Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT01731600
Sponsor trial ID:	NN7088-3885
Official title of study:	A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A
Document date:	13 November 2015

16.1.1 Protocol and protocol amendments

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Protocol

Trial ID: NN7088-3885

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A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Redacted protocol
Includes redaction of personal identifiable information only.

Trial phase: 3

Protocol originator:
Name: [redacted]

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List of abbreviations

ABR	annualised bleeding rate
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated Partial Thromboplastin Time
AUC	area under the curve
BMI	body mass index
BU	Bethesda units
BW	body weight
CHO	Chinese hamster ovary
CL	Clearance
CNS	central nervous system
CRF	case report form
CRO	contract research organisation
DUN	dispensing unit number
eCRF	electronic case report form
ED	exposure days
eDiary	electronic diary
EMA	European Medicines Agency
ePRO	electronic patient reported outcomes
EOT	end of trial
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FU	follow up
FVIII	coagulation factor VIII
FIX	coagulation factor IX
FX	coagulation factor X
FXa	activated coagulation factor X
GCP	Good Clinical Practice
HCV	hepatitis C
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee

IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IR_{30min}	incremental recovery
i.v.	Intravenous
IV/WRS	interactive voice/web response system
LAR	legally acceptable/authorised representative
MESI	medical event of special interest
MRT	mean residence time
N	total number
N8-GP	Glycopegylated recombinant coagulation factor VIII (NNC 0129-0000-1003)
PEG	polyethylene glycol
PK	Pharmacokinetic
PRO	patient reported outcome
PTP	previously treated patient
PUP	previously untreated patient
rFVIII	recombinant human coagulation factor VIII
SAE	serious adverse event
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half life
TMM	trial materials manual
UTN	Universal Trial Number
V	visit
vWF	Von Willebrand Factor
WFH	World Federation of Haemophilia

1 Summary

Primary objective

- To evaluate immunogenicity of NNC 0129-0000-1003 (hereafter referred to as N8-GP)

Primary endpoint

- Incidence of inhibitory antibodies against coagulation factor VIII (FVIII) ≥0.6 Bethesda units during the main phase of the trial (from 0-26 weeks of treatment)

Key secondary objectives

- To evaluate safety other than immunogenicity of N8-GP
- To evaluate efficacy of N8-GP in prophylaxis and treatment of bleeding episodes
- To evaluate pharmacokinetic properties of N8-GP and compare to previous FVIII product

Key secondary endpoints

- Frequency of adverse events including serious adverse events reported during the trial period
- Haemostatic effect of N8-GP when used for treatment of bleeding episodes and assessed as: Excellent, Good, Moderate, or None
- Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)
- Consumption of N8-GP per bleeding episode (number of injections and U/kg)
- Consumption of N8-GP during prophylaxis (number of injections and U/kg per month and year)
- Incremental recovery (defined as the peak level recorded 30 min after end of injection) evaluated for previous FVIII product and N8-GP
- Area under the curve evaluated for previous FVIII product and N8-GP
- Terminal half-life evaluated for previous FVIII product and N8-GP
- Clearance evaluated for previous FVIII product and N8-GP

Timeframes for evaluation of the key secondary endpoints

The pharmacokinetic endpoints on previous FVIII product will be based on assessments performed 2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product. The pharmacokinetic endpoints on N8-GP will be based on assessments performed from 1 hour prior to and up to 96 hours after initial administration of N8-GP.

All secondary safety and efficacy endpoints will be analysed and reported separately for the main phase (from 0-26 weeks of treatment) and the extension phase of the trial (from 26 weeks to the last patient has completed the trial).

Trial design:

This is a multi-national, open-labelled and non-controlled trial to assess safety including immunogenicity, efficacy and pharmacokinetics of N8-GP in prophylaxis and treatment of bleeding episodes in previously treated paediatric patients with severe haemophilia A.

The trial consists of a main phase and an extension phase. The duration of the main phase for each patient will be approximately 26 weeks. After completion of the main phase, the patients can continue in an extension phase lasting until N8-GP is commercially available in the relevant countries or if the N8-GP program is terminated or otherwise required by national regulations.

For UK only: The end of the extension phase is defined as the planned last patient last visit date, May 2018.

The patients will be recruited evenly from two age groups; 0-5 years and 6-11 years. A minimum of 12 patients in each age group will complete pharmacokinetic assessment of previous FVIII product and of N8-GP. The trial has one treatment arm where all patients receive N8-GP twice weekly for prophylaxis. An increase in dose frequency from twice weekly to every third day is permitted at the investigators discretion (based on bleeding pattern).The prophylaxis dose is 60 U/kg body weight (whole mL dosing is allowed within the dose range 50-75 U/kg body weight). In the extension phase the patient should remain on the prescribed prophylaxis regimen until one year of treatment is completed. Hereafter the investigator is permitted to prescribe extra coverage before physical activities.

In addition, N8-GP will be administered to treat bleeding episodes during the trial period. Bleeding episodes will be treated with doses of 20-75 U/kg body weight N8-GP depending of severity and/or location of bleeding episode.

Trial population:

Approximately 60 patients will be enrolled and started on trial product in order for approximately 25 patients in each age group to complete the main phase of the trial.

The trial population is characterised by the following key inclusion and exclusion criteria:

Key Inclusion Criteria

- Male patients with severe congenital haemophilia A (FVIII activity level < 1%)
- Age below 12 years
- Weight ≥10 kg
- Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 0-5 years

Key Exclusion Criteria

- Any history of FVIII inhibitors

Safety assessments:

Inhibitory antibodies against FVIII, adverse events and FVIII activity will be assessed at each visit throughout the main phase of the trial (except assessment of inhibitory antibodies against FVIII at visit 3). During the extension phase of the trial inhibitory antibodies against FVIII, adverse events and FVIII activity will be assessed at intervals not exceeding 6 months. Furthermore, vital signs, physical examination, haematology and biochemistry will be measured during the course of the trial in intervals not exceeding 1 year.

Efficacy assessments:

Haemostatic effect of N8-GP when used for treatment of bleeding episodes (excellent, good, moderate, none), number of bleeding episodes during prophylactic treatment, consumption of N8-GP per bleeding episode and consumption of N8-GP during prophylaxis. Furthermore, patient reported outcomes will be assessed.

Pharmacokinetic assessments:

The pharmacokinetic sessions with previous product will be performed at Visit 1. The main parameters assessed are incremental recovery, area under the curve, terminal half-life and clearance. Due to limit on blood sampling volume four blood samples will be collected from patients weighing 10.0 -19.9 kg, and five blood samples will be collected from patients weighing ≥20.0 kg. The first sample will be collected within one hour prior to dose administration and the last sample will be collected up to 30 hours post dose.

The PK sessions with N8-GP will be performed at Visit 2. The main parameters assessed are the same as for previous product. Six blood samples will be collected from patients weighing 10.0 -19.9 kg, and seven blood samples will be collected from patients weighing ≥20.0 kg. The first sample will be collected within one hour prior to dose administration and the last sample will be collected 96 hours post dose.

Trial product(s):

The following trial products will be supplied by Novo Nordisk:

- N8-GP 500 U/vial
- N8-GP 2000 U/vial

N8-GP is supplied as a sterile, freeze-dried powder in a 2-8°C (36-46°F) stable formulation single use vial with a nominal content of 500 U/vial or 2000 U/vial to be reconstituted with 4.3 mL 0.9% sodium chloride solution for intravenous injections.

2 Flow chart

Table 2-1 Flow chart for the main phase

Visit purpose	Screen[1]	1st dose	2nd dose	N8-GP dosing visits				End of main phase	Inhibitor follow-up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	
Time of visit (weeks)	-4w	0	4 days	6w	11w	16w	21w	26w	
Visit window	±2w[2]		-1 day[3]	±1w	±1w	±1w	±1w	±1w	
PATIENT RELATED INFO/ASSESSMENTS									
Informed consent	X								
In/exclusion criteria	X	X							
Pharmacogenomic (FVIII genotype) consent and documentation (if applicable)[4]	X								
Withdrawal criteria		X	X	X	X	X	X	X	
PRO questionnaires	X[5]							X	
Concomitant illness	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X
Demography	X								
Haemophilia details	X								
Haemophilia treatment history	X								
History of bleeding episodes	X								
History of surgery	X								
Medical history[6, 7, 15, 17]	X								
Joint status at screening	X								
Date and time of last coagulation factor administration	X[8]								X
eDiary data review		X	X	X	X	X	X	X	
Bleeding episodes (severity rating)		X	X	X	X	X	X	X	X
ADVERSE EVENTS and CLINICAL ASSESSMENTS									
Adverse events	X	X	X	X	X	X	X	X	X[9]
Body measurements - Height - Body weight	 X X	 X		 X	 X	 X	 X	 X X	
Physical examination	X	X		X		X		X	
Vital signs		X[10]	X[10]					X	X

Visit purpose	Screen[1]	1st dose	2nd dose	N8-GP dosing visits				End of main phase	Inhibitor follow-up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	
Time of visit (weeks)	-4w	0	4 days	6w	11w	16w	21w	26w	
Visit window	±2w[2]		-1 day[3]	±1w	±1w	±1w	±1w	±1w	
LABORATORY ASSESSMENTS									
Haematology	X		X		X			X	
Biochemistry	X		X		X			X	
Antibodies - FVIII inhibitors - N8-GP binding antibodies	 X X	 X X		 X X	 X X	 X X	 X X	 X X	 X X
PK sampling (FVIII)[11]	X	X							
FVIII activity - FVIII trough level - FVIII recovery	 X	 X X[12]	 X X	 X X	 X X	 X X	 X X	 X X[13]	X[14] X[14]
Hepatitis screen	X[15]								
HIV - HIV antigen/antibody screen test - CD4+ T cells	 X[15] X[16]								
Lupus anticoagulant	X[6]								
von Willebrand factor (vWF)	X[17]				X[17]				
FVIII genotype testing (if applicable)[4]	X[18]								
TRIAL MATERIAL									
Administration of previous FVIII product (if applicable)	X[19]								
Administration of N8-GP		X	X	X	X	X	X	X[13]	
N8-GP dispensing		X	X	X	X	X	X	X[13]	
Drug accountability		X	X	X	X	X	X	X	
IV/WRS call	X	X	X	X	X	X	X	X	
TRAINING AND REMINDERS									
Trial card dispensing	X								
Patient information packs	X								
Home treatment training			X	X[20]					
eDiary dispensing and training	X	X[20]							
Washout requirements prior to next visit	X	X	X	X	X	X	X	X	

Footer	Description
1	For patients participating in PK assessments in the trial, PK sampling of previous FVIII product is required at visit 1. Visit 1 may be extended with as many days as necessary, as long as there are maximum 6 weeks between Visit 1 and Visit 2
2	Blood volumes should be respected and therefore taken into account when planning Visit 2 (see section 8.4.1)
3	For patients participating in PK assessments, Visit 3 must be in consideration of last PK sampling time point
4	If applicable, i.e. following patient/LAR consent and in accordance with local law. If genotype is available in medical file and patient/LAR has consented the results can be transferred. Consent for genotyping can be obtained at any time during the main phase of the trial, but preferably at Visit 1.
5	PRO questionnaire can be completed at either Visit 1 or Visit 2, but must be completed prior to dosing with N8-GP
6	If historical results for lupus anticoagulant are available in medical file they can be transferred to medical history and retesting is not required
7	Record blood type, if available in medical history
8	The patient should not use FVIII product 72 hours prior to Visit 1
9	Recording of inhibitor related AEs only
10	At Visit 2 and 3 vital signs must be performed pre-dose and 60 min (±15min) post-dose
11	Only applicable for the subset of patients participating in PK assessments. Please refer to Table 2-3 and section 8.1.1.1 and 8.1.2.1 for further details on PK sampling schedules
12	Not applicable for patients participating in PK assessment
13	Only if continuing in extension phase
14	Only applicable if patient is treated with a FVIII product
15	If historical results for HIV, hepatitis B and/or hepatitis C are available in medical file within 6 month of screening they can be transferred to medical history and retesting is not required
16	Assessment of CD4+ T cells is only applicable if HIV test is positive
17	If two historical results for von Willebrand factor are available in medical file they can be transferred to medical history and retesting is not required. If only one result is available in the medical records, an additional sample should be collected at the screening visit.
18	Genotype sample can be collected at any visit during the main phase of the trial following consent. Should preferably be collected at Visit 3 or later due to the volume of blood collected at Visit 1 and 2
19	Only applicable for patients participating in PK assessments
20	Follow up training, if applicable

Table 2-2 Flow chart for the extension phase

Visit purpose	N8-GP dosing visits						EOT extension	Inhibitor follow-up
Visit number	V9, V10, V11	V12	V13, V14, V15	V16	V17, V19, V21,...[1]	V18, V20, V22,..[1]		
Time of visit (months)[2]	+3m +6m +9m	+12m	+15m +18m +21m	+24m	+27m +33m +39m +…	+30m +36m +42m +…	Min 4 days after last dose	
Visit window	±2w	±2w	±2w	±2w	±2w	±2w		
PATIENT RELATED INFO/ASSESSMENT								
Withdrawal criteria	X	X	X	X	X	X	X	
PRO questionnaires		X		X		X[3, 4]	X[4]	
Concomitant illness	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration								X
eDiary data review	X	X	X	X	X	X	X	
Bleeding episodes (severity rating)	X	X	X	X	X	X	X	X
ADVERSE EVENTS and CLINICAL ASSESSMENTS								
Adverse events	X	X	X	X	X	X	X	X[5]
Body measurements: Height Body Weight	 X	X X	 X	X X	 X	X[6] X	X X	
Physical examination	X	X	X	X	X	X	X	
Vital signs							X	X
LABORATORY ASSESSMENTS								
Haematology	X[7]	X	X[7]	X		X	X	
Biochemistry	X[7]	X	X[7]	X		X	X	
Antibodies: FVIII inhibitors N8-GP binding antibodies	X X	X X	X X	X X		X X	X X	X X
FVIII activity: FVIII trough level FVIII recovery	X X	X X	X X	X X		X X	X	X[8] X[8]
TRIAL MATERIAL								
Administration of N8-GP	X	X	X	X		X		
N8-GP dispensing	X	X	X	X	X	X		
Drug accountability	X	X	X	X	X	X	X	
IV/WRS call	X	X	X	X	X	X	X	
REMINDERS								
Washout requirements prior to next visit	X	X	X	X	X	X		
eDiary collection							X	

Footer	Description
1	The visit can be repeated until N8-GP becomes commercially available in the patient's country. **For UK only**: The end of the extension phase is defined as the planned last patient last visit date, May 2018
2	Time of visit is related to Visit 8
3	PRO questionnaires only to be collected yearly (Visit 20, 24 etc.)
4	Only HAEMO-QoL
5	Collection of inhibitor related AEs only
6	Height only to be measured yearly (Visit 20, 24 etc.)
7	Haematology and biochemistry every half year (Visit 10, 12, 14, 16 etc.)
8	Only applicable if patient is treated with a FVIII product

Table 2-3 Flow chart for PK assessments

Only applicable for the subset of patients participating in PK assessments. All time points are relative to completion of injection of FVIII product. Please refer to section 8.1.1.1 and 8.1.2.1.

	Nominal time			Dosing	Parameters		
	hours	min	Sample window (min)		PK sample	Vital signs	Adverse events
VISIT 1[1]							
Day1	-01		+55		X		X
	00	00		X[3]			
	00	30	+15		X		
	06		±60		X		
Day 2	24		±120		X		X
	30[2]		±180		X		
VISIT 2							
Day1	-01		+55		X	X	X
	00	00		X[4]			
	00	30	+15		X		
	01	00	±15			X	
	06		±60		X		
Day2	24		±120		X		X
	30[2]		±180		X		
Day 4	72		±120		X		X
Day 5	96		±120		X		X

Footer	Description
1	Visit 1 PK is only applicable if no recent half-life investigation is available. Please refer to section 8.1.1.1
2	Sample should only be collected from patients weighing ≥20.0 kg due to blood volume
3	Patient should be dosed with usual dose of previous FVIII product
4	Patient should be dosed with 60 U/kg BW N8-GP

3 Background information and rationale for the trial

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 Basic information

3.1.1 Haemophilia A

Haemophilia A is a recessive X-linked congenital bleeding disorder caused by mutations in the coagulation factor VIII (FVIII) gene on the long arm of the X-chromosome. According to the World Federation of Haemophilia (WFH), there are globally 320,000 – 340,000 patients with haemophilia A of which only approximately one quarter receives adequate care[1].

With a deficiency or absence of FVIII, activation of coagulation factor X becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis [2]. The haemostatic plug formed in these patients is, if formed, fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis, prolonged bleeding episodes and re-bleeding. The bleeding episodes in patients with severe haemophilia A are typically spontaneous or after mild trauma in joints, muscles and soft tissues. The bleeding episodes often occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis. In repeated cases this is followed by synovitis in the affected joint. Recurrent bleeding episodes in the same location, may lead to chronic arthropathy, muscular atrophy and deformities [3]. Bleeding episodes may occur in any organ or anatomic location including life-threatening bleeding episodes in the central nervous system (CNS), throat, neck, gastrointestinal tract, retroperitoneum or external injuries. As the Human Immunodeficiency Virus (HIV) and Hepatitis C (HCV) epidemics have subsided, the most serious complication to haemophilia treatment is inhibitor development. Inhibitors are allogeneic antibodies to FVIII that reduce or eliminate the activity of FVIII proteins in clotting factor concentrates. Inhibitors neutralize endogenous as well as administered FVIII. This condition develops in as many as 30–35% of previously untreated patients (PUPs) with severe haemophilia A [4,5]. Hence, the risk of inhibitor development related to the individual product should initially be evaluated in previously treated patients (PTPs) as these patients are considered to be at a low risk of developing inhibitors and therefore the most suitable trial population.

