatment at trial site and at home (after V2):

…

8.6.1 Assessment of bleeding episodes and treatment response

Table 8-1 *Haemostatic response for bleeding episode* - 4-point scale

8.7 Surgery

Before any surgery is performed blood samples for assessment of inhibitors must be taken and send to central lab unless a test has been taken and send to central lab within 30 days (but the results does not have to be available before the surgery).

Preventive N8-GP treatment before minor surgery including placement or removal of central venous access port can be performed *during* ~~within~~ this trial at the investigator's discretion according to local guidelines. A dose of 40-75 U/Kg N8-GP prior to minor surgery is recommended to prevent perioperative bleeding episodes, see Table 5-1. Major surgeries are only allowed after 50 EDs ~~and when the results from the pathfinder™6 (NN7088-3860) is available~~. *Prior to major surgery a dose of maximum 75 U/kg is recommended , see Section 5.3.5.*

Preventive N8-GP treatment prior to surgery should be captured in eCRF or in the eDiary.

Emergency surgeries are allowed in this trial if adequate supply of N8-GP is available at site to ensure haemostasis and wound healing.

Patients undergoing surgery will continue the regular visit schedule, but additional visits may be performed in the peri-operative period as decided by the investigator. Surgery will be documented as unscheduled visits. It is up to the investigator to decide how long the post-surgery period should be and when the patient should resume regular prophylaxis or pre-prophylaxis treatment. All N8-GP doses administered in relation to a surgery must be registered on the surgery from in the eCRF.

~~**8.7.1 Minor surgery**~~

~~Definition of minor surgery, see Section 5.3.4~~

~~For minor surgery the following should be recorded~~

- ~~Date, time and volume of preventive dose before surgery~~
- ~~Type of surgery~~
- ~~Indication for surgery~~
- ~~Date of surgery~~
- ~~Start time of surgery*~~
- ~~Withdrawal criteria (if other than the trial drug is used)~~

8.7.1 Data collection during ~~Major~~ surgery

Definition of *minor and* major surgery, see Section 5.3.5

FVIII inhibitor sample should be taken prior to surgery and analysed at the central laboratory.
For ~~major surgery~~ *surgeries* the following should be recorded in the eCRF:

- Date, time and volume of preventive dose before surgery
- Type of surgery
- Indication for surgery
- Date of surgery
- Start *and stop* time of surgery*
- *Dosing of N8-GP in relation to the surgery*
- Clinical evaluation of haemostatic response, see Table ~~8-1~~ *8-2*
- *Concomitant medication incl. blood products*
- *Adverse events*
- Clinical narrative of the procedure
- *Withdrawal criteria (e.g. if other than the trial drug is used)*

**Start and stop of surgery is defined as knife-to-skin and last stitch, or similar that seems appropriate.*

Injections with N8-GP administered after surgery has been completed should be reported either in the eCRF (injections administered at site) or in the eDiary (injections administered at home), see Section 12.3

Clinical evaluation of haemostatic response to be evaluated upon completion of the surgical procedure by the Surgeon, Anaesthesiologist and/or Investigator, based on experience as follows:

Table 8–2 Haemostatic response for Surgery - 4-point scale

Classification	***Description***
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*

.

…

8.8.2 Home treatment training

….

A home treatment guide for the reconstitution ~~and administration process~~ will be available as hands-out for the patient's parent(s)/LAR(s). Training in reconstitution and administration must be performed until parent(s)/LAR(s) feel comfortable in handling the treatment. The training must be documented in the medical records.

….

8.8.3 Electronic diary (eDiary)

…

During the home treatment period the patient's parent(s)/LAR(s) must ensure that all pre-prophylaxis and prophylactic home treatment, bleeding episodes, treatment of bleeding episodes as well as haemostatic evaluation of the treatment of bleeding episodes are captured in the eDiary.

The details of bleeding episodes should be entered by the parent(s)/LAR(s) in the eDiary. In case a parent(s)/LAR(s) is unable to enter a bleeding episode in the eDiary, or in case the patient is hospitalised, the Investigator will report the bleeding episode in the eCRF.

…

8.8.4 Contact between the investigator/medically qualified person and the patient

….

The expiry date of the drug *and solvent* that the patient has received should be checked by the site staff before the patient's next visit to determine if an extra dispensing is relevant and to inform the patient of which unused vials to return to the site. *Expiry of injection kits should be discussed.*

….

9 Trial supplies

9.1 Trial product

….

After reconstitution the appropriate volume of the vials will be drawn into a syringe. *Maximum 4 mL can be withdrawn from each vial of reconstituted N8-GP and the content of several vials may be combined into one syringe.* ~~The content of several vials may be combined in one syringe.~~ N8-GP may not be added to or mixed with any other material *than Sodium Chloride Solution.*

…

Novo Nordisk will not supply any Non Investigational Medical Products (NIMPs). *0.9% Sodium Chloride Solution for reconstitution of the N8-GP trial product will be supplied by Novo Nordisk.*

…

9.3 Storage

….

The trial product N8-GP powder and Sodium Chloride Solution must be stored in a secure place at trial site. For N8-GP under refrigeration at 2-8°C, and for Sodium Chloride Solvent at 2-30°C, both protected against light and are hereby stable until the expiry date given. It is recommended to use the reconstituted N8-GP immediately following reconstitution. If not used immediately, the reconstituted product can be stored in the vial for up to 4 hours below 30°C. Exposure to direct sunlight as well as freezing must be avoided after reconstitution. As for other parenteral

preparations, the product should be inspected visually for particulate matter and discoloration prior to administration and discarded if either is present. *In use time starts from completion of the reconstitution see the handling instruction for further details.*

….