Haemophilia A is classified according to the plasma activity level of FVIII , as severe (FVIII activity level <1% of normal), moderate (FVIII activity level 1-5%) or mild (FVIII activity level 6-40%) [6].The distribution of severity among patients with haemophilia A in the world is difficult to estimate since many of the mild cases remain undiagnosed, but in countries with registries the numbers are about 50% severe, 20% moderate and 30% mild.

With access to treatment the life expectancy for Haemophilia A patients is estimated to 65 – 72 years. The major cause of death is intra-cerebral haemorrhage[7].

Haemophilia care is based on treatment of an active bleed with a haemostatic agent (on-demand use) or haemostatic agents are administered for longer periods to prevent bleeding (bleeding prophylaxis). The standard treatment of patients with haemophilia A is replacement of the FVIII protein. Currently available FVIII products are all lyophilised products for intravenous (i.v.) injection and either plasma derived or recombinant. This replacement therapy can be provided either as prophylaxis or as on-demand treatment of bleeding episodes.

3.1.2 N8-GP

Glycopegylated recombinant coagulation factor VIII (NNC 0129-0000-1003; hereafter referred to as N8-GP) represents a new recombinant human FVIII (rFVIII) with a longer terminal half-life ($t_{½}$) than currently available rFVIII products. Clinical areas of interest include prophylactic treatment 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.

N8-GP is a rFVIII covalently coupled to a single 40K-PEG (polyethylene glycol) molecule at a unique B-domain-O-glycan of turoctocog alfa (Novo Nordisk rFVIII product) resulting in a product consisting of one exact molecular form. Glycopegylation is carried out enzymatically whereby terminal sialic acids on the O-glycan structures are replaced with another sialic acid conjugated to a branched 2x20K PEG through a glycine-based linker. Since the O-glycan in turoctocog alfa is located in the B-domain, N8-GP is converted to rFVIIIa upon activation by thrombin. In this process, the pegylated activation peptide is released[8].

Human rFVIII is synthesised at Novo Nordisk A/S in Chinese hamster ovarian (CHO) cells, a mammalian cell line that is well characterised and has been used in the production of other recombinant proteins such as turoctocog alfa.

3.1.3 N8-GP clinical data

In accordance with the European Medicines Agency (EMA) Guidelines [9], the clinical programme for N8-GP was initiated with a pharmacokinetic (PK) trial in order to document the essential PK characteristics of the product and to acquire initial safety information.

In the first human dose trial (NN7088-3776) with N8-GP 26 adult PTPs with haemophilia A were dosed with single escalating doses, investigating safety and PK. The phase 1 trial has successfully been concluded with no safety concerns. No new FVIII inhibitors were detected and no treatment related serious adverse events (SAEs) were reported. The $t_{½}$ was approximately 1.6-fold prolonged compared to the patient's previous FVIII product.

A pivotal trial and a surgery trial, in adult and adolescent PTPs, are on-going. The pivotal trial 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 aims to document the safety and efficacy of N8-GP during major surgery.

In accordance with the EMA guideline and United States Food and Drug Administration (FDA) requirement, the current paediatric PTP trial can start when data from the pivotal trial are available from 20 patients each having used N8-GP for 50 exposure days (ED).

For further information on medicinal aspects, non-clinical data and quality of N8-GP please refer to the Investigator's Brochure (IB) [10].

3.1.4 Risks and benefits

N8-GP has a longer half-life than currently available rFVIII products and thus the potential to improve the quality of life for haemophilia A patients by offering a more convenient prophylaxis treatment, reducing the burden of frequent injections.

The glycoPEGylation of rFVIII has in animal models, and in a first human dose trial, been shown to result in a product with equivalent activity of FVIII but with a longer half-life. PEG is used widely in foods and drugs and is also used for pegylation of other licensed medicines including protein drugs for injection. Overall, it is evaluated as unlikely that adverse events will occur in humans specifically as a result of the PEG used to pegylate a biological product[11]. Non-clinical and clinical data on N8-GP do not suggest any alteration to the established rFVIII safety profile, or any additional risk of thromboembolic complications.

The primary concern in the clinical development of any new rFVIII product is the potential risk of the development of neutralising antibodies to FVIII. This N8-GP clinical trial has been designed in order to minimise the risk of inhibitor development. Selection of patients for the clinical trial is in accordance with current regulatory guidelines and recommendations and intends to minimise the risk of inhibitor formation and the variation in response parameters. Therefore, the risk of patients in this trial developing antibodies against N8-GP is considered to be low.

Eligibility criteria have been designed in order to exclude patients for whom treatment with N8-GP may present a risk. For example, patients with other severe conditions such as severe renal or hepatic dysfunction are excluded. The safety of the patients enrolled in the clinical trial will be carefully and closely monitored.

To minimise the switching between FVIII products, the patients can continue in the extension phase lasting until N8-GP is commercially available in the relevant countries or until the N8-GP programme is terminated, or otherwise required by national regulations.

For UK only: The end of the extension phase is defined as the planned last patient last visit date, May 2018.

3.2 Rationale for the trial

This trial will document the safety, including immunogenicity, efficacy and pharmacokinetics of N8-GP in PTPs below 12 years of age with severe haemophilia A (FVIII <1%). The design of the present trial (age distribution, number of exposure days, and number of patients in total and with PK) has been developed according to the EMA guideline [9] on clinical investigations of FVIII products effective from February 1st, 2012.

The current trial is part of a clinical development programme that includes a phase 1 trial (NN7088-3776, completed) and two on-going trials in patients 12 years of age and above: a pivotal phase 3a trial (NN7088-3859) and a surgery trial (NN7088-3860). A trial in previously untreated patients (NN7088-3908) is also planned.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

- To evaluate immunogenicity of N8-GP

4.1.2 Secondary objectives

- To evaluate safety other than immunogenicity of N8-GP
- To evaluate efficacy of N8-GP in prophylaxis and treatment of bleeding episodes
- To evaluate pharmacokinetic properties of N8-GP and compare to previous FVIII product (only PK assessments)
- To support a population based PK model for N8-GP (only PK assessments)
- To evaluate patient reported outcomes (PRO)

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Incidence of inhibitory antibodies against FVIII ≥0.6 Bethesda units (BU) during the main phase of the trial (from 0-26 weeks of treatment)

4.2.2 Secondary endpoints

Safety endpoints

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the extension phase of the trial (from 26 weeks to the last patient has completed the trial)
- Frequency of adverse events (AEs) including SAEs reported during the trial period

Efficacy endpoints

- Haemostatic effect of N8-GP when used for treatment of bleeding episodes and assessed as: Excellent, Good, Moderate, or None
- Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)
- Consumption of N8-GP per bleeding episode (number of injections and U/kg)
- Consumption of N8-GP during prophylaxis (number of injections and U/kg per month and year)

- Changes in PRO scores from baseline to the end of treatment in the main phase, and during the extension phase

Pharmacokinetics endpoints on previous FVIII product and N8-GP

- Incremental recovery (IR_{30min}), (defined as the peak level recorded 30 min after end of injection and reported as [U/mL]/[U/kg])
- Area under the curve (AUC), (h×U/mL)
- Terminal half-life ($t_{½}$), (h)
- Clearance (CL), (mL/h/kg)

Timeframes for evaluation of the endpoints

The pharmacokinetic endpoints on previous FVIII product will be based on assessments performed 2-6 weeks prior to initial dosing with N8-GP and up to 30 hours after administration of previous FVIII product. The pharmacokinetic endpoints on N8-GP will be based on assessments performed from 1 hour prior to and up to 96 hours after initial administration of N8-GP.

All safety and efficacy endpoints will be analysed and reported separately for the main phase (from 0-26 weeks of treatment) and the extension phase of the trial (from 26 weeks to the last patient has completed the trial).

5 Trial design

5.1 Type of trial

This is a multi-national, open-label single-arm, and non-controlled trial to assess safety including immunogenicity, efficacy and PK of N8-GP. The trial product will be given for prophylaxis and treatment of bleeding episodes to patients below 12 years of age with severe haemophilia A who have undergone >50 ED with previous FVIII products.

The trial consists of a main phase and an extension phase. The duration of the main phase for each patient will be approximately 26 weeks (corresponding to 50 ED). The screening period will add 2-6 weeks to each patient's trial participation. After completion of the main phase, the patients can continue in an extension phase lasting until N8-GP is commercially available in the relevant countries or until the N8-GP programme is terminated, or otherwise required by national regulations.

For UK only: The end of the extension phase is defined as the planned last patient last visit date, May 2018.

Patients will be recruited evenly from two age groups; 0-5 years and 6-11 years. 12 patients within each age group will complete PK assessment with both their previous FVIII product and with N8-GP.

The trial has one treatment arm. All patients will receive N8-GP twice weekly for prophylaxis. During the extension phase the prophylaxis regimen may be modified by the investigator. In addition, N8-GP will be administered to treat bleeding episodes during the trial period.

After approximately 25 patients in each of the two age groups (0-5 and 6-11 years) have completed the main phase, any patients who have not yet completed the main phase will be offered continued treatment in the extension phase. The patient's next scheduled visit will then be visit 8 (end of main phase).

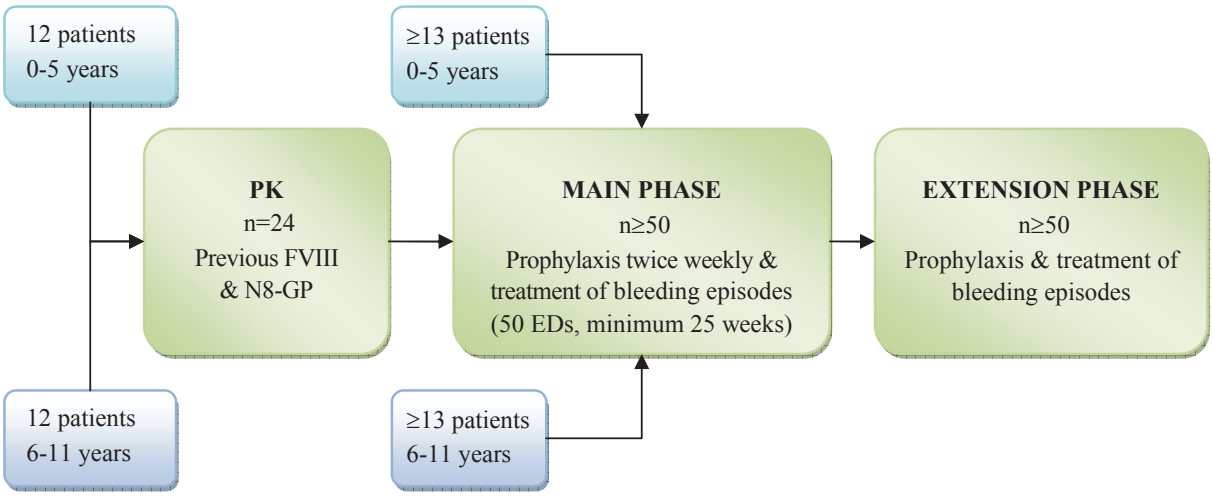

Figure 5-1 Trial overview.

5.2 Rationale for trial design

The trial design will provide information on safety, efficacy and PK of N8-GP in paediatric PTPs below 12 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 PTPs. In addition, PK of N8-GP will be evaluated and compared to PK of previous FVIII product.

The main phase of the trial will generate safety and efficacy, aiming for at least 50 ED per patient during a minimum of 25 weeks continuous treatment with N8-GP. This number of ED is required by the EMA guideline [9] for evaluation of new FVIII products. One 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.

Patients continuing in the extension phase must remain on the twice weekly prophylaxis regimen until one year of treatment is completed.

The trial does not include a placebo control group, as it is considered unethical to administer an ineffective treatment to patients with haemophilia.

There will be no randomisation due to the single-arm nature of the trial. However, the patients will be sampled equally from the two age groups at screening; 0-5 years and 6-11 years, both inclusive.

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" [9].

The rationale for choosing a multinational design is to ensure a sufficient screening pool of patients with this rare disorder, to meet local regulatory requirements and to represent the future patient population.

5.3 Treatment of patients

Approximately 70 patients will be screened, approximately 60 patients will commence treatment with trial product, and at least 25 patients in each age group are anticipated to complete the main phase of the trial.

The duration of single patient's treatment with N8-GP in the main phase of the trial is approximately 26 weeks corresponding to at least 50 ED. The duration of N8-GP treatment in the extension phase is until N8-GP is commercially available in the relevant countries or until the N8-GP programme is terminated, or otherwise required by national regulations.

For UK only: The end of the extension phase is defined as the planned last patient last visit date, May 2018.

For each patient 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. After the two initial doses of N8-GP, home treatment can be initiated. The patients will be on home treatment in between clinic visits in the remaining part of the trial. The investigator should ensure that patients and/or parent(s)/caregivers are sufficiently trained and confident with home treatment, including both prophylaxis and treatment of bleeding episodes. The patients can come to the trial site for their N8-GP injections until they are comfortable with home treatment.

5.3.1 Prophylaxis treatment

In the main phase and up to one year of treatment all patients will be treated prophylactically with a fixed dose of N8-GP via i.v. injection twice weekly. The dose is approximately 60 U/kg BW, however it is allowed to dose according to Table 5-1, enabling whole mL dosing. The table is based on a dose range of 50-75 U/kg BW. Doses should be separated by at least 3 calendar days and no more than 4 calendar days. The recommended dose level and range is chosen based on data from the phase 1 PK trial (NN7088-3776). The regimen is expected to give measureable FVIII trough activity >1% in the majority of patients.

Table 5-1 Prophylaxis doses

		500 U/vial		2000 U/vial	
BW (kg)	**Dose (U)**	**mL**	**Number of vials**	**mL**	**Number of vials**
10.0-13.9	750	6	1.5		
14.0-18.9	1000	8	2		
19.0-19.9	1250	10	2.5		
20.0-26.9	1500			3	0.75
27.0-35.9	2000			4	1
36.0-41.9	2500			5*	1.25
42.0-53.9	3000			6	1.5
54.0-70.0	4000			8	2

*2 mL should be aspirated from one vial and 3 mL from the second vial.

It is expected that two administrations of N8-GP per week will provide the same FVIII prophylactic coverage as three to four administrations of other currently marketed FVIII products due to the longer plasma half-life of N8-GP. However, an increase in dose frequency from twice weekly to every third day is permitted at the investigators discretion (based on bleeding pattern).

The dose to be administered at PK session Visit 2 must be 60 U/kg BW N8-GP.

5.3.1.1 Extension phase

All patients should continue the twice weekly or every third day prophylaxis regimen as prescribed in the main phase. However, after 12 months treatment with N8-GP (main phase and extension phase combined) the investigator is permitted to prescribe extra coverage before physical activities.

5.3.2 Treatment of bleeding episodes

Treatment requiring bleeding episodes will be treated with doses of N8-GP ranging from 20 to 75 U/kg BW, according to the severity and location of the bleeding episode. For recommended dose levels see Table 5-2.

The bleeding episode should be treated immediately at home if possible. The need for a second dose should be evaluated within eight hours of the initial dose. If two doses are not sufficient to treat the bleeding episode or in case of a severe bleeding episode the clinic must be contacted as soon as possible for further instructions and/or transport to the clinic for an unscheduled visit. Single doses should not exceed 75 U/kg BW and total daily dose should not exceed 200 U/kg BW. For bleeding severity definition, see section 8.5.1.

If a haemostatic response cannot be achieved after 48 hours using adequate doses of N8-GP when treating bleeding episodes, another FVIII product may be selected at the discretion of the investigator. This will result in withdrawal of the patient (see section 6.4).

Table 5-2 Recommended dose levels for treatment of bleeding episodes

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

All N8-GP doses used for treatment of bleeding episodes should be recorded as such. 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). 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.

In case a treatment requiring bleeding episode occurs between the two first scheduled doses of N8-GP (at Visit 2 and 3) the patient should return to the clinic for treatment of the bleeding episode with N8-GP. In case a bleeding episode occurs between Visit 2 and 3 that requires immediate treatment or the investigator judges it as necessary, the patient can treat the bleeding episode at home with a commercially available FVIII product, preferably the patient's previous product. This will not result in withdrawal of the patient (see section 6.4) and is not considered protocol deviation, however it is only allowed until Visit 3.

5.3.2.1 Treatment of suspected bleeding episodes

In case of abdominal or head trauma where there is a risk of a severe traumatic bleeding episode it is allowed to initiate treatment before symptoms arise. This is defined as preventive treatment of suspected severe traumatic bleeding episode. The recommended dose is equivalent to treatment of a severe bleeding episode (see Table 5-2).

In case of a suspected severe bleeding episode trial site must be contacted as soon as possible for further instructions and/or transport to the trial site for an unscheduled visit.

5.3.3 Surgery

Minor surgeries, dental extractions and placement of central venous access ports can be performed while participating in this trial by administering an extra dose of N8-GP equivalent to dose administered for a severe bleeding episode (see Table 5-2), or aligned to local practice.

Patients in need of major surgery will be withdrawn from the trial.

Definition of minor surgery: Any invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated.

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

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

5.3.4 Prohibited medication

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

- Bypassing products: activated recombinant factor VII (rFVIIa), plasma-derived prothrombin complex concentrates (pd-PCC) and plasma-derived activated prothrombin complex concentrates (pd-aPCC).
- Coagulation factor containing products: FVIII, FIX and FVII-containing products other than N8-GP, including fresh frozen plasma (FFP) and cryoprecipitate.
  Exception: Previous FVIII product is allowed until 72 hours before visit 2 and in case of home treatment of a bleeding episode requiring immediate treatment between Visit 2 and 3.
- Anti-coagulants such as heparin and vitamin-K antagonists. Heparin is allowed for sealing of central venous access ports.

5.4 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[12]. The longer half-life of N8-GP will allow for prophylaxis with fewer injections which may improve compliance and reduce the long term consequences of poor treatment compliance, such as deteriorating joint condition and mobility. It could also contribute to an improved quality of life for the patients and their families.

In the main phase of the trial, the dose is a fixed dose of approximately 60 U/kg BW twice weekly as i.v. injections, however doses in the range of 50-75 U/kg BW are allowed. The dose level is based on PK modelling of 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 (NN7088-3859) a fixed dose of 50 U/kg BW is administered i.v. every fourth day. Due to an anticipated higher CL of FVIII in children, compared with adults [13] a slightly higher and more frequent dose schedule has been chosen for this trial.

The maximum dose to be administered to a patient within 24 hours is 200 U/kg BW. The dose should be divided into several injections and will only be considered under exceptional circumstances such as serious trauma or severe bleeding episodes. Single doses must not exceed 75 U/kg BW.

Please refer to the IB and any updates hereof for further non-clinical and clinical data [8].

6 Trial population

6.1 Number of patients

Countries planned to participate: Australia, Brazil, Canada, France, Germany, Greece, Israel, Italy, Japan, Macedonia, Malaysia, Poland, Portugal, South Korea, Spain, Switzerland, Turkey, Ukraine, United Kingdom and United States

Planned number of patients to be screened: approximately 70

Planned number of patients to be enrolled/started on trial product: approximately 60

Planned number of patients to complete the main phase of the trial: at least 50

- Minimum 25 patients must be 0-5 years old at screening, of which 12 patients must complete PK assessment of previous FVIII product and N8-GP
- Minimum 25 patients must be 6-11 years old at screening, of which 12 patients must complete PK assessment of previous FVIII product and N8-GP

Recruitment of patients participating in PK sessions is preferred before recruitment of the remaining patients can be initiated.

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male patients with severe congenital haemophilia A (FVIII activity level < 1%, according to medical records)
3. Age below 12 years at screening
4. Weight ≥10 kg at screening
5. Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 0-5 years
6. The patient and/or parent(s)/caregiver are capable of assessing a bleeding episode, keeping an electronic diary (eDiary), capable of conducting home treatment and otherwise able to follow trial procedures.

6.3 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or to related products
2. Previous participation in this trial defined as withdrawal after administration of trial product
3. Dosing of any investigational drug within 30 days prior to screening except for turoctocog alfa. (**For Brazil, only**: Participation in other trials within one year prior to screening visit (visit 1) unless there is a direct benefit to the research subject at the Investigator's discretion)
4. Any history of FVIII inhibitors. For required documentation see section 8.2.1.1.
5. FVIII inhibitors ≥0.6 BU, measured by Central Laboratory at screening
6. HIV positive, defined by medical records, with CD4+ count ≤200/µL or a viral load of >400000 copies/mL. If the data are not available in medical records within last 6 months, CD4+ will be measured at the screening visit
7. Congenital or acquired coagulation disorders other than haemophilia A
8. Previous significant thromboembolic event (e.g. myocardial infarction, cerebrovascular disease or deep vein thrombosis) as defined by medical records
9. Platelet count <50,000 platelets/µL, measured by Central Laboratory at screening
10. ALT > 3 times above the upper limit of normal reference ranges, measured by Central Laboratory at screening
11. Creatinine level ≥1.5 times above the upper limit of normal reference ranges, measured by Central Laboratory at screening
12. Any disease (liver, kidney, inflammatory and mental disorders included) or condition which, according to the Investigator's judgement, could imply a potential hazard to the patient, interfere with trial participation or trial outcome
13. Surgery planned to occur during the main phase of the trial (exceptions are port placement, dental extractions, and minor, uncomplicated emergent procedures)
14. Ongoing treatment or planned treatment during the trial with chemotherapy, immuno-modulatory agents (e.g. intravenous immunoglobulin, routine systemic corticosteroids)
15. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from parents or child
16. Documented diagnosis of obesity (only for patients in the PK part) defined as body mass index (BMI) equal to or greater than the 95th percentile for age for children ≥2 years (please refer to Appendix A)

Patients who are non-compliant with any of the eligibility criteria, but included in the trial, should be withdrawn from N8-GP treatment immediately and attend an EOT Visit. If extraordinary circumstances speak in favour of maintaining the patient in the trial this is only acceptable if justified and approved by the independent ethics committee (IEC)/institutional review board (IRB), and if the regulatory authorities are notified according to local requirements.

6.4 Withdrawal criteria

The patient may withdraw at will at any time. The patient's parent(s) or legally acceptable/authorised representative (LAR) may withdraw the patient from the trial at any time.

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 any of the following applies:

1. FVIII inhibitor (≥0.6 BU) as confirmed by re-testing by Central Laboratory
2. Haemostasis not achievable with N8-GP. The bleed is not controlled after 48 hours of appropriate N8-GP treatment
3. Allergy/anaphylaxis related to trial product
4. Major surgery scheduled for the main phase of the trial (see section 5.3.3 for definition)
5. Use of coagulation factors other than N8-GP or anti-coagulants (see section 5.3.4 for details).
   Exception: Previous FVIII product is allowed until 72 hours before Visit 2 and in case of home treatment of a bleeding episode requiring immediate treatment between Visit 2 and 3. Heparin is allowed for sealing of central venous access ports.
6. Significant thromboembolic event
7. Incapacity or unwillingness to follow trial procedures

6.5 Patient replacement

Withdrawn patients may be replaced to ensure that 25 patients in each of the two age groups complete the main phase of the trial, achieving at least 50 ED. It is estimated that 60 patients must begin treatment with N8-GP in order to obtain 50 completed patients. This number may be adjusted during the trial based on the observed withdrawal rate.

6.6 Rationale for trial population

The current trial will enrol male patients with haemophilia A as they are a target population for N8-GP treatment. The age range is 0-11 years of age, recruited evenly with minimum 25 patients in the age ranges 0-5 years and 6-11 years respectively, at the time of screening. The patients will remain and count in the age group to which they were initially assigned throughout their participation in the trial. Since patients aged ≥12 years of age are already enrolled in the N8-GP pivotal trial (NN7088-3859), N8-GP will be investigated in all the age groups required by regulatory authorities.

A weight limit has been set at ≥10kg to ensure sufficient blood sampling volume can be drawn without jeopardising patient's safety.

The eligibility criteria are in line with previously studied recombinant FVIII products, and comply with the EMA guideline [9].

7 Trial schedule

Planned duration of recruitment period: 10 months

- Planned date for first patient first visit: February 2013
- Planned date for last patient last visit in main phase: August 2014
- Planned date for last patient last visit: May 2018

All investigators will be notified immediately when the required number of patients for PK sessions have been included.

All investigators will be notified immediately when the recruitment period comes to an end and the interactive voice/web response system (IV/WRS) will be closed for further screening.

End of trial (EOT) is defined as last patient last visit in the extension phase.

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[14], the Food and Drug Administration Amendment Act (FDAAA)[15], European Commission Regulation for EudraCT[16] 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.

In some countries Investigator and site information will be disclosed at public websites.

8 Methods and assessments

8.1 Visit procedures

Procedures for the scheduled visits are described in the section below and in the flow charts (section 2). For overview of the visit flow, please refer to Figure 8-1.

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

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

Throughout the trial all dosing visits should be scheduled taking into account the patient's prophylaxis dose days ensuring sufficient washout prior to the visit. All visits including PK visits should be rescheduled if the patient is in a bleeding state. Furthermore visits should be rescheduled in case of insufficient washout.

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

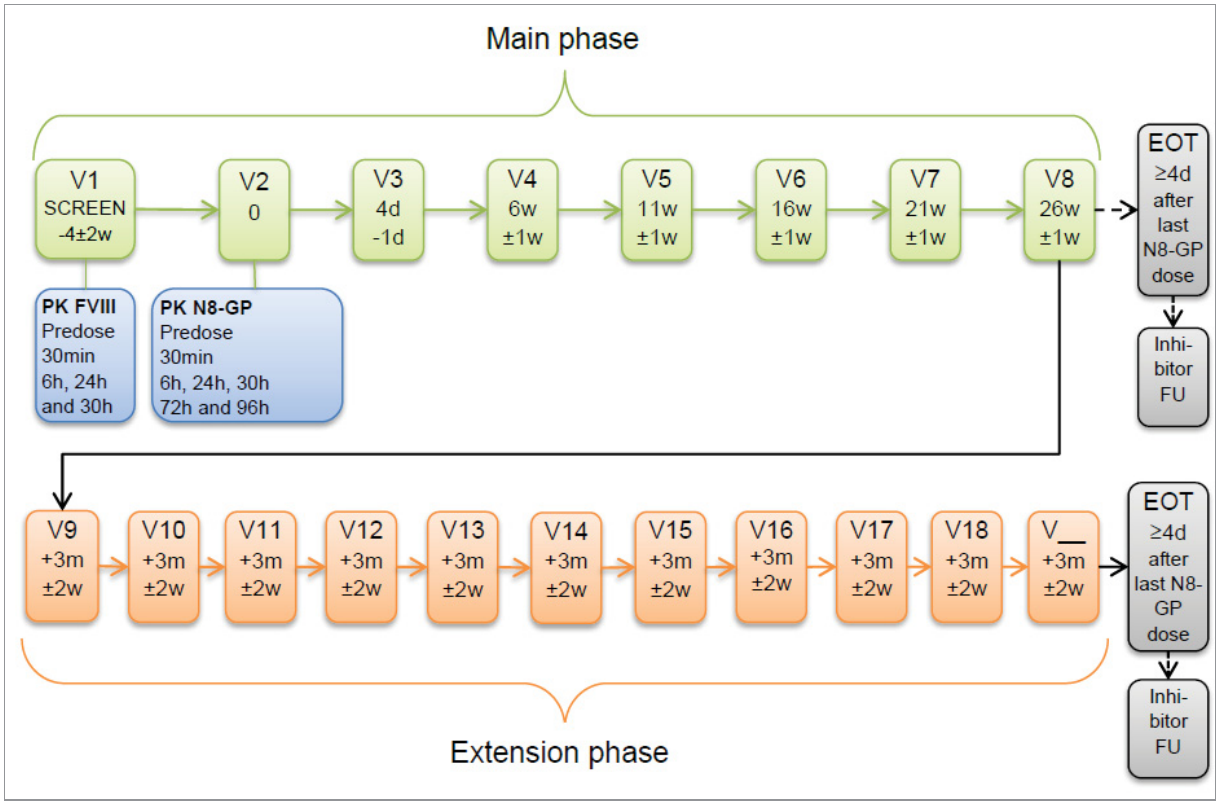

Figure 8-1 Overview of visits in main and extension phase

The <u>main phase</u> consists of the following visits:

Visit 1: Screening and PK of previous FVIII product for first 12 patients in each age group
Visit 2: 1st dose of N8-GP at the clinic and PK of N8-GP for first 12 patients in each age group
Visit 3: 2nd dose of N8-GP at the clinic 4 days after Visit 2. Start of home treatment schedule.
Visit 4-7: Dosing visits at the clinic. Home treatment in between visits.
Visit 8: End of main phase. Dosing visit at the clinic for patients continuing in the extension phase. For patients <u>not</u> continuing in the extension phase this is the EOT visit, unless inhibitor development necessitates further follow-up.

The <u>extension phase</u> consists of the following visits:

Visit 9 – Visit X (X = 10 and onwards): Dosing visits at the clinic every 3 months

End of trial: Last visit at the clinic, which should be scheduled ≥4 days after last N8-GP dosing.

Inhibitor follow-up (FU) visit: Conditional inhibitor follow-up visits, which must be conducted if patient is withdrawn due to FVIII inhibitor (≥0.6 BU) development.

Screening failure: Screening failures are defined as patients for whom the parent(s)/LAR have signed the Informed Consent Form, but fail to comply with the inclusion and exclusion criteria or if the consent is withdrawn after the first trial related procedure but prior to dosing. For screening failures the screening failure form must be completed with the reason for not continuing in the trial and a screening failure session must be made in the IV/WRS. SAEs and AEs from screening failures must be transcribed by the investigator into the eCRF. Follow-up of all AEs (including SAEs) should be carried out according to section 11.

Screening failures may be re-evaluated for participation in the trial and this is allowed once. It requires a renewed informed consent to be obtained from the parent(s)/LAR, a new eCRF should be started and the patient should be allocated a new patient number.

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 undertake the procedures for the last visit as soon as possible, if possible. If the patient is withdrawn prior to Visit 8, an end of main phase visit (Visit 8) should be scheduled, and if the patient is withdrawn after Visit 8, an EOT visit should be scheduled. The end of trial form must be completed, final drug accountability must be performed and the eCRF case book must be signed, even if the patient is not able to come to th site. All data collected in the period the patient participated in the trial will be entered into the eCRF. A withdrawal session must be performed in IV/WRS. If a patient is withdrawn due to inhibitor development, the patient must be followed according to section 8.1.9.

Although a patient is not obliged to give his 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) (AE, non-compliance with protocol or other) for discontinuation must be specified in the eCRF

8.1.1 Visit 1 Screening visit

Screening will take place within 4 weeks ± 2 weeks prior to visit 2. Prior to any trial related procedure the investigator must obtain informed consent from the patient's parent(s) and/or LAR. The patient should sign a child assent form if capable, and if required by local regulations. This can be performed on a separate day prior to Visit 1. For detailed description of the informed consent process, please refer to section 17.1.

It is voluntary for the patient to consent to having a blood sample drawn for genotyping, or if performed previously, to have genotype information made available for this trial. Consent for genotyping can be obtained at any time during the main phase of the trial

Visit 1 should be planned taking the patient's FVIII dose regimen in consideration since there should be at least 72 hours between last dose and laboratory assessments of Visit 1. Visit 1 is defined as the period until Visit 2.

Blood samples required at Visit 1 can be collected at any time from the day informed consent is signed until visit 2 (prior to N8-GP dosing) with the following restrictions:

- FVIII inhibitors, N8-GP binding antibodies, FVIII activity (trough). - Can be collected until two weeks prior to Visit 2. Washout should be ≥72 hours from last FVIII dosing. If the dosing interval in the patient's regular prophylactic regimen is less than 72 hours, washout is considered a trial-related activity, and informed consent must be obtained beforehand.
- Haematology, biochemistry and CD4+ (if applicable). - Can be collected until two weeks prior to Visit 2 to ensure that results are available for eligibility assessment at visit 2.
- Pre-dose PK sample of previous FVIII product does not have to be completed on the day of screening. - Can be collected until two weeks prior to Visit 2. Washout ≥72 hours from last FVIII dose.
- HIV and hepatitis testing (if applicable). - Any time prior to first N8-GP dose at Visit 2

- Lupus anticoagulant. - Any time prior to first N8-GP dose at Visit 2.
- Von Willebrand Factor (vWF). - Any time prior to first N8-GP dose at Visit 2.
- FVIII genotyping. - Any time during the main phase of the trial, if consent is provided.

At Visit 1 the patient and/or parent(s)/caregiver will receive an eDiary for recordings of all doses taken and all bleeding episodes occurring during the entire trial period. The investigator or delegated staff should ensure that patients and/or parent(s)/caregivers, are sufficiently trained and confident with the use of the eDiary. eDiary data should be reviewed at every visit, and additional training should be provided to the patient and/or parent(s)/caregiver if needed. Please refer to section 8.5 for required information on treatment and bleeding episodes.

Table 8-1 Visit 1 procedures

Visit 1 assessments to be performed and/or recorded in the electronic case report form (eCRF)
• Informed consent, signed and dated
• Pharmacogenomic (FVIII genotype) consent and FVIII genotype documentation (if applicable)
• Inclusion and exclusion criteria
• PRO questionnaires
• Demography
• Medical history and concomitant illness including blood type
• HIV, hepatitis and lupus anticoagulant status documentation. If not available, blood sampling for analysis hereof should be done (see below)
• Joint status
• Haemophilia treatment history including history of bleeding episodes
• Haemophilia details
• History of surgery

• Concomitant medication • Date and time of last coagulation factor administration • Body measurements (height and BW) • Physical examination • AEs
Blood sampling • Haematology • Biochemistry • Viral assessment (HIV and hepatitis), if applicable • CD4+, if HIV positive • Coagulation related parameters (Lupus anticoagulant and vWF), if applicable • FVIII activity (trough level) • FVIII inhibitors • N8-GP binding antibodies • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once)
Training and reminders • IV/WRS screening call • Dispensing of trial card and other patient information packets • eDiary dispensing and training. The patient and/or parent(s) should use the eDiary to record all bleeding episodes and previous FVIII product consumption until Visit 2 • ≥72 hours washout of FVIII product before scheduled Visit 2, otherwise Visit 2 has to be rescheduled • Patients participating in the PK part will have to undertake PK sampling for N8-GP at Visit 2, which will take place over 4 days

8.1.1.1 Visit 1 PK procedures

Only applicable for patients participating in PK assessments. For overview of PK sampling schedule please refer to flowchart (Table 2-3).

PK assessment of previous FVIII product can be transcribed if already available in patient's medical file and fulfilling the following requirements:

- PK assessment must have been performed within one year of Visit 1
- There must be minimum three PK time points available within 24 hours (one pre-dose and two post dose). The exact time points will be recorded in the eCRF
- Time since last dose of FVIII product prior to PK sampling should be known (wash-out period)
- The results of the FVIII activity tests for each time point (IU/mL or IU/dL or %)
- Method of laboratory assessment used (chromogenic or one stage clotting assay)
- Dose, time and trade name or generic name of FVIII product administered in connection with the PK assessment

Provided historical data are available, they should be recorded in the eCRF. PK patients with historical PK data will undergo a FVIII recovery test with previous product at visit 1.