9.4 Drug accountability and destruction

…

Drug accountability is not required for Sodium Chloride Solution used for reconstitutions, *but it is the responsibility of the investigator or delegate to follow Sodium Chloride Solution expiry and prevent patient use after expiry.*

9.5 Auxiliary supply

Auxiliary supplies are equipment such as needles, syringes, butterflies, sterile swabs, vial adaptor etc. These will be provided by Novo Nordisk*, if applicable*.

11 Adverse events and technical complaints

11.1 Definitions

……

Definition of an acute, evolving, or recent myocardial infarction:

1. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria a*)* and b*)* below are fulfilled):

a) Increase in troponin T above the "diagnostic" limit: i.e. > 0.03 µg/L

b) Patients with:

ST-segment elevation: New ST-segment elevation at the J point in two or more contiguous leads with the cut-off points >= 0.2mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)

……

Clinical criteria for diagnosing anaphylaxis *(infants and children only)* (Sampson et al. 2006[24]):

…

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

- ~~a.~~ Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP *from that patient's baseline**

~~b. Adults: systolic BP of less than 90 mm Hg or greater than~~

* ~~30% decrease from that person's baseline~~ *Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2x age]) from 1 to 10 years.*

….

11.5 Precautions and/or overdose

As with any protein injected i.v. hypersensitivity reactions may occur. The possible events include rash, pruritus, fever, nausea, headache, vomiting and changes in blood pressure. If any of these events are suspected, further N8-GP administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines *prior to further treatment with N8-GP.*

….

11.6.2 Rules for putting the enrolment on hold

A safety analysis will be performed to evaluate the development of inhibitor at the following predefined time point:

• after the first 25 patients have *reached* ~~been to visit 6 (~~20 ~~– 25~~ exposure days)

….

12 Case report forms

….

In addition paper AE forms, safety information forms and Technical Complaint forms will be provided. These must be used when access to the eCRF is revoked *or if the eCRF is unavailable*.

….

12.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within *3* ~~5~~ days after the visit. Once data have been entered, it will be available to Novo Nordisk for data verification and validation purposes.

….

12.3 Electronic diary

Novo Nordisk will provide the patient's parent(s)/LAR(s) with an eDiary for electronic recording of details of their child's prophylaxis administration, bleeding episodes, ~~surgery~~ and treatment hereof, see Sections 8.1.12.1and 8.6. The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

…..

It is the responsibility of the Investigator *or delegate* to review and thereby ensure the eDiary data quality. Following must be checked as minimum that the eDiary data is complete, consistent and according to the requirements defined in this protocol. Upon review the Investigator *or delegated staff* must document that the review has taken place and any actions required e.g. retraining of patients.

…

13 Monitoring procedures

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

~~The first~~ *A* monitoring visit must be performed as soon as possible after FPFV and no longer than 4 weeks after. The monitoring intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between monitoring visits must not exceed 12 weeks whilst patients are in the trial *at site between V0 and V14. If all patients at site are in the period after V14, intervals between monitoring visits must not exceed 26 weeks, provided on site contact at least every 12 weeks. .*

….

16 Statistical considerations

Novo Nordisk will be responsible for the statistical analysis.

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.

The main statistical reporting of the trial will be performed when 50 patients have completed main phase (minimum 25 weeks) with at least 50 EDs and completed visit 9. EDs during ITI treatment will ~~not~~ count in the determination of when a patient has reached 50 EDs.

….

16.2 Definition of analysis sets

Descriptions and analysis of efficacy data will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines.[26] The FAS includes all patients exposed to N8-GP. The safety analysis and descriptions will be based on the Safety Analysis Set (SAS). The SAS will consist of all patients exposed to N8-GP.

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

….

16.4.2.6 Other assessments

…

FVIII trough level is defined as the activity recorded immediately before N8-GP injection, and reported as (*I*U/mL). IR_{30min} is defined as the peak activity recorded 30 minutes after the end of N8-GP injection, and reported as [*I*U/mL]/[*I*U/Kg]. It is calculated by subtracting the FVIII trough level from the FVIII activity recorded 30 minutes after ended N8-GP injection, and dividing the difference by the dose injected at time 0 expressed as U/Kg bw.

…

16.6 Sequential safety analysis and safety monitoring

…

after the first 25 patients have reached ~~been to visit 6 (~~20 ~~–25~~ exposure days~~)~~

….

17 Ethics

…

17.1 Informed Consent

…

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

The informed consent contains a section explaining that Novo Nordisk is asking to store left over blood from blood samples and use it to analyse for further analyses within the trial characterising biomarkers within the trial.The accept is voluntary and independent on participation in the trial.

…

20 Critical documents

…

- List of IRB/IEC members and/or constitution *(or a general assurance number/statement of compliance)*

….

For local lab parameters the following will be collected:

….

- Laboratory methods *(only non-standard assays) and/or analytic methods*

…..

21 Responsibilities

…..

The investigator is accountable for the conduct of the trial at his/her trial site. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients. *At least investigator must be trained in the protocol at a Novo Nordisk meeting or by web training in the protocol provided by Firecrest. It is recommended that all site staff takes the Firecrest protocol training.*

….

22 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained

during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. *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 studies in this trial.*

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

…

23 Retention of clinical trial documentation and human biospecimens

23.1 Retention of clinical trial documentation

…

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

23.2 Retention of human biospecimens

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

Blood samples apart from antibody and biospecimen samples will be destroyed after the finalisation of the CTR. Antibody *and other biospecimen* samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). ~~All remaining blood samples will be stored until the trai lhas been evaluated by appropiate authorities~~ or until the project terminates, but no longer than 15 years from end of trial. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of N8-GP may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral bio-repository with access to the samples. Samples might be transferred to other countries, if not prohibited by local regulations. The patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and bio-repository personnel (if applicable) will have access to the stored bio specimens.

…..

24 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

…..

During the trial, the investigator or sponsor, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC (not applicable for Japan).

….

25 Indemnity statement

…..