Procedures for collecting PK samples of previous product

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

- Major surgery within one month
- Use of FVIII product within 72 hours
- Illness or fever within 48 hours
- In a bleeding state. If a treatment-requiring bleeding episode interferes with PK sampling and assessments, rescheduling of PK sessions can be done at the discretion of the Investigator taking the patient's safety and the bleeding episode severity into account

Assessments to be performed and/or recorded in the eCRF

- Administration of previous FVIII product with patient's usual dose
- Dose, date and time (start and stop of injection) to be recorded
- Actual date and time of completion of collection for each PK blood sample

Blood sampling

Blood sampling volumes should be respected, please refer to section 8.4.1.

- FVIII activity pre-dose. The sample requires ≥72 hours washout and should be collected within one hour prior to dose administration
- FVIII activity post-dose. Should be collected at 30min (+15min), 6h ±1h, 24h ±2h and 30h ±3h post previous FVIII product dosing. The 30h sample should only be collected from patients weighing ≥20.0 kg due to limit on blood sampling volume.

The blood samples should be taken from the contralateral arm as compared to the arm used for injection of previous FVIII product within a time period of at least 24 hours post-dosing.

If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injection. If so, the first portion of blood must be discarded (1 ml in patients < 20 kg of BW; 3-5 ml patients > 20 kg of BW)

Blood may not be drawn from port-a-cath or other central venous access devices. Blood may not be drawn from heparinised venous access devices

8.1.2 Visit 2 First N8-GP dosing for all patients

Visit 2 should preferably take place 2-6 weeks after Visit 1. Prolongation of the window is acceptable in case the patient experiences one or several bleeding episodes making it impossible to keep the scheduled date for Visit 2 due to washout restrictions.

The visit should be rescheduled if any of the following applies:

- Major surgery within one month
- Use of FVIII product within 72 hours
- Illness or fever within 48 hours

Table 8-2 Visit 2 procedures

Visit 2 assessments to be performed and/or recorded in the eCRF • Confirmation of inclusion and exclusion criteria • Withdrawal criteria (post N8-GP dosing) • PRO questionnaires if not performed at Visit 1 (must be completed prior to N8-GP dosing) • AEs • Concomitant illness • Concomitant medication • Physical examination incl. joint assessment • BW • Vital signs pre-dose and 60 min (±15 min) post N8-GP dosing • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported between Visit 1 and 2
Blood sampling • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose) • FVIII inhibitors • N8-GP binding antibodies • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once)
IV/WRS • N8-GP dispensing call for site dosing • Confirm the dispensing date for the dispensed trial products in IV/WRS Drug Accountability module.
Training, review and reminders • eDiary review of patient recorded FVIII product administrations and bleeding episodes from Visit 1 to Visit 2. Re-training of eDiary use, if applicable • ≥84hours washout of N8-GP before scheduled Visit 3 (96 ±2hours for PK patients), otherwise Visit 3 has to be rescheduled

If a treatment requiring bleeding episode occurs ≤48 hours after first N8-GP dose, an unscheduled visit should be made to the site and a rescheduled visit 3 should follow after 3±1 days.
If a bleeding episode occurs >48 hours after first N8-GP dose and is treated at the hospital/clinic this can be considered as visit 3 provided the required visit 3 assessments (except for FVIII trough level) are performed. This will not be considered a protocol deviation.

8.1.2.1 Visit 2 PK procedures

Only applicable for patients participating in PK assessments. For overview of PK sampling schedule, please refer to flowchart (Table 2-3).

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

- Major surgery within one month
- Use of FVIII product within 72 hours
- Illness or fever within 48 hours
- In a bleeding state. If a treatment-requiring bleeding episode interferes with PK sampling and assessments, rescheduling of PK sessions can be done at the discretion of the Investigator taking the patient's safety and the bleeding episode severity into account

Assessments to be performed and/or recorded in the eCRF

- Administration of N8-GP. The dose to be administered is 60 U/kg BW
- Dose, date and time (start and stop of injection) to be recorded
- Actual date and time of completion of collection for each PK blood sample

Blood sampling

Blood sampling volumes should be respected, please refer to section 8.4.1.

- FVIII activity pre-dose. The sample requires ≥72 hours washout and should be collected within one hour prior to dose administration
- FVIII activity post-dose. Should be collected at 30min (+15min), 6h ±1h, 24h ±2h, 30 ±3h, 72 ±2h and 96 ±2h post N8-GP dosing. The 30h sample should only be collected from patients weighing ≥20.0 kg due to limit on blood volume. 96 hour sample corresponds with Visit 3 N8-GP pre-dose sample.

The blood samples should be taken from the contralateral arm as compared to the arm used for N8-GP injection within a time period of at least 24 hours post-dosing.

If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injections. If so, the first portion of blood must be discarded (1 ml in patients < 20 kg of BW; 3-5 ml in patients > 20 kg of BW)

Blood may not be drawn from port-a-cath or other central venous access devices. Blood may not be drawn from heparinised venous access devices

8.1.3 Visit 3 Second N8-GP dosing for all patients

Visit 3 should take place 3-4 days (96 ±2hours for PK patients) after Visit 2 with ≥84 hours washout of N8-GP.

Table 8-3 Visit 3 procedures

Visit 3 assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • AEs • Concomitant illness and Concomitant medication • Vital signs pre-dose and 60 min (±15 min) post N8-GP dosing • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported between Visit 2 and 3
Blood sampling • Haematology • Biochemistry • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose). For PK patients the trough FVIII activity equals 96 hours PK sample • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once)
IV/WRS • N8-GP dispensing call for site dosing and home treatment • N8-GP drug accountability in IV/WRS drug accountability module
Training, review and reminders • eDiary review • Training in N8-GP handling and administration for home treatment. Trial staff should evaluate patient and/or parent(s)/caregivers confidence of home treatment and assessment of bleeding episodes. If preferred patients can come to the trial site for N8-GP administration • Remind of ≥84 hours washout of N8-GP before scheduled Visit 4, otherwise Visit 4 has to be rescheduled (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours) • Dispense N8-GP for home treatment, and give directions for use orally and/or in writing • Remind patients and/or parent(s)/caregiver to return all used vials at next visit for drug accountability

8.1.4 Visit 4 – 7 N8-GP dosing visits for all patients

Visit 4-7 should take place 6, 11, 16 and 21 weeks after Visit 2 respectively. Visit windows ±1 week. Before visits ≥84 hours washout is required (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours).

Table 8-4 Visit 4 - 7 procedures

Visit 4-7 assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • AEs • Concomitant illness and Concomitant medication • Physical examination incl. joint assessment, only at visit 4 and 6 • BW • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported since last visit
Blood sampling • Haematology (only at Visit 5)

• Biochemistry (only at Visit 5) • vWF (only at visit 5) • FVIII inhibitors • N8-GP binding antibodies • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose) • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once)
IV/WRS • N8-GP dispensing call for site dosing and home treatment • N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability module
Review and reminders • eDiary review • Remind of ≥84 hours washout of N8-GP before next scheduled visit, otherwise the visit has to be rescheduled (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours) • Training in N8-GP handling and administration for home treatment, if applicable (only at Visit 4) • Dispense N8-GP for home treatment, and give directions for use orally and/or in writing • Remind patient/parent(s) to return all used vials at subsequent visits for drug accountability

8.1.5 Visit 8 End of main phase

Visit 8 should take place 26 ±1 week from Visit 2. ≥84 hours washout required before visit (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours).

Table 8-5 Visit 8 procedures for patients continuing in the extension phase

Visit 8 assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • PRO questionnaires • AEs • Concomitant illness and Concomitant medication • Physical examination incl. joint assessment • Vital signs • Body measurements (height and BW) • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported since last visit
Blood sampling • Haematology • Biochemistry • FVIII inhibitors • N8-GP binding antibodies • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose)
IV/WRS • N8-GP dispensing call for site dosing and home treatment • N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability module

Review and reminders • eDiary review • Remind of ≥84 hours washout of N8-GP before next scheduled visit, otherwise the visit has to be rescheduled (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours) • Dispense N8-GP for home treatment, and give directions for use orally and/or in writing • Remind patient/parent(s) to return all used vials at subsequent visits for drug accountability

For patients NOT continuing in the extension phase

This is the last scheduled visit; unless the patient has developed an inhibitor, which would require further follow-up (see section 8.1.9). In addition to procedures listed in Table 8-5 the following procedures should be performed .

- IV/WRS – Treatment completion call
- eDiary review and collection of eDiary

The following procedures from table 8-5 can be disregarded:

- Administration of N8-GP. Dose, date and time to be recorded
- FVIII recovery
- N8-GP dispensing call in IV/WRS for site dosing and home treatment
- Reminders

8.1.6 Visit 9 – 16 N8-GP dosing visits for all patients

Visit 9 should take place 3 months (±2 weeks) after Visit 8. The intervals between Visit 9-16 should be 3 months (±2 weeks). Before visits ≥84 hours washout is required (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours).

Table 8-6 Visit 9 - 16 procedures

Visit 9 - 16 assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • PRO questionnaires, only at Visit 12 and 16 • AEs • Concomitant illness and Concomitant medication • Physical examination incl. joint assessment • Height, only at Visit 12 and 16 • BW • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported since last visit
Blood sampling • Haematology, only at Visit 10, 12, 14 and 16 • Biochemistry, only at Visit 10, 12, 14 and 16 • FVIII inhibitors

• N8-GP binding antibodies • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose)
IV/WRS • N8-GP dispensing call for site dosing and home treatment • N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability module
Review and reminders • eDiary review • Remind of ≥84 hours washout of N8-GP before next scheduled visit, otherwise the visit has to be rescheduled (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours) • Dispense N8-GP for home treatment, and give directions for use orally and/or in writing • Remind patient/parent(s) to return all used vials at subsequent visits for drug accountability

8.1.7 Visit 17 – X N8-GP dosing visits for all patients

Visit 17 should take place 3 months (±2 weeks) after Visit 16. Following Visit 17 visits should be scheduled with intervals of 3 months (±2 weeks) until end of trial. These additional visits are referred to as "Visit X", where X can be any sequential number from 18 and onwards.

≥84 hours washout required before visits where N8-GP is administered at trial site (Visit 18, 20, 22,…). If the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours.

Table 8-7 Visit 17 – X procedures

Visit 17 - X assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • PRO questionnaire (only HAEMO-Qol), only to be collected yearly at Visit 20, 24,.... • AEs • Concomitant illness and Concomitant medication • Physical examination incl. joint assessment • Height, only to be measured yearly at Visit 20, 24,…. • BW • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary, only at visit 18, 20, 22,… • Severity rating of bleeding episodes reported since last visit
Blood sampling – only at Visit 18, 20, 22,… • Haematology • Biochemistry • FVIII inhibitors • N8-GP binding antibodies • FVIII activity, trough (within 1 hour pre-dose) and recovery (30 min (+15 min) post-dose)
IV/WRS • N8-GP dispensing call for site dosing, only at visit 18, 20, 22,… • N8-GO dispensing call for home treatment • N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability

module
Review and reminders • eDiary review • For Visit 18, 20, 22,… Remind of ≥84 hours washout of N8-GP before next scheduled visit, otherwise the visit has to be rescheduled. If the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours • Dispense N8-GP for home treatment, and give directions for use orally and/or in writing • Remind patient/parent(s) to return all used vials at subsequent visits for drug accountability

8.1.8 End of trial visit

The EOT visit should take place at least 4 days after last dose of N8-GP. Before the EOT visit ≥84 hour washout is required (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours).

This is the last scheduled visit; unless the patient has developed an inhibitor, which would require further follow-up (see section 8.1.9).

Table 8-8 EOT visit procedures

EOT assessments to be performed and/or recorded in the eCRF • Withdrawal criteria • PRO questionnaire (only HAEMO-Qol) • AEs • Concomitant illness and Concomitant medication • Physical examination incl. joint assessment • Vital signs • Body measurements (height and BW) • Severity rating of bleeding episodes reported since last visit
Blood sampling • Haematology • Biochemistry • FVIII inhibitors • N8-GP binding antibodies • FVIII activity, trough
IV/WRS • Perform completion session in IV/WRS • N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability module
Review and reminders • eDiary review and collection of eDiary

8.1.9 Inhibitor follow-up visit

In case of withdrawal due to FVIII inhibitor development, the patient should be scheduled for an EOT Visit as soon as possible and within 1 week after a positive inhibitor test is confirmed via re-testing, preferably prior to initiation of treatment with another FVIII product. One month (4 weeks ± 2 weeks) after the EOT Visit the patient must attend a FU Visit, please see section 8.4.2.7. At each FU Visit, it will be evaluated if further FU Visits are required. The additional FU Visits will be arranged at intervals of 4 weeks ± 2 week as long as clinically warranted.

Table 8-9 Inhibitor follow-up visit procedures

The following will be performed and/or recorded in the eCRF • Concomitant medication • Date and time of last coagulation factor administration • Vital signs • Bleeding episodes since last visit • Inhibitor related AE
Blood sampling • FVIII inhibitor • N8-GP binding antibodies • FVIII activity and FVIII recovery, if applicable

8.1.10 Unscheduled visit

Unscheduled visits can be introduced if required by patients or trial site. An unscheduled visit can be performed any time after enrolment and until the EOT visit, either as a telephone visit or a site visit. Patients can attend an unscheduled visit due to a (severe) bleeding episode, suspicion of inhibitor development, any AE, or sampling for laboratory tests etc.

If the patient attends the site for an unscheduled visit, the Unscheduled Visit Form in the eCRF should be completed unless the patient visits/contacts the site regarding non-trial related activities or solely to obtain additional trial products or auxiliary supplies. If this is the case, only drug accountability is collected via IV/WRS and the patient notes should be updated accordingly.

8.2 Medical history and concomitant illness

Complete medical history and status on concomitant illness is to be obtained during the screening procedure. Medical history: is an account of medical events that the patient has experienced in the past. A concomitant illness is any illness that is present at the start of the trial (i.e. at Visit 1).

The information collected for concomitant illness and medical history should include diagnosis, date of onset, date of resolution or continuation. If diagnosis is unknown, the description of symptoms will be recorded. All chronic and all significant medical events within the last 5 years should be recorded.

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

Blood type: As part of the medical history evaluation of blood type parameter (0 type or non-0 type) should, if available and allowed by local law, be transcribed from medical records at screening visit.

All **vaccinations** in the last 12 months of screening should be captured as concomitant medication (section 8.3).

8.2.1 Haemophilia details

Haemophilia details transcribed from the patient's medical file will be reported separately in the eCRF. The following information will be captured:

- Date of diagnosis of haemophilia A
- Underlying gene defect (if known and consent provided for disclosure)
- Haemophilia A severity classification, corresponding to native FVIII activity level (%) from medical history
- Historical clinical suspicion of FVIII inhibitors (yes/no)
- Dates and results of historical FVIII inhibitor tests and/or
- Dates and results of historical FVIII recovery tests
- Number of previous ED. If it is not possible to count the actual number of exposures in the patient's medical records, the investigator should make a written statement with an estimate based on, eg, patient age, treatment frequency, medical history, discussion with previous doctor/transfer note, and other relevant information
- History of switching FVIII products (type of product, start and stop) if available
- Relatives with haemophilia A (yes/no). If yes – specify any relatives with haemophilia A and inhibitors (as recalled by patient or parent)

8.2.1.1 Documentation of inhibitor status

A positive historical inhibitor test excludes the patient. The historical laboratory cut-off value (assay sensitivity or lower limit of quantification) for a positive Bethesda inhibitor titre must not be higher than 1.0 BU/mL.

Documentation of inhibitor status should include:

Negative FVIII inhibitor test(s) and/or measurable FVIII activity level(s) within expected range(s) within the first 50 exposure days.

8.2.2 Haemophilia treatment history including history of bleeding episodes

History of haemophilia treatment and bleeding episodes transcribed from the patient's medical file will be reported separately in the eCRF.

For patients currently on prophylaxis, the following should be recorded:

- Current recombinant or plasma-derived FVIII product
- Dose and frequency of dosing of current treatment
- Dose and number of doses commonly used to treat a bleeding episode
- Number of different coagulation factor products previously used
- Number of months on prophylaxis
- Age at start of prophylaxis
- Bleeding rate (annualised)
- Number of bleeding episodes within the last 12 months while on prophylaxis
- Number of bleeding episodes within the last 12 months prior to prophylaxis, if applicable

For patients currently on on-demand treatment, the following should be recorded:

- Current recombinant or plasma-derived FVIII product
- Dose and number of doses commonly used to treat a bleeding episode
- Number of different coagulation factor products previously used
- Number of months currently on on-demand
- Bleeding rate (annualised)
- Number of bleeding episodes within the last 12 months

8.2.3 History of surgeries

Historical surgeries transcribed from the patient's medical file will be reported in the eCRF. The following information will be captured:

- Type of surgery
- Date of surgery
- Type of FVIII product used (rFVIII or pdFVIII)

8.2.4 Joint status at screening

Details on joints status, including historical information transcribed from the patient's medical file, will be reported separately in the eCRF:

- Current target joint(s), including number of bleeding episodes for the last 12 months in each current target joint. - A target joint is defined as a joint with three or more bleeding episodes

within a consecutive period of 6 months. When there has been no bleeding episode in the joint for 12 months, it is no longer considered a target joint.
- List of joints which during the patient's life have caused special problems, in terms of repeated or frequent bleeding episodes. This list can be compiled through discussion between the patient/ parent(s) and investigator
- List of joints with arthropathy

8.3 Concomitant medication

A **concomitant medication** is any medication, other than the trial product N8-GP, which is taken during the trial, including the screening period. Details of any concomitant medication must be recorded at trial entry (ie at the first visit). Any 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 is due to an AE, then this must be recorded and reported according to section 11. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

All **vaccinations**, including historical within the last 12 months of screening should be captured as concomitant medication.

8.4 Laboratory assessments

8.4.1 Blood sampling volume

Blood samples for laboratory analysis will be drawn as outlined in Table 2-1, Table 2-2 and Table 2-3. If available, local guidelines on blood sampling volumes for children should be followed, otherwise the blood sampling volume for the patient should follow recommendations in Directive 2001/20/EC [17]. According to the directive the recommended blood sampling volume for the patient should not exceed 1% of the total blood volume at one occasion or 3% within 28 days. Please see Appendix B for further information.

The investigator should ensure that the blood sampling volumes are not exceeded. A list of blood sampling prioritisation is given in Appendix B. Furthermore it is permitted to perform visit 1 procedures over several days to accommodate blood sampling from patients in the lowest weight group.

8.4.2 Central laboratory assessment

The central laboratory will analyse and report all central laboratory results to Novo Nordisk electronically in a manner where anonymity of patients will be maintained. The central laboratory results will be reported to the investigator by fax or email. Upon review of the results the investigator must sign and date the laboratory reports. A clinically significant value must be recorded as an AE, or if present at Visit 1 it should be recorded as concomitant illness.

A central laboratory manual describing procedures for blood sampling, sample handling, and shipment of samples will be provided. The laboratory manual will contain normal reference ranges for analyses performed at central laboratory. All materials such as test tubes and labels will be provided by the central laboratory.

All remaining central laboratory blood samples will be destroyed after finalisation of the clinical trial report, except for antibody samples. The antibody samples may be stored for possible future testing at least until evaluation of the clinical trial by regulatory authorities.

8.4.2.1 Haematology

- Platelet count (thrombocytes) ($x10^9$/L)
- Haemoglobin (mmol/L)
- Red blood cell count (erythrocytes) ($x10^{12}$/L)
- Mean corpuscular volume (MCV) (fL)
- Packed cell volume (haematocrit) (PCV) (%)
- White blood cell count (leucocytes) ($x10^9$/L)
- Differential white blood cell count (% or $x10^9$/L)
  - Lymphocytes
  - Monocytes
  - Neutrophils
  - Eosinophils
  - Basophils

During screening sampling and analysis can be performed at any time, provided laboratory results are available for Visit 2 evaluation of eligibility.

8.4.2.2 Biochemistry

- Sodium (mmol/L)
- Potassium (mmol/L)
- Creatinine (µmol/L)
- Albumin (g/L)
- Total bilirubin (µmol/L)

- Aspartate aminotransferase (AST) (U/L)
- Alanine aminotransferase (ALT) (IU/L)
- Gamma glutamyl transferase (GGT) (U/L)
- Alkaline phosphatase (IU/L)
- C-reactive protein (CRP) (mg/L)

Historical results within one month of Visit 1 may be used for preliminary Visit 1 evaluation of eligibility (ALT and creatinine), however laboratory results must be available for Visit 2 evaluation of eligibility.

8.4.2.3 Viral assessments

- HIV 1 and 2 antibodies
- CD4+ lymphocyte count

If the patient has previously been tested for HIV 1 and 2 antibodies and results are available in the medical records within the last 6 months, results can be transcribed to the eCRF and analysis for these parameters is not required. If the patient's HIV status is unknown or if negative HIV test results in the medical records are older than 6 months, HIV status should be tested at Visit 1. If the patient is HIV positive and the data of CD4+ count or a viral load is not available in medical records within the last 6 months, the CD4+ lymphocyte count must be determined and laboratory results must be available for Visit 2 evaluation of eligibility.

- Surface antigen of hepatitis B (HBsAg)
- Anti-HCV antibodies (hepatitis C)

If the patient has previously been tested for hepatitis B and C, and results are available in the medical records within the last 6 months, results can be transcribed to the eCRF and analysis for these parameters is not required.

8.4.2.4 Coagulation related parameters

- Lupus anticoagulant
- vWF

If the patient has previously been tested for lupus anticoagulant, and the result is available in the medical records, the result can be transcribed to the eCRF and analysis for this parameter is not required. The same applies to vWF, however two results are required. If only one result is available in the medical records, an additional sample should be collected at the screening visit.

8.4.2.5 FVIII genotype testing

FVIII gene mutation type is one of the most important predictors of the risk of inhibitor development in severe haemophilia A [18].

At Visit 1 all patients and parent(s)/LAR will be asked about previous FVIII genotype tests. If documentation hereof is not available FVIII genotype testing will be offered at Visit 1 or any visit in the main phase of the trial provided blood sampling volume limits are not exceeded, and if allowed according to local law.

Investigator, patients and parent(s) or LAR have the right to refuse to provide patients' FVIII genotype documentation or to refuse genotyping. The FVIII genotype is analysed using DNA isolated from patient's leucocytes at a laboratory selected by Novo Nordisk A/S. No further analysis will be carried out for any other parameters and samples will be disposed appropriately after the test. All test results are kept strictly confidential.

8.4.2.6 FVIII activity analysis

- FVIII activity (U/mL)

Blood samples for FVIII activity will be collected at every visit pre- and 30 min (+15min) post dosing, except for patients participating in the PK sessions at Visit 1 and 2, where FVIII activity samples are collected for PK assessment instead (see 8.1.1.1 and 8.1.2.1).

The blood samples should be taken from the contralateral arm as compared to the arm used for FVIII injection within a time period of at least 24 hours post-dosing. If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injection. If so, the first portion of blood must be discarded (1 ml in patients < 20 kg of BW; 3-5 ml in patients > 20 kg of BW)

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

- FVIII chromogenic assay
- FVIII one-stage clotting 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 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 is a modified one-stage aPTT (activated Partial Thromboplastin Time) assay based on the use of FVIII depleted plasma as assay matrix. The one-stage clotting assay measures the FVIII activity of the compound in a specific process (clot formation).

In each assay both an internal N8-GP specific calibrator and a standard human plasma calibrated against the WHO international FVIII standard are used as assay calibrators, and the FVIII activities of plasma samples and Quality Controls (QCs) are measured against the plasma calibrators (for measurements performed on previous product only the WHO international FVIII standard is used). The measured FVIII activities are reported in U/mL when obtained using N8-GP calibration and in IU/mL when obtained using the standard human plasma. The potency of the trial products will be measured using the same methods as for FVIII activity.

The PK analysis will be based on FVIII chromogenic data and FVIII one stage clot data. Both analyses will be performed at a laboratory selected by Novo Nordisk. Sites will receive results based on the FVIII chromogenic assay using the N8-GP specific calibrator.

FVIII chromogenic assay

The assay is a chromogenic two-stage activity assay (Coamatic® from Chromogenix, Milan, Italy) and is based on measuring the generation of factor Xa (FXa). FX is activated to FXa by FIXa and FVIII acts as a cofactor for the reaction and accelerates the conversion of FX to FXa. At optimal concentrations of Ca^{2+}, phospholipids and FIXa, and an excess of FX, the rate of activation of FX is linearly related to the amount of FVIII. The end product, FXa hydrolyses a chromogenic substrate, thereby releasing the chromogenic group p-nitroanilide, and the colour of this reaction is followed photometrically at 405 nm. The generated factor Xa, and thus the intensity of colour, is proportional to the FVIII activity in the sample.

FVIII one-stage clot assay

The assay is a aPTT-based one-stage clotting assay. Briefly, the aPTT reagent SynthASil from Instrumentation Laboratory (IL) is used as contact activator and to provide a lipid surface for the tenase and prothrombinase complexes. By performing the assay in a plasma matrix depleted of FVIII the reaction becomes dependent on the FVIII activity present in the plasma test sample. Ca^{2+} is added to restore the ability of the complexes to bind and assemble and the observed time to fibrin clot formation (turbidity measured as optical density at 880 nm) is inversely proportional to the FVIII activity.

8.4.2.7 Antibody and inhibitor assessments

Blood samples for assessment of antibody formation against N8-GP will be drawn at every visit (except visit 3), and potentially at an unscheduled visit(s) if there is any suspicion of inhibitor development. The samples will be analysed using the Nijmegen-modified Bethesda assay[19]

identifying inhibitory antibodies towards FVIII and using an assay capable of identifying antibodies towards N8-GP including rFVIII cross-reactivity.

A wash-out of 72 hours for previous FVIII product and 84 hours for N8-GP is required prior to blood sampling (if the patient has changed to an every third day treatment regimen the washout requirement is ≥72 hours).

N8-GP antibody assay

Binding antibodies towards N8-GP in plasma will be analysed on an ongoing basis.

The presence of N8-GP binding antibodies will be determined by a radioimmunoassay validated according to internationally recognised guidelines and recommendations. For samples with a result above the cut-off the presence of anti-N8-GP antibodies will be confirmed in a confirmatory assay by addition of excess of unlabelled N8-GP. Furthermore, cross-reactivity to rFVIII will be measured in the confirmatory assay in parallel with excess of un-labelled rFVIII. Only samples positive in the confirmatory assay will be characterized as anti-N8-GP or anti-rFVIII antibody positive.

Levels of N8-GP binding antibodies will be compared to pre-dose samples throughout the trial. If an inhibitor negative patient develops N8-GP binding antibodies and the incremental recovery value at that visit is less than 60% of screening value, a new inhibitor sample 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 can continue in the trial.

This algorithm will not apply for those who enter the trial with positive N8-GP binding antibodies and will not be triggered more than twice for an individual patient. Furthermore, a 7 days wash-out period will only be applied if the 84 hours wash-out is insufficient to avoid drug interference in the Bethesda inhibitor assay.

FVIII inhibitors

All patients will be examined for the development of FVIII inhibitors at scheduled visits. A positive inhibitor test is defined as ≥0.6 BU/mL. If FVIII inhibitor development is suspected (increased number of spontaneous bleeding episodes, bleeding episodes difficult to treat, recovery and trough levels below expected values) during the course of the trial, additional inhibitor tests can be taken at Unscheduled Visits. All inhibitor tests must be analysed by the Central Laboratory.

Blood samples for measurement of inhibitors towards FVIII will be analysed according to the Nijmegen modification of the Bethesda assay[19]. Any sampling for the inhibitor test must be performed at least 84 hours after last administration of N8-GP to allow for wash-out of the drug.

In the event that a patient has a positive inhibitor test (≥0.6 BU/mL), the patient must attend an Unscheduled Visit as soon as possible or within 1 week after the result is available to take a confirmatory inhibitor test on a separately drawn sample. This second sample should preferably be taken prior to any change of treatment. At this Unscheduled Visit, a recovery test must also be performed. If the second inhibitor test is also positive, the patient must be withdrawn by discontinuing trial product and attending the EOT Visit within 1 week after the result is available.

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

In case of inhibitor development the patient will be withdrawn from the trial. A follow-Up Visit must be scheduled 4 weeks ±2 weeks after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted (see section 8.1.9).

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

If the Investigator decides to send a sample for inhibitor testing to a local laboratory, the Investigator must also send a duplicate sample for inhibitor testing to the Central Laboratory. The data from the Central Laboratory will then be used in the official analysis. Any single positive inhibitor test must be reported as a MESI (please refer to section 11.1)

A patient having an initial positive inhibitor test and a second negative inhibitor test, will be regarded as inhibitor negative and continue in the trial.

If more than two patients are verified inhibitor positive, the safety committee will meet and a decision whether to continue, modify or stop the trial will be made, see section 11.6.1.1.

8.4.2.8 Antibody assessments in case of severe allergic reaction/anaphylaxis

If a patient experiences a severe allergic reaction/anaphylaxis, extra blood samples should be taken as soon as convenient, and not later than within 2 months after the event (please refer to the laboratory manual). The blood samples must be analysed for inhibitors and antibodies against trial product content (e.g. IgG/IgE and host cell proteins). Patients developing anaphylaxis should be carefully investigated and followed-up for inhibitor development.

If it is judged necessary, the same analysis will be performed for all patients enrolled in the trial using available blood samples.

- IgE, HCP
- Inhibitor

- IgG

8.4.3 Local laboratory assessments

The Investigator can at any time during the trial perform FVIII inhibitor tests and FVIII activity tests at his/her discretion. However, blood sampling volumes should be respected, please refer to section 8.4.1.

Please see Section 8.4.2.7 for procedures regarding inhibitor testing at local laboratory.

When FVIII activity measurements are made at local laboratories, clot or chromogenic assays must be used, and an N8-GP specific calibrator must be used. The N8-GP specific calibrator will be provided by Novo Nordisk together with a description of how to handle, store and use it.

If FVIII activity is analysed locally in connection with minor surgeries the results should be reported in the eCRF. All other local laboratory results should not be recorded in the eCRF, except for clinically significant findings which must be reported as an AE, or if present at Visit 1, should be reported as Concomitant Illness.

If a measured FVIII-activity is significantly different from the expected recovery the finding should be reported as an AE and control measurement should be performed, preferably at the Central Laboratory. The cause of the deviant FVIII activity (i.e. inhibitor development) should be investigated.

Storage, handling, and disposition of samples analysed at local laboratories, will be performed according to local laboratory procedures. Laboratory equipment in local laboratories may provide standard analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the eCRF or the trial database, but must be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and adverse events and report these according to this protocol.

Local laboratory results (reports) are considered source data and should be kept in the patients file for source data verification. The investigator or delegated person must sign, date and categorise (if applicable) the local laboratory results.

8.5 Assessments for efficacy

8.5.1 Bleeding episodes

During the entire trial period all bleeding episodes will be entered by the patient or parent(s)/caregiver in an eDiary provided by Novo Nordisk. In case a patient or parent(s)/caregiver

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.

If a patient experiences a treatment-requiring bleeding episode at home, treatment with N8-GP should be initiated irrespective of severity of the bleeding episode, please refer to section 5.3.2 for details. If the bleeding episode is mild/moderate, the treatment responsibility is with the patient's parent(s)/caregiver and/or Investigator. For severe bleeding episodes, the treatment responsibility is always with the Investigator and the patient's parent(s)/caregiver should contact the clinic and bring the patient for an unscheduled visit. Treatment of severe bleeding episodes should be initiated as soon as possible by the patient or parent(s)/caregiver, before coming to the clinic. It is the responsibility of the Investigator to assess the severity of the bleeding episodes and to ensure that all data are recorded correctly in the patient's eDiary.

For bleeding episodes the following will be recorded in Patient's eDiary or eCRF:

- Date and time of onset of bleeding episode
- Location of the bleeding episode
- Cause of bleeding episode (spontaneous, traumatic)
- Treatment requiring (Yes/No)
- Date(s) and time(s) of N8-GP administration (or previous FVIII product between Visit 1 and Visit 2)
- Dose(s) administered (mL)
- Stop of bleeding episode (date and time)
- Use of other haemostatic drug
- Pain relieving medication (yes/no)
- Other therapy used (compression, ice or other)
- symptoms (e.g. pain, swelling, loss of movement)
- Haemostatic effect evaluated after 8 hours (excellent, good, moderate or none)

- Categorisation of the bleeding episode (mild/moderate or severe) by the investigator

A need for haemostatic rescue therapy with another FVIII product will be assessed by the Investigator via phone or during the site visit. Patients treated with FVIII products other than N8-GP must be withdrawn from the trial (exception: previous FVIII is allowed until 72 hours before Visit 2 and in case of home treatment of a bleeding episode that requires immediate treatment between Visit 2 and 3).

The Investigator must carefully instruct the patient's parent(s)/caregiver in how to evaluate a bleeding episode, the haemostatic effect after treatment and how to complete the eDiary.

The entries made by the patient's parent(s)/caregiver in the eDiary will be reviewed by the Investigator together with the patient and parent(s)/caregiver during every visit to ensure consistency/compliance. The information in the patient's eDiary is regarded as source data. In case information missing in the eDiary is available in the medical records, this information can be used.

8.5.1.1 Severity of bleeding episodes

Mild/moderate: Bleeding episodes that are uncomplicated joint bleeding episodes, muscular bleeding episodes without compartment syndrome, mucosal- or subcutaneous bleeding episodes.

Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeding episodes must be categorised as severe. Muscle bleeding episodes with compartment syndrome and bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dL) should also be reported as severe. Traumatic bleeding episodes at other locations than described above can always be considered severe at the investigators discretion. Severe bleeding episodes should be treated immediately or at the local emergency room and trial personnel must be contacted. The details of severe bleeding episodes should be entered by the patient or parent(s)/caregiver in an eDiary. In case a patient or parent(s)/caregiver 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.

8.5.1.2 Haemostatic effect

Haemostatic effect of the treatment of bleeding episodes should be evaluated by the patient and/or parent(s)/caregiver 8 hours after the first injection and recorded in the eDiary.

Definition of haemostatic effect:

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 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

8.5.1.3 Classification of re-bleed

Will be performed by the trial statistician at the time of the statistical analysis according to the following criteria: A re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after completed treatment. If a bleeding episode occurs in the same location later than 72 hours after completed treatment it is considered a new bleeding episode.

8.5.2 Prophylaxis and preventive treatment

All prophylactic (scheduled regimen) and preventive doses of N8-GP will if possible be recorded in the eDiary. If this is not possible the information can be recorded in the eCRF.