Only applicable for Poland: Novo Nordisk carries liability for the Study exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal of Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Study, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law'

Only applicable for Portugal: For venous punctures, pain control measures are allowed according to local practice.

Protocol Amendment

no *3*
to Protocol, final version *3.0*
dated 17 April 2015

Trial ID: NN7088-3908

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previous Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to *all countries*

Amendment originator:

[redacted], International Trial Manager

Department: Biopharm, Trial Operations 2

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1 Introduction including rationale for the protocol amendment

This protocol amendment has been prepared to include the following changes to the protocol:

- Addition of ITI treatment secondary endpoint in order to assess the outcome of ITI. ITI treatment outcome assessment updated and description of the ITI treatment secondary endpoint added to the statistical section of the protocol in relation to this. No new blood samples will be required as the samples collected for checking criteria for successful ITI treatment will be used.
- Added clarification that the dose of 60 U/kg of N8-GP to be used before taking the samples to assess the outcome of ITI is recommended. This provides more flexibility to investigator if he/she wants to keep the patient on a constant dose.
- Half life of FVIII changed from 9 h to 6 h after assessment of available data on FVIII activity from paediatric trial NN 7088-3885 using the time points for half life activity calculation provided in the pathfinder^{TM}6 protocol.
- 72 h time post-dose sample is equally important to other samples in half-life evaluation, therefore, the word optional has been deleted.
- Added clarification about categorisation of clinical significance for lab parameters which are out of range due to underlying condition.
- Monitoring of antibody development against Host Cell Protein (HCP) has been added. No new blood samples will be required as the samples collected for the N8-GP binding antibody analysis will be used. The rationale for implementing the HCP antibody analysis is based on a recommendation from the U.S. Food and Drug Administration (FDA).
- Assessment of severity of the bleeding episode added into the list of information to be collected on the bleeding episode in order to align with all the trials in NN7088 program.
- Blood sampling for N8-GP binding antibodies at ITI-visits has been added in order to have an overview of inhibitor dynamics in relation to the whole N8-GP binding antibody dynamics for ITI patients.
- Allowed collection of additional PEG antibodies samples at a scheduled or unscheduled visit per investigator's discretion. The rational is to provide flexibility to investigator if he/she suspects the development of PEG antibodies at any given stage of the trial.
- Addition of several data points to be source data verified for screening failures in order to comply with the CDISC format.

In this protocol amendment:

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

2 Changes

Table 2–2 Flow chart explanatory descriptions

9	Blood samples must be collected prior to dosing at dosing visits. Please check that the required washout period has been met for inhibitor testing, see section 8.1.1.3 Before any surgeries are performed an inhibitor test must be taken if this test is more than 30 days. *HCP antibodies will be analysed using samples taken for the N8-GP binding antibodies at the time points described in section8.4.2.2.*

4.2.2 Secondary Endpoint

Frequency of Adverse events (AEs) including serious AEs and Medical Events of Special Interest (MESI).*
Incidence of confirmed high titre inhibitors (defined as inhibitor titre > 5BU)*
Number of breakthrough bleeding episodes during prophylaxis with N8-GP (annualised bleeding rate).*
Haemostatic effect of N8-GP in treatment of bleeding episodes, assessed by a predefined 4-point haemostatic response scale ("excellent", "good", "moderate" and "none").*
Consumption of N8-GP for prophylaxis (number of injections and U/Kg per month and per year)
Consumption of N8-GP for treatment of bleeding episodes (number of injections and U/Kg required per bleeding episode)
Total consumption of N8-GP per patient (prevention and treatment of bleeding episodes) per month and annualised value
Outcome of ITI, assessed by a predefined 4-point ITI outcome scale ("success", "partial success", "failure", "other")

5.3.6.1 ITI therapy with N8-GP

…

Criteria for ~~successful~~ *assessing the outcome of* ITI therapy with N8-GP:

Success: in line with international consensus[13], and based on the mean N8-GP half-life observed in adults (18.5h) and children < 6 years of age (15h), successful N8-GP ITI outcome is based on the achievement of three stringent efficacy criteria

- Undetectable inhibitor titre < 0.6 BU
- Normalized FVIII in vivo recovery, defined as ≥ 66% of expected incremental recovery
- N8-GP half-life ≥ ~~9~~ *6* hours after a 72 h treatment-free washout period

Partial success:

- *Reduction in inhibitor titre to ≤ 5 BU*
- *Clinical effect of N8-GP therapy as judged by the investigator*

Failure:

- *Failure to attain defined success or partial success within 24 months of uninterrupted ITI with N8-GP*
- *Inhibitor decrease <20% after one year of ITI treatment*

Other:

- *Not fulfilling above criteria, e.g. early withdrawal from ITI treatment etc.*

Once the inhibitor is confirmed to be negative, FVIII recovery should be measured after an injection of *recommended* 60 U/kg of N8-GP without washout period. When FVIII recovery is shown to be ≥66% of the expected incremental recovery, based on PK data obtained in paediatric PTPs, a FVIII half-life study needs to be conducted after administration of *recommended* 60 U/kg of N8-GP after a 72 hours treatment-free washout period. This half-life study should be repeated, if necessary based on investigators discretion, until the half-life is confirmed to be ≥ *6* hours. Blood samples for FVIII half-life evaluation should be taken pre-dose and 1h, 6h, 24 h, 48 h, and ~~optional~~ 72 h post-dose (see Section 8.4.2.2). If half-life is < ~~9~~ *6* hours ~~the~~ ITI *therapy* should continue.