The following information will be recorded in the eDiary or eCRF:

- Reason for treatment (e.g. prophylaxis, minor surgery, suspected severe traumatic bleeding episode, physical activity (physical activity only in extension phase after 12 months treatment in main and extension phase combined))
- Date and time of N8-GP administration
- Dose administered (mL)

8.5.3 Surgical procedures

For definition of allowed surgeries and recommended treatment please refer to section 5.3.3.

For minor surgeries, dental extractions and placement of central venous access ports the following information will be recorded in the eDiary or the eCRF:

- Date and time of preventive dose before surgery
- Type of surgery
- Indication for surgery
- Date of surgery
- Start and stop time of surgery
- FVIII activity measured locally, if applicable

8.6 Other safety assessments

8.6.1 Adverse events

Adverse events will be collected throughout the trial from the first trial related activity until EOT or inhibitor FU period according to procedures described in section 11.

For recording of bleeding episodes, please refer to sections 8.5.1 and 11.1.

8.6.2 Physical examination

Physical examination will be performed according to local procedure and should include:

- General appearance
- Ears, eyes, nose, throat and neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system, including mouth
- Musculoskeletal system
- Central and peripheral nervous system (general evaluation)
- Skin
- Lymph node palpation

Special emphasis should be applied to joint status, including target joints, arthropathy and severity hereof. Any findings should be recorded under 'Musculoskeletal system'.

Clinically significant findings present at screening should be recorded as concomitant illness and during the trial as AEs. Any changes in the examination which fulfil the criteria of an AE or an update to concomitant illness must be recorded as such (see section 11).

8.6.3 Vital signs

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

Vital signs assessment includes:

- Systolic and diastolic blood pressure (mm Hg)
- Pulse (beats/min)
- Body temperature (°C or °F)

Results of vital signs must be reported in the eCRF. Clinically significant findings present at screening must be documented as concomitant illness and during the trial as AEs.

8.7 Other assessments

8.7.1 Demography

Following information will be collected, deviation may occur as per local law and regulations:

- Date of birth and age (for Germany only: Year of birth and age)
- Ethnicity
- Race

8.7.2 Body measurements

- Body weight (registered with one decimal), wearing light clothing only and without shoes (kg or pounds)
- Height, without shoes (cm or inches)
- Body mass index calculation (kg/m^2), Visit 1 only (done automatically in the eCRF)

8.7.3 Patient reported outcomes

The PRO questionnaires should preferably be completed before other trial related activities take place at these visits. The PRO questionnaires measure disease and age specific health related quality of life (Haemo-QOL) and treatment satisfaction (Hemo-Sat). The patient(s) and parent(s)/LAR will continue with the same questionnaires as completed at Visit 1 regardless of changes in age.

The following PRO questionnaires should be completed by the patient and/or parent(s)/LAR:

Patient age	PRO instruments children	PRO instruments parents
0-3	-	Hemo-Sat (parents)
4-7	Haemo-QOL (CI)	Haemo-QOL (PI) Hemo-Sat (parents)
8-12	Haemo-QOL (CII)	Haemo-QOL (PII) Hemo-Sat (parents)

Patients not completing the main phase of the trial due to sufficient number of completers (refer to section 5.1) should not complete the PRO questionnaires at Visit 8 (end of main phase) or while being in the extension phase.

The PRO questionnaires are generic as well as disease and age-group specific and are designed to minimise the burden on the patient/parent/LAR in providing the information. The questionnaires are originally developed and validated in UK English, and have been translated and linguistically validated into other languages. However, a translated and linguistically validated questionnaire may not be available for all patients in all countries in which case the questionnaire is not to be completed. It is the responsibility of the Investigator to review the PRO questionnaires for possible AEs.

The PRO questionnaires are in paper, and should be forwarded to Novo Nordisk for data entry and analysis.

8.8 Patient compliance

Assessment of patient compliance with protocol procedures for determination of continuation in the trial will be done at the investigator's discretion. The Investigator or designee can at any time access the patient data from the eDiary in a web portal.

Compliance with the N8-GP treatment should be addressed at each visit. In the twice weekly prophylaxis regimen, doses should not be separated by more than 96 hours. If patients experience bleeding episodes due to exceeding the time between doses indicated above, the Investigator must retrain the patient/parent/caregiver. The training must be documented in the medical records.

If a patient deviates from the prescribed dosing regimen, but the dose is administered on the correct day, this is not considered a protocol deviation.

Treatment compliance:

- Drug accountability of all dispensed trial product will be performed on an on-going basis by trial staff and monitor (see section 9.4)
- Review of patient e-diary will be performed at every visit by the investigator/trial staff

8.8.1 Definition of treatment compliance in the main phase

Good compliance: If the prophylaxis dose of N8-GP is within the range 50-75 U/kg BW/kg for at least 80% of the prophylaxis injections, and the time interval between two prophylaxis injections is at least 3 calendar days and no more than 4 calendar days for at least 80% of the doses.

Less compliance: If the prophylaxis dose of N8-GP is outside the range 50-75 U/kg BW for more than 20% of the prophylaxis injections, or if there is less than 3 calendar days or more than 4 calendar days between two prophylaxis doses for more than 20% of the doses.

8.8.2 Definition of treatment compliance in the extension phase

Good compliance: If the prophylaxis dose of N8-GP is within the prescribed dose range for at least 80% of the prophylaxis injections, and is within the prescribed time interval between two prophylaxis injections for at least 80% of the doses.

Less compliance: If the prophylaxis dose of N8-GP is outside the prescribed dose range for more than 20% of the prophylaxis injections, or if it is outside the prescribed dose interval between two prophylaxis doses for more than 20% of the doses.

9 Trial supplies

Trial products comprise investigational medicinal product (IMP) and non-investigational medicinal products. Auxiliary supplies comprise supplies other than trial products.

9.1 Trial products

The following IMP (hereafter referred to as the trial product) will be supplied by Novo Nordisk:

- N8-GP 500 U/vial 53µg/vial
- N8-GP 2000 U/vial 211 µg/vial

N8-GP is supplied as a sterile, freeze-dried powder in a 2-8°C (36-46°F) stable formulation single use vial with a nominal content of 500 U/vial or 2000 U/vial to be reconstituted with 4.3 mL 0.9% Sodium Chloride Solution for i.v. injection.

After reconstitution each vial contains 125 U/mL or 500 U/mL N8-GP, respectively (4 mL can be withdrawn from the vial). Please refer to IB for additional information regarding the trial products.

NaCl solution will be provided by Novo Nordisk.

The reconstituted solution is colourless and clear to almost clear with a pH of 6.9. The reconstituted solution must not be further diluted. It is recommended to use N8-GP immediately after reconstitution. Exposure to direct sunlight and/or freezing must be avoided. N8-GP must not be added or mixed with other material (other than NaCl solution).

For detailed instructions regarding reconstitution of N8-GP, please refer to the Trial Materials Manual (TMM) provided by Novo Nordisk. The direction for use including reconstitution and administration procedure will be translated into local language(s) and given to the patient together with the trial product.

The BW for dose calculation will be measured at all relevant visits. After reconstitution, the appropriate volume will be drawn into a syringe. The contents of several vials may be combined in one syringe.

The appropriate volume of N8-GP should be administered as a slow bolus i.v. injection over approximately 2 minutes (from start to completion of injection).

N8-GP administrations will primarily be performed as home treatment injections, although patients can come to the trial site for N8-GP injections, if preferable. All patients and/or caregivers will be

instructed by the investigator or delegated site staff how to handle home administrations prior to the first N8-GP administration at home.

9.2 Non-investigational medicinal product(s)

For patients participating in the PK part: The patient will be dosed with his previous FVIII product or another commercially available FVIII product at Visit 1. In this case, the patient's FVIII product is defined as a non-IMP. Traceability of the FVIII products will be ensured by recording the brand or generic name and batch number in the eCRF.

Novo Nordisk will not provide the previous FVIII products but will reimburse trial sites for the cost of the patient's previous FVIII product used in the PK session at Visit 1.

For Germany only: In accordance with German GCP-Verordnung, the patient's previous FVIII product is also defined as an IMP. The patient's previous FVIII product could be any of the products currently authorised in Germany. The Summary of Product Characteristics (SmPC) for the actual IMP will be submitted.
In accordance with GCP-Verordnung §5, for IMPs (8) currently authorised in Germany, and which are intended for use in the clinical trial without any additional manufacturing steps, special labelling on the containers and outer packaging is not necessary. This is allowed by the concept of the clinical trial. The particulars according to GCP-Verordnung §5 (1) will be shown in an accompanying document.

For UK only: The patient's previous FVIII product is defined as an IMP. Previous FVIII products could include recombinant FVIII or marketed plasma derived FVIII products available in UK. In line with advice from the MHRA for a similar Novo Nordisk trial, the protocol does not need to specify the brand used. In addition, since the participants will already be taking the FVIII product, clinical trial specific labelling will not be required.

9.3 Labelling

Novo Nordisk will label and pack the trial product. Labelling will be in accordance with Annex 13[20], local law and trial requirements.

N8-GP and NaCl solution will be provided in separate boxes. All trial products will be packed open labelled.

The boxes will be provided with pre-printed labels. Each N8-GP box will have a unique Dispensing Unit Number (DUN) for identification and traceability.

For details on packaging and labelling of N8-GP, please refer to the TMM provided by Novo Nordisk.

9.4 Storage, accountability and destruction

N8-GP must be stored at 2-8°C, protected from light. NaCl solution must be store at 2-30°C. It is recommended to use the trial product immediately following reconstitution. If not used immediately, the reconstituted product can be stored in the vial for up to 4 hours at room temperature (below 30°C) or 24 hours at 2-8°C. Once the reconstituted product has been withdrawn into the syringe it must be used immediately. 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 not used if either is present.

The investigator must ensure the availability of proper storage conditions, and record and evaluate the temperature. The storage facilities must be checked frequently using a calibrated temperature recorder, as defined below. A temperature log for temperature recording (including actual minimum and maximum temperature on working days) must be kept at the trial site. The investigator must inform Novo Nordisk immediately if any trial product has been stored outside defined conditions (e.g. outside temperature range).The investigator should take appropriate action to avoid recurrence of the detected deviation.

The temperature recorder should be either:

- electronic with minimum interval of logging of 1 hour or
- manual with a min-max calibrated thermometer; the actual, minimum and maximum temperature must be logged

Trial products that have been stored improperly must not be dispensed to any patient before it has been re-evaluated and approved for further use by Novo Nordisk.

Destruction will be done according to local procedures after accountability is finalised at the site. Destruction of products must be documented.

The investigator or delegated person must carefully instruct the patient and/or caregivers in how to store the trial product at home and to read the labels with special attention to storage conditions and expiry.

Dispensing and Drug Accountability

The IV/WRS will allocate trial product in uniquely packed DUNs to the patient at each dispensing visit. According to the patient's BW, the correct number of DUNs will be allocated to the patient.

The investigator must indicate if the patient is prescribed nominal or whole mL dosing (see section 5.3.1).

No trial product should be dispensed to any person not enrolled in the trial.

The Investigator or delegated person e.g. trial nurse will perform drug accountability in the IV/WRS Drug Accountability module. All trial product vials (used, partly used, unused and lost/damaged) must be accounted for. Drug Accountability will not be performed for NaCl solution.

All used and partly used trial products must be returned at each visit. Unused trial products must be returned as instructed by the investigator (see TMM for further details). Drug accountability must be performed for all returned trial products at each visit.

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

All trial products must be retained for inspection 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 product.

For Japan only: Responsibility for storage and drug accountability of the trial products at the trial site rests with the head of the trial site. The head of the trial site should assign some or all of the responsibilities for accountability of the trial products at the site to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial products in accordance with procedures specified by the sponsor. 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

All medical devices used in this trial will be provided by Novo Nordisk such as syringes, butterflies, sterile swabs, vial adaptors etc.

For detailed information regarding auxiliary supply, please refer to the TMM.

10 Interactive voice/web response system

A trial-specific IV/WRS will be set up which can be accessed at any time via the internet or telephone. Some sessions may be available only as web sessions and can be accessed via internet. Access to the IV/WRS must be restricted to and controlled by authorised persons. As a minimum, the system will be used for:

- Screening of patients
- Screening failure
- Medication arrival
- Controlling of expiry date of trial product
- Ordering of trial product
- Dispensing of trial product
- Withdrawal
- Treatment completion
- Drug accountability
- Data change

Since trial product will not be shipped to the site before screening, the Investigator or delegated person should be encouraged to perform screening call in the IV/WRS immediately upon screening of the patient, otherwise the trial product may not be available for Visit 2.

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

11 Adverse events and technical complaints

11.1 Definitions

Adverse Event

An **AE** is any untoward medical occurrence in a patient administered a product, and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

Note: This includes events from the first trial related activity after the parent(s)/LAR have signed the informed consent and until post treatment follow-up period as defined in the protocol.

AEs include:
- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event: 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:
- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the patient has signed the informed consent.

An AE is either an SAE or a non-serious AE.

Serious Adverse Event

An 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 this definition.[d]

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

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

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

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

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 dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

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

Severity assessment definitions:

- **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.

The following terms and definitions are used when assessing the relationship between each 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

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered** - The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering** - This term is only applicable if the patient has completed the trial or has died from another AE. The condition is improving and the patient is expected to recover from the event.
- **Recovered 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** - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **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", "recovering", "recovered with sequelae" or "not recovered". 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.

11.1.1 Technical complaint

A **technical complaint** is any communication that alleges defects on trial supplies. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

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

11.1.2 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 should be reported according to the same reporting requirements and timelines as for SAEs (see section 11.2) irrespective of whether the MESI fulfils any SAE criterion.

The following are defined as MESIs in this trial:

1. **Medication errors concerning trial products:**
    - Administration of wrong drug
    - Wrong route of administration, such as subcutaneous instead of intravenous
    - Administration of a high dose with the intention to cause harm (eg suicide attempt)
    - Administration of an accidental overdose ie. a dose which may lead to significant health consequences, as judged by the investigator, irrespective of whether any SAE criterion is fulfilled

2. Inhibitor formation against FVIII

Blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk and if positive (BU ≥0.6/mL) should be reported as a MESI. A patient is only considered to be inhibitor positive if the inhibitor test is positive (BU ≥0.6/mL) at two consecutive tests - sampled preferably within 2 weeks. The result of the second test should be reported as follow-up on the MESI reported after the first test no matter if it is positive or negative.

3. Allergic reactions including anaphylactic reactions

Anaphylactic reactions should be diagnosed according to the criteria defined by [21]. Allergic reactions include but are not limited to any acute immunoglobulin E (IgE) mediated reaction or delayed type hypersensitivity (clinical signs may include various types of skin rashes) that do not meet the definition of anaphylaxis.

All hypersensitivity reactions reported should be followed up with a hypersensitivity follow-up form.

Clinical Criteria for Diagnosing Anaphylaxis (Sampson et al. 2006[21])

Anaphylaxis is highly likely when any ***one of the following three*** criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   - Respiratory compromise (e.g. dyspnea, wheese-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   - Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   - Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g. dyspnea, wheese-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (<90 mm Hg in children ≥10 years of age)

4. Thromboembolic events

Clinical signs or laboratory indications of any arterial or venous thromboembolic event.

5. Suspected transmission of an infectious agent via a trial product

11.1.3 Disease related bleeding episodes

Bleeding episodes and other symptoms related to bleeding episodes that are evaluated by the Investigator to be entirely caused by the underlying disease should not be reported as AEs/ SAEs unless the event is life threatening or fatal. A bleeding episode evaluated as related to trial product or procedure must be reported as an AE/SAE.

All bleeding episodes related to the underlying disease will be captured in the eCRF/eDiary.

11.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until the end of the post-treatment follow-up period. The events must be recorded in the applicable forms in a timely manner.

During each contact with the trial site staff (site visits and telephone contacts), the patient 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:

- IB, N8-GP
- European SmPC on previous FVIII product

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.

All AEs must be recorded by the investigator on the AE form. A separate AE form should be used for each diagnosis or sign and symptom. For each SAE a safety information form should be completed in addition to the standard AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form may be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial.

- The investigator must enter the AE in the eCRF and tick the seriousness and/or MESI box **within 24 hours** of obtaining knowledge of the SAE or MESI

- The safety information form (paper based form) must be completed and forwarded to Novo Nordisk by fax, email or courier **within 5 calendar days** of obtaining knowledge of the SAE or MESI.

If for some reason the eCRF is unavailable, the AE information should be reported to Novo Nordisk by fax, telephone, e-mail or courier within the same timelines.

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

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSAR) in accordance with local requirements and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP)[22]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change to any trial procedure.

Novo Nordisk must inform the IRBs/IECs in accordance with local requirement and GCP, unless locally this is an obligation of the investigator, as for example in the US.

Novo Nordisk must always inform the regulatory authorities in accordance with local requirements and GCP.

11.3 Follow-up of adverse events

All SAEs and MESIs must be followed up until the outcome of the event is “recovered”, “recovered 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” or “not recovered”, when the patient has completed the follow up period.

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

Non-serious AEs must be followed until the outcome of the event is “recovering”, “recovered” or “recovered 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. The end of the follow-up period is defined as the EOT visit or the last inhibitor follow-up visit for patients who have developed inhibitors. Cases of chronic conditions or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome “recovering” or “not recovered”.

Queries or follow-up requests from Novo Nordisk should be responded to within 13 calendar days.

The investigator must forward follow-up information on SAEs and MESIs within 24 hours of obtaining the follow-up information by updating the AE form in the eCRF and/or completing a new

safety information form marked follow-up, and forward this to Novo Nordisk. If for any reason the eCRF is unavailable or, after access to edit the eCRF is revoked, the investigator must record any SAE and MESI follow-up information on the provided paper CRFs and send the information by fax, telephone, e-mail or courier to Novo Nordisk.

The investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. If the eCRF is revoked after access to edit, the investigator must record any follow-up information on the provided paper CRFs.

11.4 Technical complaints and technical complaint samples

11.4.1 Reporting of technical complaints

All technical complaints on N8-GP and NaCl solution which occur from the time of first usage of trial supplies until the time of the last usage of trial supplies must be collected and reported to Novo Nordisk.

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 and must be completed for each trial product and for NaCl solution listed on the technical complaint form. If the technical complaint involves more than one batch number or DUN, a technical complaint form for each batch number or DUN must be completed.

The investigator must complete the technical complaint form in the eCRF, within the same timelines as for reporting AEs, SAEs and MESIs as follows:

- Technical complaint assessed as related to an SAE and/or MESI within 24 hours of the trial site obtaining knowledge of the complaint
- All other technical complaints within 5 calendar days

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. The monitor must initiate the shipment to Novo Nordisk and ensure the sample is sent in accordance with local regulations and as soon as possible to Novo Nordisk complaint centre. A print of the technical complaint form recorded in the eCFR must be sent with the sample.

The investigator should ensure that the technical complaint sample contains the batch number and, if available, the DUN.

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

Storage and shipment of the technical complaint sample must be done in accordance with the conditions prescribed for the product (see section 9).

11.5 Precautions

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

11.6 Committees related to safety

11.6.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal safety committee performing ongoing safety surveillance of N8-GP. The safety committee is working according to an internal guideline describing information to be reviewed, and actions and recommendations needed. The N8-GP safety committee meets every 3 months unless no new information is available and it is agreed to cancel the meeting. The safety committee can take action with regard to patient safety for all the N8-GP trials based upon observations of the overall safety information for N8-GP.

11.6.1.1 Stopping rules

If one of the below mentioned stopping criteria is fulfilled in the trial, enrolment of additional patients will be put on hold. All Investigators will be informed in writing. An urgent safety committee meeting will be called for to decide whether or not the trials can continue with or without modifications. During the evaluation of the stopping rules no new patient will be recruited. Dosing of patients on treatment may continue while further evaluation of the SAE/MESI is made by the safety committee unless otherwise decided by the safety committee. The evaluation of fulfilment of the below stopping rules by the safety committee will take into consideration whether or not the patient was dosed according to protocol.

The following will result in enrolment in the N8-GP phase III trials being put on hold:

- Inhibitor formation (Bethesda Unit of ≥0.6 BU/mL) in more than 2 patients. A patient has inhibitor formation if the patient has been tested positive for inhibitors at two consecutive tests from the central laboratory.
- Death related to trial product assessed by Novo Nordisk or by the Investigator

11.6.2 Data monitoring committee

As this trial is open-label and non-randomised a data monitoring committee will not be established. The internal N8-GP safety committee has the responsibility of overseeing the safety of the patients enrolled in the trial. Since the safety committee is responsible for all N8-GP trials it can take action with regard to patient safety based upon observations of the overall safety information for N8-GP.

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 data entry instructions.

The following will be provided as paper CRFs:

- Safety information forms
- Hypersensitivity follow-up form
- PRO questionnaires

In addition paper AE and Technical Complaint forms will be provided. These must be used if access to the eCRF is temporarily unavailable.

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

If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (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 is consistent with the source documentation. By electronically signing the case book, the investigator confirms that the information in the eCRF and including related forms are 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.

For corrections in paper CRFs the following apply:

Corrections to the data in CRFs may only be made by drawing a straight line (so that data is visible and readable) 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 CRFs have been removed from the trial site must be documented on a data clarification form or a monitor-initiated discrepancy form. If the affirmation statement for the patient has not yet been signed, any corrections must be approved by the investigator or her/his authorised staff. If the affirmation statement for the patient has already been signed, the investigator must approve any correction.

12.2 Case report form flow

The investigator must ensure that data are recorded in the eCRF or paper CRFs as soon as possible after the visit, preferably within 3 days. Once data have been entered, they will be available to Novo Nordisk for data verification and validation purposes.

Site specific CRF data (in an electronic readable format) will be provided to the investigator after the trial database is released, and access to update the trial data in the eCRF has been removed. These data will be retained by the trial site.

When the final clinical report is available the data will be archived by Novo Nordisk.

12.3 Electronic diary

Novo Nordisk will provide the patient or parent(s)/caregiver with an eDiary for electronic recording of details of their prophylaxis administration, bleeding episodes and treatment hereof, see section 8.5.1 and 8.5.2. The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

At Visit 1, the patient's parent(s)/caregiver will receive the eDiary and be trained in the use hereof by the investigator or delegated person. The eDiary will be returned by the patient's parent(s)/caregiver at either visit 8 (for patients not continuing in the extension phase) or at the EOT visit.

Data will be entered by the parent(s)/caregiver in the eDiary device. All data entered will be automatically transferred from the device to the electronic patient reported outcomes (ePRO)

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 contain built in edit checks, to ensure that all relevant questions are answered.

The eDiary device is not intended to support the subsequent review and modification of completed entries. In case corrections to the transferred data are needed, a query flow must be initiated by the investigator. Upon review by Novo Nordisk, data will be corrected accordingly by the vendor. An audit trail will be maintained.

Data in the ePRO database will be viewable to relevant site and Novo Nordisk personnel on a secure web portal, which is password protected. Data will be transferred to the Novo Nordisk clinical database at defined intervals.

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 visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The monitor should visit a site soon after a patient has been screened. After that the intervals between visits should not exceed 12 weeks.

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

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

All data must be verifiable in source documentation other than the eCRF. There must be a source document agreement at each site. There should only be one source defined at any time for any data element.

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

Treatment information on previous FVIII product (in screening phase) and N8-GP, and information on bleeding episodes will be collected in the eDiaries (please refer to section 8.5.1 and 8.5.2). The completed eDiaries are considered source data. The patient will only be identified by patient number and the monitor will verify and ensure that the eCRFs and eDiaries are completed.

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. 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 ID and trial identification number. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients in all presentations and publications as required by local, regional and national requirements.

15 Computerised systems

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

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

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11[23] and ICH E6 (EU directive for personal data protection). After trial finalisation, each trial site will be supplied with long-life DVDs. These DVDs will contain site-specific patient records including the patient's diaries 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 analyses.

All endpoints will be summarised in total and by age group (children 0-5 years old at screening and children 6 -11 years old at screening).

Summaries for continuous endpoints will include total number (N), mean (SD), median and min/max and for pharmacokinetic endpoints also geometric mean and CV%. Summaries for discrete endpoints will include N, number (n) and percentages (%) for each outcome category.

16.1 Sample size calculation

No formal sample size calculations have been performed. The sample size is based on the EMA guideline from July 2011 requirement[9].

16.2 Definition of analysis sets

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

Safety analysis set

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

Full analysis set

All trial patients allocated to treatment for which at least one of the PK or efficacy endpoints is assessed will be included in the FAS. The FAS trial patients will be analysed according to their received treatment.

Exceptional outlier PK profiles and/or individual plasma activities may be excluded when analysing PK endpoints based on the FAS. The decision to exclude data points from analysis of PK endpoints based on the FAS will be made during a review prior to database lock according to ICH-E9, and it will be the joint responsibility of the clinical pharmacology scientist and the trial statistician to decide upon this. The profiles or observations to be excluded from the FAS and the reason for their exclusion will be documented and signed by the clinical pharmacology scientist and the trial statistician as part of the database lock minutes. This will also be described in the clinical trial report. The documentation will be stored together with the remaining trial documentation.

16.3 Primary endpoint

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the main phase of the trial (from 0-26 weeks of treatment)

The patients with inhibitors will be listed. Only patients exposed to N8-GP will count.

The inhibitor rate will be calculated by dividing number of patients with neutralizing inhibitors with the number of patients with at least 50 exposure days. A one-sided, upper 97.5% confidence limit will be provided based on an exact calculation in the binomial distribution.

16.4 Secondary endpoints

All secondary safety and efficacy endpoints will be analysed and reported separately for the main phase (from 0-26 weeks of treatment) and the extension phase of the trial (from 26 weeks to the last patient has completed the trial).

16.4.1 Safety endpoints

- Incidence of inhibitory antibodies against FVIII ≥0.6 BU during the extension phase of the trial (from 26 weeks to the last patient has completed the trial)

The patients with inhibitors will be listed. Only patients exposed to N8-GP will count.

The inhibitor rate will be calculated by dividing number of patients with neutralizing inhibitors with the number of patients with at least 50 exposure days in the trial. A one-sided, upper 97.5% confidence limit will be provided based on an exact calculation in the binomial distribution.

- Frequency of adverse events (AEs) and serious adverse events (SAEs) reported during the trial period

All AEs, SAEs and MESIs will be summarised by frequency of events, frequency of patients with any event and rate of events per exposure year. The summaries will be made for the main part, the extension part and in total. Similar summaries cross-classified by severity and by causal relation to trial product will also be made.

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

Other safety assessments

All additional safety parameters such as laboratory parameters, vital signs and physical examinations will be summarised by visit for all patients. Furthermore, the laboratory reference ranges and abnormal laboratory values will be listed.

16.4.2 Efficacy endpoints

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

This endpoint will be summarised and listed.

In addition success will be defined as a response of Good or Excellent while failure will be defined as Moderate, None or Missing. Success/failure will be summarised both in total and by location of bleed, by cause of bleed and by country. The haemostatic effect as success/failure will also be summarised without missing included.

- Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)

The annualised bleeding rate (ABR) of treatment requiring bleeding episodes will be estimated by a Poisson regression model with log(prophylaxis duration) as offset and estimating over-dispersion by Pearsons scale. The estimated ABR will be presented together with a 2-sided 95% confidence interval.

The analysis of ABR will be repeated to investigate the potential impact of early withdrawals by imputing number of bleeding episodes for withdrawals. For patients withdrawing prematurely the number of bleeding episodes counting in the analysis will be imputed up to what they could be expected to have had if they had completed the trial. If e.g. a patient withdraws after 2 months with 3 bleeding episodes, but the patient should have been in the study for 12 months, then this patient will in the analysis count as having had 18 bleeding episodes in 12 months. This is similar to LOCF and will avoid positive bias occurring from patients with many bleeding episodes withdrawing early. For patients who withdraw within 1 month imputation, will be conducted by assuming an annualised bleeding rate of 24 for the missing period

ABRs will also be estimated by age group (0-5 years and 6-11 years), by cause of bleed, by location of bleed, by country, by month in trial and by time since last dose (0-24 hours, 24-48 hours, 48–72 hours and >72 hours). It will be tested if the bleeding rate increases with time since last dose. This will be done in a model similar to the primary model but with Day since last dose and Patient as fixed effects and for each patient there will be number of bleeding episodes for period 0-24 hours, 24-48 hours, 48-72 hours and 72-96 hours since last dose. The offset will be log(total exposure time in the period).

As a secondary analysis it will be investigated if time since last dose has impact on the ABR. Specifically this will be done by taking the average bleeding rates on day 1 and 2 after last dose and compare it with the bleeding rate from 48 hours and until next dose (max up to 96 hours). This will

be done in a model similar to the primary, but with a number of bleeds and an offset for each period, and with Patient as a fixed effect.

- Consumption of N8-GP per bleeding episode (number of injections and U/kg)

This endpoint will be summarised and listed.

- Consumption of N8-GP during prophylaxis (number of injections and U/kg per month and year)

This endpoint will be summarised and listed.

- Changes in PRO scores from baseline to the end of treatment in main phase, and during the extension phase

This endpoint will be summarised and listed, see also Section16.9.

16.4.3 Pharmacokinetics endpoints on previous FVIII product and N8-GP

- IR_{30min}
- AUC
- $t_{½}$
- CL
- and PK parameters as listed in Table 16-1

PK will be reported for both previous FVIII product and N8-GP for each assay and each calibrator used.

The PK parameters will be calculated using non-compartmental method as defined in Table 16-1. The actual samplings points will be used in the calculation of PK parameters. Profiles with a pre-dosing activity level >5% will be excluded from the PK analysis.

PK parameters will be log-transformed prior to analysis by an ANOVA model with patient and treatment as systemic effect, and estimates with 95 % confidence interval will be presented. Mean residence time (MRT) will not be log-transformed prior to analysis. This will be done in total and by age group. Furthermore individual data on PK endpoints will be summarised and listed.

Table 16-1 Definition and Calculation of PK Parameters

Parameter	Description	Calculation
IR_{30min}	Peak level recorded 30 min after end of injection, adjusted for dose ([U/mL]/[U/kg])	The incremental recovery is calculated as (FVIII:C activity measured in plasma 30 min after dosing - FVIII:C activity measured in plasma immediately before dosing) / (dose

		injected at time 0 min), where the dose is expressed as U FVIII product per kg BW
$t_{½}$	Terminal half-life	$t_{½} = \ln(2) / \lambda_z$, where λ_z is the terminal elimination rate. The terminal elimination rate will be estimated using linear regression on the terminal part of the time versus log(concentration) curve
AUC	Area under the concentration versus time from time zero to infinity	$AUC = AUC_{last} + (C_{(t)} / \lambda_z)$, where $C_{(t)}$ is the last measurable concentration
CL	Total plasma clearance of drug after intravenous administration	CL= Dose/AUC
C_{max}	The maximal concentration	The maximal observed concentration
MRT	Mean Residence Time	MRT = AUMC/AUC, where AUMC is the area under the first moment curve, i.e. the area under the curve $t \times C(t)$, calculated with the same method as AUC (linear trapezoidal method + extrapolated area)
V_{ss}	Apparent volume of distribution at equilibrium	$V_{ss} = CL \times MRT$
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the last measurable concentration	AUC_{last} is calculated using the linear trapezoidal method from time 0 to the time for the last measurable concentration. The concentration at time 0 will be estimated by log-linear extrapolation of the two initial post-administration concentrations (see below) and used in the calculation of AUC_{last}
AUC%Extrap	The extrapolated part of AUC	$100 \cdot (C_{(t)} / \lambda_z)/AUC$. This is not a PK parameter. It is only a description of the extent of extrapolation in the AUC calculation

$T_{½}$ (log transformed) will be compared between previous FVIII (international standard) and N8-GP (N8-GP specific calibrator) in an ANOVA model with patient and treatment as systematic effect. The estimated difference with a 2-sided 95% confidence interval will be reported.

FVIII:C activity will be summarised and listed for both previous FVIII and N8-GP and for each assay used.

The following plots will be made (for all and by age group as applicable):

- Mean curves for all PK patients for previous FVIII and N8-GP and for all assays used in the same plot (3 plots)
- Mean curves on log scale (means of log transformed values) (3 plots)
- Individual plots for previous FVIII and N8-GP and for all assays used in the same plots (one per patient)
- Individual plots on log scale for previous FVIII and N8-GP and for all assays used in the same plots (one per patient)

16.5 Interim analysis

All data from the main phase of the trial will be analysed and reported before the extension phase is completed. All main conclusions from the trial will be based on this reporting. An interim analysis may be performed on the extension phase to report all available data at the time of finalisation of the main phase.

A partial data base lock will be performed including data from the main phase of the trial, followed by full data base lock at end of trial.

The trial is an Open- Label and Non-Controlled trial and therefore it is not expected that the knowledge of results from the main phase of the trial will induce any bias into the extension phase of the trial.

16.6 Sequential safety analysis/safety monitoring

Novo Nordisk will constitute an internal safety committee to perform on going safety surveillance. The trial will be subject to stopping rules evaluated by this safety committee (section 11.6.1).

16.7 Reporting of FVIII genotype

Information about underlying gene defect of FVIII will be listed in the clinical trial report (not applicable for Brazil). No statistical analysis will be performed.

16.8 PK modelling

Population PK modelling will be done with the main scope of assessing the influence of demographic covariates such as body weight and possibly race on PK properties of N8-GP. The

population PK model of which maximum-likelihood parameter values are to be estimated is a linear one-compartment model parameterised with CL and volume of distribution V.

The final output of the PK modelling is predictions of FVIII activity exposure parameters (C_{max} and AUC_{τ}) at steady state in proposed prophylactic dosing regimens.

The population PK modelling is considered an exploratory analysis that will be reported outside the Clinical Trial Report. The PK assay results to be used for modelling are chromogenic FVIII activities measured against N8-GP laboratory standard material.

16.9 Patient reported outcomes

PRO data will be scored according to established scoring algorithms (where applicable) and changes from first assessment (at Visit 1 or Visit 2 prior to N8-GP dosing) to end of main phase of the trial, and yearly during extension phase of the trial will be summarised and listed using descriptive statistics. Further analysis will be performed separately by Novo Nordisk Health Economics Department.

17 Ethics

The trial will be conducted in compliance with the protocol, ICH GCP[22] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki[24].

After completion of the main phase, patients will continue with prophylaxis in the extension phase until N8-GP becomes commercially available in the patient's country. However, if the N8-GP programme is terminated or if the regulatory authorities in the patient's country reject the marketing application or if the commercialisation of N8-GP is not possible in the country, the extension phase will be stopped and treatment with N8-GP will be ended. If the patient does not wish to continue in the extension phase, he will consult with the investigator to decide on the best available treatment.

For UK only: The end of the extension phase is defined as the planned last patient last visit date, May 2018.

17.1 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[22] and the requirements in the Declaration of Helsinki[24].

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

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

Consent: As a child is unable to provide legally binding consent, informed consent must be sought from the 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.

Assent: When a patient deemed legally incompetent, such as a child, is able to give assent to decisions about participation in trial, the investigator must offer the possibility for the child to give assent in addition to the consent of the parent(s)/LAR. An "assent form" will be provided and can be used when appropriate and when the child is capable of forming an opinion and assessing.

The requirement for using a patient's parent(s)/LAR 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 will be obtained from the patient's parent(s)/LAR before any trial-related activity.