…

8.4 Laboratory assessments

…

Laboratory results being out of normal range must be categorised as “out of normal range, not clinically significant” or “out of normal range, clinically significant”. A laboratory result evaluated as “out of normal range, clinically significant” must be recorded as an AE, or if present at V0 it should be recorded as concomitant illness. *Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters (parts of the underlying disorder) and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: e.g. FVIII activity, FVIII inhibitors, binding FVIII antibodies, PEG antibodies, HCP antibodies and genotype testing including HLA.*

The central laboratories provide results to the trial site in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

…

8.4.2.2. Antibody assessments

The analysis will be performed at a laboratory selected by Novo Nordisk or at a Novo Nordisk laboratory. The procedures for analyses will follow the recommendations provided by Novo Nordisk. A description of the method will be included in the final report of this trial.

Plasma samples will be collected for assessment of:

N8-GP/FVIII binding antibodies
Host Cell Protein (HCP) antibodies
PEG antibodies
FVIII inhibitor

Antibody assessment should be measured according to Table *2–1* ~~5–1~~. Antibody samples taken within ±1 week from the visit (for EOT only – 1 week) and send to central lab can be used for the visit assessment if the requirements for 72 hours wash out.
…

HCP antibodies

A selection of the samples collected for the N8-GP/FVIII binding antibody analysis will be analysed for HCP antibodies. HCP are small pieces of protein remaining from the synthesis of recombinant FVIII in CHO cells. These proteins are removed during the purification, however very small amounts may be present in the drug product and could potentially cause an immune response. This analysis will be performed depending on the amount of sample available.

The analysis of HCP antibodies is planned to include samples taken at the following time points: pre-dose prior to first N8-GP exposure and hereafter approximately every 6 months until the visit 9, hereafter every 12 months.

If deemed necessary more samples may be analysed to fully characterise the individual patient's HCP antibody profile.

PEG antibodies

Screening for PEG antibodies is based on assays that are validated according to international recognised guidelines.[19-21] Samples measured above the assay cut-point will be subject to a confirmation test.

PEG antibodies should be measured according to Table 2–1 and if required, investigator may take additional PEG-antibodies samples at other visits. Samples will be analysed for PEG binding antibodies at the end of trial or whenever considered relevant.

8.6.1. Assessments of bleeding episodes and treatment responses

…

Bleeding Episode – information to be collected

Information about bleeding episodes prior to the 2 ED (V2) should always be recorded in eCRF. In case the patient is treated outside the trial site the trial site should be informed in case of a bleeding episode and the details hereof. After 2 EDs bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see Section 12.3.

Date and time the bleeding episode started

Date and time the bleeding episode stopped

Cause of the bleeding episode

i.e. spontaneous, traumatic or due to surgery

Anatomical location of bleeding episodes

Severity of the bleeding episode, assessed by the investigator as defined in 8.6.1

Amount, and time of each dose of N8-GP

Haemostatic response assessed by the 4-point scale defined in Table 8–1

…

13 Monitoring procedures

…

A monitoring visit must be performed as soon as possible after FPFV and no longer than 4 weeks after. The monitoring intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between monitoring visits must not exceed 12 weeks whilst patients are in the trial at site between V0 and V14. If all patients at site are in the period after V14, intervals between monitoring visits must not exceed 26 weeks, provided ~~on~~ site contact at least every 12 weeks.

…

For screening failures: Data for the screening visit must be entered in the eCRF within preferably 3 days after data are available and the Screening Failure Form must be completed. Source data verification is not required except for informed consent, *date of visit, demographics (sex, date of*

birth and race), violated inclusion/exclusion criteria, screening failure form ~~reason for screening failure~~ and ~~for~~ data relating to any AEs if applicable. All data entered in the eCRF will be transferred into the trial database.

…

16 Statistical considerations

……

Patients initiating ITI treatment will for the statistical analyses be considered like withdrawals and data collected during ITI treatment period will be summarised and reported separately. ~~Evaluation of these data will be considered exploratory only.~~

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. If created, the SAP will be finalised

16.4.2.7 Outcome of ITI

Outcome of ITI, assessed by a predefined 4-point ITI outcome scale ("success", "partial success", "failure", "other"), for patient(s) who undergo ITI treatment during the trial, will be summarised.

Protocol Amendment

no 4

to Protocol, version 4 dated 01-November-2016

Trial ID: NN7088-3908

pathfinder™6

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

Trial phase: 3a

Applicable to Israel

Amendment originator:

[redacted], Clinical Trials Manager
Department: Haemophilia, Clinical Operations NN IL

Table of Contents

1 Introduction including rationale for the protocol amendment

Patients with congenital haemophilia A have a mutation in coagulation Factor 8 (F8) gene. The different types of mutations in the F8 gene are associated with different probabilities for development of inhibitors. Inhibitors are antibodies that neutralises the factor VIII activity thereby rendering treatment with replacement factor products, such as N8-GP, difficult.

Israel was excluded from F8 and HLA genotype testing however, since the incidence of FVIII inhibitors is the primary endpoint of the trial and certain mutations are related to very high inhibitor rates, the mutation composition of the trial population is pivotal for the understanding of the immunogenicity.

With the current protocol amendment Novo Nordisk is seeking permission to obtain the F8 genotype from the patients in Israel, if already available. If not available or if it needs to be re-tested, based on the investigators discretion, F8 and HLA genotype testing will be offered.

The results will be part of the clinical data analysis and reporting and used for trial specific purposes only. All information will be kept confidential.

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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8.4.2.6 F8 and HLA genotype testing ~~(not applicable for Israel)~~ 64

Table 2–2 Flow chart explanatory descriptions

Footer 12. F8 and HLA genotype sample is only allowed upon patient's parent(s)/LAR(s) signing the consent for genotyping and should only be done if not already documented in patient's medical record. The sample can be collected at any visit between V0 and V8, taking the limitation of the allowed blood sampling volume into account. ~~Genotype is not applicable for Israel~~

8.1 Visit procedures

Informed consent procedure

The patient's parent(s)/LAR(s) will be provided with full written and verbal information about the trial prior to conduct of any trial-related procedures/activities, in accordance with GCP and local requirements, see Section 17.1.
A child assent form will be provided to patients above 3 years of age according to local requirements. This can be performed on a separate day. As this is a long term trial the investigator should check the progressing maturation of the child and its ability to assent throughout the trial.
Informed consent for obtaining genotyping must be collected, if applicable. ~~Genotype consent is not applicable for Israel.~~

8.4.2.6 F8 and HLA genotype testing ~~(not applicable for Israel)~~

~~At Visit 0, a~~All patient's parent(s)/LAR(s) will be asked about documentation of previous Factor VIII gene (F8) and Human Leucocyte Antigen (HLA) genotype tests. If not available or if it needs to be re-tested, based on the investigators discretion, F8 and HLA genotype testing will be offered if allowed according to local law. The F8 and HLA genotype analysis will be performed at a

laboratory selected by Novo Nordisk, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than F8 and HLA. Samples will be disposed appropriately after the test and all test results are kept confidential.
Investigator and/or patient's parent(s)/LAR(s) have the right to refuse to provide patient's F8 and HLA genotype documentation or to refuse genotyping. This will not prevent the patient from participating in the trial.
F8 and HLA genotype can be measured any time ~~from visit 0 to visit 8~~ *during the trial*.
Applicable for Japan only: If documentation of the patient´s genotype already exists, the patient is offered to provide his data for the trial. If no previous data exists and genotyping consent is obtained, FVIII and HLA genotype analysis is performed at the laboratory in Bonn, Germany, using DNA isolated from leucocytes from the patient's blood. No analysis will be performed concerning other genes than F8 and HLA. Samples will be disposed appropriately after the test and all test results are kept confidential.
~~Applicable for Israel only: No genotype testing or genotype information will be collected.~~

16.7 Reporting of F8 and HLA genotype

Information about underlying gene defects of F8 and HLA will be listed in the clinical trial report, ~~except for Israel~~. No statistical analysis will be performed.

17.1 Informed consent

F8 and HLA genotype testing/collection of previous genotype ~~documentation (not applicable for Israel)~~:

Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient and/or the patient's parent(s)/LAR(s) must give their consent before the data can be collected for trial purpose. Prior to any trial-related activity, the investigator must provide the patient's parent(s)/LAR(s) with the possibility to abstain from the genetic testing/collection of previous documentation, but still be able to participate in the trial. Only the F8 and HLA genotype will be analysed by the central laboratory selected by Novo Nordisk and no other genomic analyses will be carried out. Samples will be appropriately disposed of, after the test. All test results are kept strictly confidential in sufficient consideration of individual information.

Protocol Amendment

no 5

to Protocol, version 4 dated 01 November 2016

Trial ID:NN7088-3908

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

Trial phase: 3a
Applicable to all countries

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1 Introduction including rationale for the protocol amendment

The trial has been on-going since 2013, and a per protocol interim analysis is planned to evaluate safety and efficacy when 50 patients have reached 50 exposure days according to the previous version of the EMA Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (2011). The target of 50 patients with 50 exposure days with the present recruitment rate is estimated to be 2021.
Recruitment is extremely difficult in Previously Untreated Patients (PUPs) and the risk of developing neutralising antibodies is high. The concurrent development of many therapeutic products for hemophilia treatment decreases the availability of previously untreated patients for clinical trials, suggesting that informative studies performed in a meaningful number of PUPs will not be feasible in a timely manner. Therefore, formal PUP studies are not required according to the updated EMA guideline (2018).
However, this trial was established prior to the new stance from EMA, which now does not stipulate the need for PUP trials. Given that the original target will delay retrieval of data, it has been decided to incorporate an interim data analysis to provide valuable information within this sub-population in a more timely manner as every PUP should be closely monitored with regards to treatment performance and inhibitor development.

The following minor clarifications to protocol text have been made:

- The weighing intervals and the visit windows of the protocol have been aligned. A weight, which is measured up to 12 weeks before a visit can be used for trial product dispending in children more than 3 years of age as well as for all children after visit 15 (table 2.2 and section 8.3.1).

- During the clinical development programme it was demonstrated that the specific chromogenic assay set-up employed with NHP as calibrator over-estimated plasma FVIII activity and the one-stage clotting assay in the applied setup under-estimated the activity of N8-GP when using NHP as calibrator due to PEG interference with the aPTT reagent.

- Categorisation of clinical significance for out of range lab parameters due to underlying condition removed in order to make categorisation equal for all laboratory results.

- Administrative changes, including incorporation of previously approved local amendments.

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

2 Changes

Sections 1, 5.1, and 16:

Due to the extended time frame of the trial related to slow recruitment rate from the available PUP population, an interim analysis will be performed to retrieve safety data.

Table 2-2:

The frequency of body weight measurements should follow local practice, but should at least be measured every 10 weeks in children ≥3 years of age and within a timeframe of 6 weeks in children <3 years of age. *For practical purposes, when dispensing trial drug after V15, the body weight from an earlier measurement (or visit) can be used for all age groups if the measurement was performed within the previous 12 weeks.* Please refer to Section 8.3.1

Section 8.3.1:

Body weight should be measured in connection with regularly visit where trial drug is dispensed. For practical purposes when dispensing trial drug the weight from an earlier measurement (or visit) can be used if the measurement was performed within the previous 10 weeks (in children <3 years of age, within 6 weeks). If new body weight is not needed to be measured at a visit, the body weight from last weighing should be used. *After visit 15, a body weight measured within the previous 12 weeks for all age groups can be used.*

8.4. Laboratory assessments

…Laboratory results being out of normal range must be categorised as "out of normal range, not clinically significant" or "out of normal range, clinically significant". A laboratory result evaluated as "out of normal range, clinically significant" must be recorded as an AE, or if present at V0 it should be recorded as concomitant illness. ~~Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters (parts of the underlying disorder) and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: e.g. FVIII activity, FVIII inhibitors, binding FVIII antibodies, PEG antibodies, HCP antibodies and genotype testing including HLA.~~ …

8.4.1.1 FVIII activity

After the patient has been dosed with N8-GP, FVIII activity should be measured with a *qualified* ~~an APTT based~~ one-stage clotting assay *or chromogenic assay, which means that some assays may use* ~~calibrated by~~ an N8-GP reference standard *for calibration*. The *N8-GP* reference standard will be provided by Novo Nordisk, together with a description of how to handle, store and use. The site must ensure that the reference standard has not expired and request a new one when relevant.

Dependent on the type of aPTT reagent used *in the one-stage clotting assay*, ~~by the local lab~~ 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 aPPT based assays please contact Novo Nordisk.

8.4.2.1 FVIII activity

~~In each assay both an N8-GP reference standard and a human plasma standard calibrated against the WHO international FVIII standard are used as assay calibrators.~~

16.5 Interim reporting

An interim efficacy and safety evaluation is planned when approximately 50 patients have reached 25 exposure days. The data will be presented for separately for the main phase and extension as well as combined.

Protocol Amendment

no 6

to Protocol, version 5
dated 13 June 2019

Trial ID: NN7088-3908

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

Trial phase: 3a
Applicable to Israel

Table of Contents

1 Introduction including rationale for the protocol amendment

Patients with congenital haemophilia A have a mutation in coagulation Factor VIII (F8) gene. The different types of mutations in the F8 gene are associated with different probabilities for development of inhibitors. Inhibitors are antibodies that reduce or eliminate the activity of Factor VIII proteins thereby rendering treatment with replacement factor products, such as N8-GP, difficult.

Patients from Israel were excluded from the F8 and Human Leucocyte Antigen (HLA) genotype testing in the previous versions of protocol. However, since the incidence of Factor VIII inhibitors is the primary endpoint of the trial and certain mutations are related to very high inhibitor rates, the mutation composition of the trial population is pivotal for the understanding of the immunogenicity.

Protocol Amendment no 4 version 1.0 dated 14 June 2018 (applicable only for Israel), which has recently been approved by the Health Authorities in Israel introduced F8 and HLA genotype testing for all patients going forward. Protocol Amendment no 4 version 1.0 dated 14 June 2018 was incorporated in protocol version 5 dated 13 June 2019.

With the current protocol amendment Novo Nordisk is seeking permission to obtain the F8 and HLA genotype testing results from withdrawn patients if already available in documentation.

The results will be part of the clinical data analysis and reporting and used for trial specific purposes only. All information will be kept confidential.

In this protocol amendment:

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

2 Changes

17.1 Informed consent

F8 and HLA genotype testing/collection of previous genotype documentation:

Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient and/or the patient's parent(s)/LAR(s) must give their consent before the data can be collected for trial purpose. Prior to any trial-related activity, the investigator must provide the patient's parent(s)/LAR(s) with the possibility to abstain from the genetic testing/collection of previous documentation, but still be able to participate in the trial.

Only the F8 and HLA genotype will be analysed by the central laboratory selected by Novo Nordisk

and no other genomic analyses will be carried out. Samples will be appropriately disposed of, after the test. All test results are kept strictly confidential in sufficient consideration of individual information.

Only applicable for Israel: The parent(s)/LAR(s) of withdrawn trial patients will be approached for consent to obtaining the F8 and HLA genotype testing results if already available in documentation.

Protocol Amendment

no 7

to Protocol, version 4.0 dated 01 Nov 2016

Trial ID: NN7088-3908

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

Trial phase: 3a
Applicable to Japan

Amendment originator:
[redacted], Trial Manager, Clinical Operations, CMR, Japan

Table of Contents

1 Introduction including rationale for the protocol amendment

In accordance with Japanese regulations, the regulatory category of this clinical trial has been updated and the assessment of expectedness clarified.

In this protocol amendment:

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

2 Changes

5.1 Type of trial

…

The trial design is based on the guideline on clinical investigation of recombinant and human plasma-derived factor VIII products developed by CHMP in EU.[9]

For Japan only: The NN7088-3908 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 getting marketing approval, is replaced in the protocol and other related materials/documents with the term 'post-marketing clinical trial.'

…

11.2 Reporting of adverse events

...

All AEs, either observed by the investigator or reported by the patient, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: investigator's brochure,[7] N8-GP, current version and any updates thereto.

For Japan only: If obtaining marketing approval in Japan, sponsor's assessment of expectedness is done according to the package insert of the commercial products in Japan.

…

Protocol Amendment

no 8

to Protocol, version 1.0 dated 04 November 2013

Final Protocol version 1.0 (04-Nov-2013) including:
Amendment no. 1, version 0.1, Portugal (30-Jul-2014)
Amendment no. 2, version 2.0 (20-Mar-2015)
Amendment no. 3, version 1.0 (01-Nov-2016)
Amendment no. 4, version 1.0, Israel (14-Jun-2018)
Amendment no. 5, version 1.0 (13-Jun-2019)
Amendment no. 6, version 1.0, Israel (21-Jun-2019)
Amendment no. 7, version 1.0, Japan (02-Jul-2019)

Trial ID: NN7088-3908

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Previously Untreated Patients with Haemophilia A

Trial phase: 3a
Applicable to all countries

Table of Contents

1 Introduction including rationale for the protocol amendment

The foremost purpose of this eighth protocol amendment is to finalise the NN7088-3908 trial prior to the milestone of 100 patients achieving 100 exposure days (EDs). Novo Nordisk A/S (NN) would like to maintain the current protocol defined trial end date of 13 November 2021 (LPLV). However, NN has predicted that the trial will not reach the originally targeted 100 patients by the protocol defined end of recruitment date of 02 October 2020. Based on the number of currently recruited patients and the recruitment rate in the trial, it has been predicted that the trial would need to continue at least until Q4 2025 to reach the milestone of 100 patients with 100 EDs. Still, NN expects to have completed the main phase with 50 patients with 50 EDs and V9 by Q3 2020. It has therefore been decided to maintain the planned date of LPLV, but to terminate recruitment of patients into NN7088-3908 with a predicted lower patient number than originally planned. This decision ensures that the paediatric investigation plan (PIP) commitment to EMA is achieved. In addition, PUP trials are no longer an EMA requirement in Haemophilia (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf), consequently all regulatory commitments will be met.

On 29 May 2019, the Safety Committee for N8-GP validated a safety signal in the NN7088-3908 trial. The safety signal was related to a transient low incremental recovery (IR) following the initial administrations of turoctocog alfa pegol in the absence of detectable inhibitors in a proportion of previously untreated patients (PUPs) within the first 5 exposure days. The observed low IR was generally transient, and the majority of patients returned to baseline levels over time. To ensure additional insights into the efficacy and safety of N8-GP during low IR periods, an intensified PEG antibody analysis has been implemented. The analysis will be done from blood samples collected for N8-GP binding antibodies. Therefore, no additional blood samples will need to be collected.

Other clarifications to the protocol:

To align the protocol with the most recent monitoring process, which has been simplified to allow for more risk-based monitoring, the protocol has been updated so that monitoring on-site visits can be substituted with remote monitoring when considered feasible.

In this protocol amendment:

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

2 Changes

Following sections in the protocol are affected by this eighth protocol amendment:

1 Summary

[…]

Time frames for evaluation of Objectives/Endpoints

All objectives/endpoints will be evaluated when the first 50 PUPs have reached at least 50 exposure *days with V9* ~~dates, when the first 100 PUP have reached 100 exposure dates,~~ and at end of trial. End of trial will be up to 4 years after the *first* patient has reached 100 exposure ~~dates~~ *days*.

[…]

Trial design:

[…]

The European medical agency ~~requires~~ *required* submission of safety and efficacy data from minimum 50 exposure days in at least 50 patients for approval of the indication in PUPs~~, with a post-approval commitment to follow- at least 100 patients for a minimum of 100 exposure days~~. When the first 50 patients have reached a minimum of 50 exposure days *and V9*, the analysis and evaluation for the main trial report will be performed. ~~All patients~~ *Patients may* continue in the extension phase for the purpose of collecting data for ~~a minimum of~~ 100 exposure days ~~in at least 100 patients~~.

2 Flow chart

Table 2-1 Flow chart visits and assessments

Visit number	0[1]	1[1]	2	3	4-6	7-8	9	10-13	14	15-X[19]	EOT
Visit purpose	Screening	Dosing	Dosing	Dosing	Dosing	Dosing	End of main	Dosing	End of extension	Dosing (until EOT)	End of Trial
Time of visit (ED(s))[2]	0	1	2	5	10, 15, 20[3]	30,40	50	60, 70, 80, 90	100	NA	
Visit interval (ED(s))[2]		0	0	±1	±2	±2	+2	±2	+2	24w±4w	
CENTRAL LABORATORY ASSESSMENTS											
FVIII activity – trough[9]	X[8]	X		X	X	X	X	X	X	X	X
FVIII activity – recovery (30 min post-dose)		X		X	X	X	X	X	X	X	
N8-GP/FVIII binding antibodies[9]		X		X	X	X	X	X	X	X	X
PEG antibodies[9]		X		X	X	X	X	X	X		X
FVIII inhibitor test[9]		X[18]		X	X	X	X	X	X	X	X
HIV antibodies	(X)[10]										
CD4+ lymphocyte count and HIV viral load	(X)[10]										
Haematology	X	X[11]					X		X		X
Biochemistry	X	X[11]					X		X		X
F8 + HLA genotype testing	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]					
Allergic reaction testing	X										
TRIAL PRODUCT ADMINISTRATION											
N8-GP administration		X	X	X	X	X	X	X	X	X	
Change of regimen			X	X	X	X	X	X	X	X	
N8-GP dispensing for home treatment			X[13]	X	X	X	X	X	X	X[17]	
N8-GP accountability		X	X	X	X	X	X	X	X	X	X

[…]

Table 2-2 Flow chart explanatory descriptions

9. Blood samples must be collected prior to dosing at dosing visits. Please check that the required washout period has been met for inhibitor testing, see section 8.1.1.3 Before any surgeries are performed an inhibitor test must be taken if this test is more than 30 days. HCP antibodies *and PEG antibodies* will be analysed using samples taken for the N8-GP binding antibodies at the time points described in **section** 8.4.2.2**.**

3 Background information and rationale for the trial

[…]

3.2 Rationale for the trial

[…]

The rationale for performing the pathfinder™6 trial is to evaluate the safety (including immunogenicity) and efficacy of N8-GP in the treatment of PUPs with severe haemophilia A in accordance with EMA requirements. For Europe, EMA ~~requires~~ *required* a separate investigation in the PUP population as part of the development programme to be initiated before market authorisation. The approval of the ~~indication in PUPs~~ *paediatric investigation plan (PIP)* will be based on a clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs ~~connected with a post-approval commitment to follow up at least 100 PUPs for a minimum of 100 EDs~~. The 50 patients will continue *in an extension phase to collect long term safety data.* ~~to reach at least 100 EDs~~, ~~and additional 50 patients will be included also to reach at least 100 EDs.~~

[…]

5 Trial design

5.1 Type of trial

[…]

The number of patients to be investigated in this trial follows *a PIP by EMA which Novo Nordisk has committed to.* ~~the minimum EU guideline requirements for approval of the indication in PUPs, which will be based on a pre-authorisation clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs, connected with a post-approval commitment to follow-up at least 100 PUPs for a minimum of 100 EDs.~~

According to the *previous* EMA Guideline treatment with N8-GP in the pathfinder™6 PUP trial was able to start when 20 patients participating in the paediatric PTP trial (pathfinder™5) were available (including data from a minimum of 10 paediatric patients below 6 years of age), and pharmacokinetic investigations in paediatric PTPs were completed.

[…]

Patients will be followed in the extension phase until ~~at least 100 patients have reached at least 100 EDs each~~ *LPLV*. EDs during immune tolerance induction therapy (ITI) will count in the determination of ~~when a patient has reached 100 EDs~~ *a patient's total number of EDs reached at his EOT visit.*

5.2 Rationale for trial design

[…]

The main phase of the trial will generate safety and efficacy, aiming for a minimum of 50 EDs per patient. This number of EDs ~~is~~ *was previously* required by the EMA guideline[9] for evaluation of new FVIII products. The trial does not include a placebo control group, as it is considered unethical to administer an ineffective treatment to patients with haemophilia. An active control has not been included as extensive comparative data from recently registered rFVIII products are available in comparable global populations including patients from EU and US.[14, 15] Furthermore, the EMA guideline does not require a comparison to neither placebo nor an active comparator.

[…]

5.3.6.1 ITI therapy with N8-GP

[…]

Patients who develop inhibitors, within the pathfinder™6 trial, will be offered continued ITI treatment with N8-GP for a maximum of 24 months, *also in case this extends past LPLV of the trial*. ITI therapy with FVIII concentrates other than N8-GP is not allowed within the trial. It may also be decided by the Investigator and/or parent/legal representative to withdraw the patients developing FVIII inhibitors.

[…]

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 150

Number of patients planned to be started on trial product: 125

Number of patients expected to complete the trial: 100

Due to slow recruitment rate from the available PUP population, these patient numbers may not be met in time for LPLV.

~~6.5 Patient replacement~~

~~Withdrawn patients may be replaced to ensure that 100 patients complete the trial with at least 100 EDs. Assuming a drop-out rate of 20%, it is estimated that 125 patients must be started on N8-GP to~~

~~obtain the 100 completed patients. This may, however, be adjusted during the trial based on the actual drop-out rate~~.

[…]

7 Milestones

[…]

Patients with inhibitor*s* will be allowed to receive *continued* ITI treatment for up to 24 months, *also in case this extends after LPLV*.

[…]

8 Methods and assessments

[…]

8.1.9 End of trial visit

The EOT visit can take place at any time after completion of 100 EDs *and V14* or if the patient is withdrawn from the trial.

[…]

8.4.2.2 Antibody assessments

[…]

PEG antibodies

PEG *IgM/IgG* antibodies should be measured according to Table 2–1 and if required, investigator may take additional PEG-antibodies samples at other visits. Samples will be analysed *regularly* for PEG binding antibodies ~~at the end of trial or whenever considered relevant~~ *and results will be reported to investigators at the end of trial, or whenever considered relevant, and will be included in the CTR.*

[…]

13 Monitoring procedures

[…]

A monitoring visit must be performed as soon as possible after FPFV and no longer than 4 weeks after. The monitoring intervals will depend on the outcome of the remote monitoring of the eCRFs,

the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between monitoring ~~visits~~ must not exceed 12 weeks whilst patients are in the trial. ~~at site between V0 and V14. If all patients at site are in the period after V14, intervals between monitoring visits must not exceed 26 weeks, provided site contact at least every 12 weeks.~~

[…]

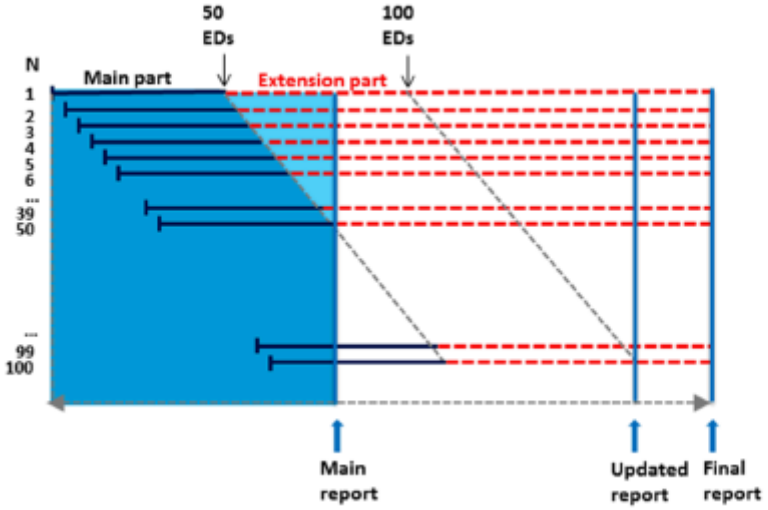
16 Statistical considerations

[…]

~~An updated reporting of the trial with supportive data will be performed when 100 patients have had at least 100 EDs. Data from all patients will be included up to latest visit prior this cut-off date. The data will be presented for the main + extension phase and the extended prophylaxis period (beyond 100 EDs) separately as well as combined.~~

A final report of the trial will be made after the LPLV cut-off on 13 November 2021. In case some ITI patients haven't finished their treatment at the time of LPLV, an addendum to the final report will be made once the last ITI patient has completed the trial.

~~All data will be reported separately in a final report when the trial is completed.~~



~~Figure 16-1 Individual patient flow and time periods for trial reporting~~

[…]

16.1 Sample size calculation

No formal sample size calculations have been performed. The sample size of 100 completers ~~is~~ *was* based on *previous* EMA guideline[9].

[…]

16.5 Interim reporting

[…]

~~An updated report will be made when the first 100 patients have had at least 100 EDs. A final report with supportive data will be made when all patients have completed both parts of the trial~~

[…]

A final report of the trial will be made after the LPLV cut-off on 13 November 2021. In case some ITI patients have not finished their treatment at the time of LPLV, an addendum to the final report will be made once the last ITI patient has completed the trial.