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 must be signed and personally dated by the person who seeks the informed consent.

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 the patient's parent(s)/LAR in a timely manner, and a revised written informed consent must be obtained.

FVIII 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 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 and/or the patient's parent(s)/LAR with the possibility to abstain from the genetic testing/collection of previous documentation, but still be able to participate in the trial.

Only the FVIII 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 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 Premature termination of the trial and/or trial site

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

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

Investigator must document and explain protocol deviations 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.

Rescheduling of visits due to bleeding episodes which results in deviations to visit windows are not considered protocol deviations.

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 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 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

Before a 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
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document. Must include documented GCP training or a certificate)
- Signed receipt of IB
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any substantial protocol amendment, if applicable
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any substantial protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution
- Financial agreement(s)
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Signed and dated Investigator Agreement
- Financial disclosure form for all investigators

For US: verification under disclosures per CFR of Financial Conflict of Interest.
For US sites: FDA Form 1572 must be completed by each investigator and individual clinical trial staff, if directly involved in the treatment or evaluation of research making a direct and significant contribution to data.

FDA form 1572:
For US sites:
- Intended for US sites
- Conducted under the investigational new drug (IND)
- All US investigators will sign FDA form 1572

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

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

As documented in writing by protocol signature, each investigator agrees to comply fully with ICH standards of current Good Clinical Practice (GCP), applicable regulatory requirements and the declaration of Helsinki.

21 Responsibilities

All staff (Novo Nordisk, site, laboratory, CRO etc) will conduct the trial in compliance with ICH GCP[22], applicable regulatory requirements and the Declaration of Helsinki[24].

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator should 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 unauthorised persons can get access to the data. The patient ID 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 (e.g. if he/she retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and 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.

The investigator to be designated with the responsibility to review and sign the Clinical Trial Report (Signatory Investigator) will be an investigator in this trial.

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.

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 invalidate the results of the entire trial.

At the end of the trial, one or more public disclosures 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.

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

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 support 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.

In a multi-centre trial based on the collaboration of all trial sites, any publication of results in a journal article must acknowledge all trial sites. Where required by the journal, the principal investigator from each site will be named in the acknowledgement.

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 the Novo Nordisk trial manager before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

22.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the ICMJE (sometimes referred to as the Vancouver Criteria [25]).

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

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

Novo Nordisk reserves the right to prior review of such publications and to ask for deferment of publication of individual site results until after the primary manuscript is accepted for publication.

22.2 Investigator access to data and review of results

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

Individual investigators will have access to their own research participants' data.

23 Retention of clinical trial documentation

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

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

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

24 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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, substantial protocol amendments, non-substantial 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.

Substantial protocol amendments must not be implemented before approval or favourable opinion, 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, substantial/non-substantial protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

25 Indemnity statement

Novo Nordisk carries product liability for its products, and liability is 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 by the clinics or doctors conducting experiments, or by persons for whom the said clinic or doctors are responsible.

Novo Nordisk accepts liability in accordance with local laws and guidelines.

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.

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Appendix A

Body Mass Index Chart

Body mass index chart

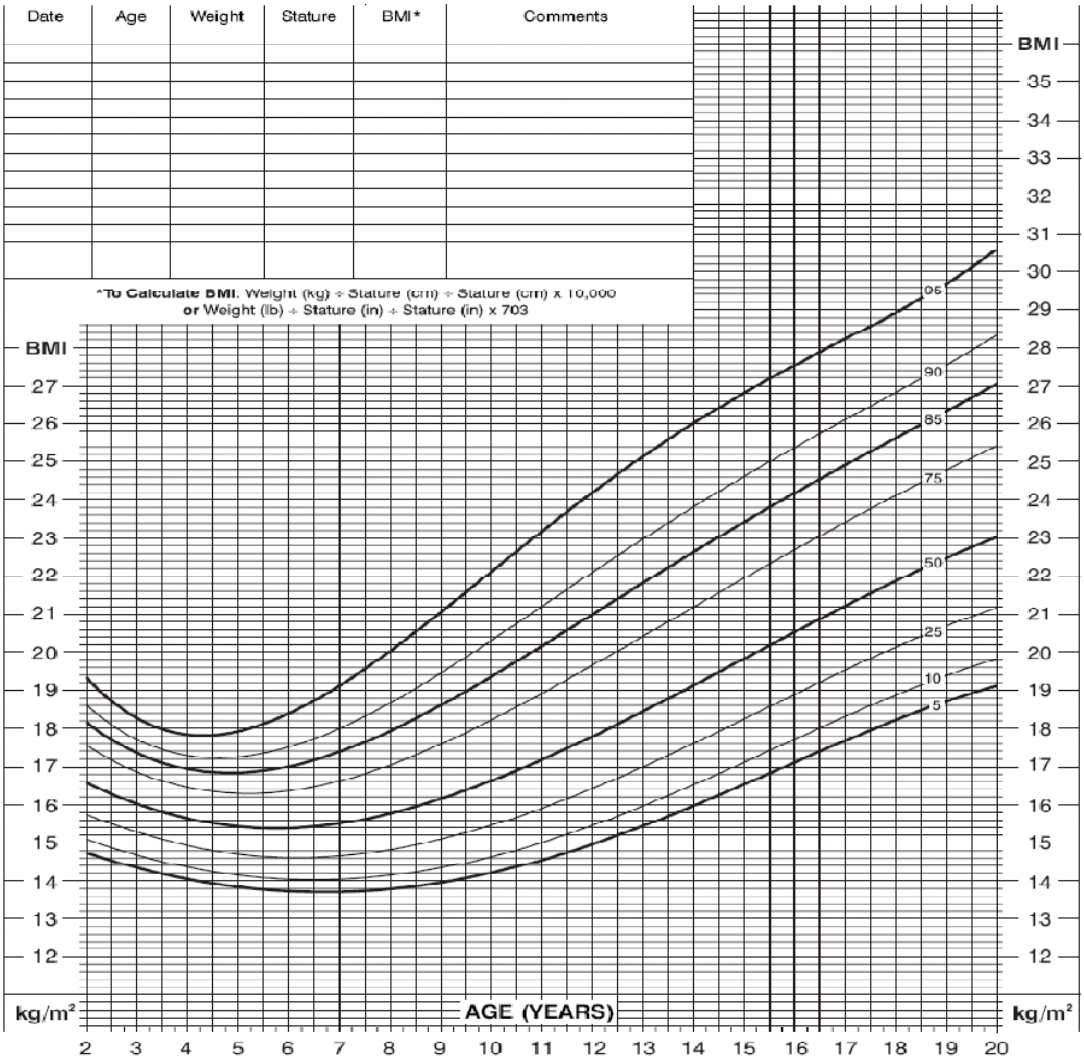
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
SAFER · HEALTHIER · PEOPLE™

Appendix B

Blood sampling volume rules

Blood sampling volume rules

The whole blood volume rule can be used as a general guide for estimation of blood sampling volumes in children. Table 1 below shows mean blood volumes per kg of body weight in children in accordance with Geigy Scientific Tables (Geigy Scientific Tables, 7th ed; 1970):

Table 1 Approximate blood volume per kg of body weight in children

Age	Blood volume per kg of body weight (mL/kg)
Children, 3 months	87
Children, 6 months	86
Children, 1 year	80
Children, 6 years	80
Children, 10 years	75

The blood sampling volume collected from the patient should not exceed 1% of the whole blood volume at any single occasion and 3% of whole blood volume in 28 days according to the European regulatory guidelines (Directive 2001/20/EC), or it should be according to local guidelines for blood sampling volumes. As a reference, table 2 below shows the estimated blood volume in children weighing 10-25 kg and maximum blood sampling volumes to be collected at any single time and within 28 days, respectively, according to EMA, and over a 24h period according to FDA guidelines.

Table 2 Estimated total blood volumes and maximum blood sampling volumes according to EMA and FDA

Body weight (kg)	Blood volume per kg body weight (mL/kg)	Total blood Volume (mL)	EMA: Maximum blood sampling volume at any single occasion (mL) 1%	EMA: Maximum blood sampling volume within 28 days (mL) 3%	FDA: Maximum blood sampling volume over a 24h period (mL)
10	80	800	8.0	24.0	20
11	80	880	8.8	26.4	22
12	80	960	9.6	28.8	24
13	80	1040	10.4	31.2	26
14	80	1120	11.2	33.6	28
15	80	1200	12.0	36.0	30
16	80	1280	12.8	38.4	32

Body weight (kg)	Blood volume per kg body weight (mL/kg)	Total blood Volume (mL)	EMA: Maximum blood sampling volume at any single occasion (mL) 1%	EMA: Maximum blood sampling volume within 28 days (mL) 3%	FDA: Maximum blood sampling volume over a 24h period (mL)
17	80	1360	13.6	40.8	34
18	80	1440	14.4	43.2	36
19	80	1520	15.2	45.6	38
20	80	1600	16.0	48.0	40
21	80	1680	16.8	50.4	42
22	80	1760	17.6	52.8	44
23	80	1840	18.4	55.2	46
24	80	1920	19.2	57.6	48
25	80	2000	20.0	60.0	50

Blood sample prioritisation

The below listed visits can in the lowest weight group lead to need of prioritisation of blood samples. It is therefore advised to draw blood samples in the below mentioned order (highest priority sample assigned 1).

It is permitted to perform Visit 1 blood sampling over several days to accommodate blood sampling from patients in the lowest weight group. It must be possible to evaluate eligibility criteria prior to Visit 2.

Visit 1:

1. FVIII inhibitors
2. N8-GP binding antibodies
3. FVIII activity
4. Haematology
5. Biochemistry
6. Viral assessments (HIV and HCV)
7. CD4+ lymphocyte count
8. Lupus anticoagulant
9. Von Willenbrand Factor
10. FVIII genotype testing

Blood sampling 1–7 must be performed prior to first N8-GP dosing.

Visit 5:

11. FVIII inhibitors
12. N8-GP binding antibodies
13. FVIII activity
14. Haematology
15. Biochemistry
16. Von Willenbrand Factor

Attachment I

Attachment versioning is independent of the protocol

List of key staff and relevant departments and CRO(s)

To be completed and maintained by the International Trial Manager

Mandatory for Japan: The responsibilities for each person/CRO must be described.

Sponsor:	Name:	Novo Nordisk
	Address:	
Sponsor's global medical expert:	Name:	
	Title:	
	Address:	
	Tel:	

If multinational trial or clinical pharmacology CDP trial:

International Trial Manager(s):	Name:
	Address:
	Tel:
	Fax:
	Mobile:
	E-mail:

List laboratory(ies), and other medical and/or technical department(s), and/or institutions involved in the trial. If multiple labs are used, describe what each lab analyses and/or responsibility. Also include which lab prepares the lab kit.

Laboratory(ies):

Name:

Address:

Tel:

Fax:

Mobile:

E-mail:

For eCRF, IV/WRS etc include each vendor:

EDC vendor:

Name:

Address:

Tel:

Fax:

Mobile:

E-mail:

IV/WRS vendor:

Name:

Address:

Tel:

Fax:

Mobile:

E-mail:

Attachment II

Insert name of country
Consider to include country code in header

It is mandatory to obtain the information listed in attachment II, but the information can be captured and updated elsewhere (eg in local regulatory documents).

List of key staff and relevant departments

To be completed and maintained for each country

If monitored by a CRO:

Monitor:

Name:

Address:

Tel of the CRO:

List for each trial site:

For countries in EU/EEA, state the National Coordinating Investigator

National Coordinating Investigator:	Name:	
	Title /qualification:	(Medical qualification [eg MD, DMD] of the investigator must be stated)
	Address:	
	Tel:	
	Fax:	
	E-mail:	
Investigator:	Name:	
	Title:	
	Address:	
	Tel:	

If the investigator is not a qualified physician, state responsible physician:

Responsible physician: Name:

Title/qualifications:

Address: (If different from above)

Tel:

Fax:

Mobile:

E-mail:

Mandatory if name(s) and address(es) of the laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial are not included in the protocol:

Local laboratory(ies): Name:

Address:

Tel:

Other medical and/or technical department(s) and/or institution(s):

Name:

Address:

Tel:

Substantial Protocol Amendment

no 1

to Protocol, final version 1, dated 07 September 2012

Trial ID: NN7088-3885

pathfinder™ 5

A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:

[redacted]

Table of contents

Page

1 Introduction including rationale for the substantial protocol amendment

This substantial protocol amendment is prepared primarily as a response to regulatory authorities requirements. Additionally, changes have been introduced to the dose table in order to extend weight predictions. Port restrictions text in connection with blood samplings has been removed, as it will be included together with detailed instructions for laboratory sampling in other trial documents (e.g. in the laboratory manual). Furthermore inconsistencies and typing errors have been corrected.

In this substantial protocol amendment:

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

2 Changes

List of abbreviations

$IR_{3}60min$	**incremental recovery**

1 Summary

Key secondary endpoints

- Incremental recovery (defined as the peak level recorded ~~3~~60 min after end of injection)

Key Inclusion Criteria

- Age below 12 years *at screening (for Turkey only: Age above 3 and below 12 years at screening)*
- Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 0-5 years *(for Turkey only: Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 3-5 years)*

Table 2–1 Flow chart for the main phase

Visit purpose	**Screen[1]**	**1st dose**	**2nd dose**	**N8-GP dosing visits**				**End of main phase**	**Inhibitor follow-up**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Time of visit (weeks)	**-4w**	**0**	**4 days**	**6w**	**11w**	**16w**	**21w**	**26w**	
Visit window	**±2w[2]**		**-1 day[3]**	**±1w**	**±1w**	**±1w**	**±1w**	**±1w**	
PATIENT RELATED INFO/ASSESSMENTS									
Date and time of last coagulation factor administration	X[8]	*X*							X
Washout requirements prior to next visit	X	X	X	X	X	X	X	X[13]	

4	If applicable, i.e. following patient/LAR consent and in accordance with local law. If genotype is available in medical file and patient/LAR has consented the results can be transferred. Consent for genotyping can be obtained at any time during the main phase of the trial, but preferably at Visit 1. *Not applicable for Israel*
10	At Visit 2 and 3 vital signs must be performed pre-dose and 60 min (±15 min) post-dose. *For patients participating in PK assessments vital signs must be measured prior to the 60 min sample collection at Visit 2.*
18	Genotype sample can be collected at any visit during the main phase of the trial following consent. Should preferably be collected at Visit 3 or later due to the volume of blood collected at Visit 1 and 2 *Not applicable for Israel.*

Table 2-2 Flow chart for the extension phase

Visit purpose	N8-GP dosing visits						EOT extension	Inhibitor follow-up
Visit number	V9, V10, V11	V12	V13, V14, V15	V16	V17, V19, V21,...[1]	V18, V20, V22,..[1]		
Time of visit (months)[2]	+3m +6m +9m	+12m	+15m +18m +21m	+24m	+27m +33m +39m +…	+30m +36m +42m +…	Min 4 days after last dose	
Visit window	±2w	±2w	±2w	±2w	±2w	±2w		
Washout requirements prior to next visit	X	X	X	X	X	~~X~~		

Table 2–2 Flow chart for PK assessments

Only applicable for the subset of patients participating in PK assessments. All time points are relative to completion of injection of FVIII product. Please refer to section 8.1.1.1 and 8.1.2.1.

	Nominal time			Dosing	**Parameters**		
	hours	min	Sample window (min)		PK sample	Vital signs	Adverse events
VISIT 1[1]							
Day 1	~~00~~*01*	~~30~~	~~±~~±15		X		X
VISIT 2							
Day 1	~~00~~	~~30~~	~~±15~~		~~X~~		X
	01	00	±15		*X*	X[5]	

Footer	Description
3	Patient should be dosed with *50 IU/kg BW* ~~usual dose of~~ previous FVIII product
4	Patient should be dosed with ~~60~~*50* U/kg BW N8-GP
5	*Vital signs must be measured prior to the 60 min sample collection*

4.2.2 Secondary endpoints

Pharmacokinetics endpoints on previous FVIII product and N8-GP

- Incremental recovery (IR_{3}~~3~~$_{60min}$), (defined as the peak level recorded ~~3~~*6*0 min after end of injection and reported as [U/mL]/[U/kg])

5.3.1 Prophylaxis treatment

Table 2–3 Prophylaxis doses

		500 U/vial		2000 U/vial	
BW (kg)	**Dose (U)**	**mL**	**Number of vials**	**mL**	**Number of vials**
10.0-13.9	750	6	1.5		
14.0-18.9	1000	8	2		
19.0-19.9	1250	10	2.5		
20.0-26.9	1500			3	0.75
27.0-35.9	2000			4	1
36.0-41.9	2500			5*	1.25
42.0-53.9	3000			6	1.5
54.0-70.0	4000			8	2
70.1-84.9	*5000*			*10*	*2.5*
85.0-99.9	*6000*			*12*	*3*
100.0-114.9	*7000*			*14*	*3.5*
115.0-120	*8000*			*16*	*4*

*2 mL should be aspirated from one vial and 3 mL from the second vial.

The dose to be administered at PK session Visit 2 must be ~~6~~*5*0 U/kg BW N8-GP.

6.2 Inclusion criteria

3. Age below 12 years at screening *(for Turkey only: Age above 3 and below 12 years at screening)*

5. Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 0-5 years *(for Turkey only: Documented history of > 150 ED to FVIII products for patients aged 6-11 years and > 50 ED to FVIII products for patients aged 3-5 years)*

8.1 Visit procedures

Visit 1: Screening and PK of previous FVIII product for ~~first~~ 12 patients in each age group
Visit 2: 1st dose of N8-GP at the clinic and PK of N8-GP for ~~first~~ 12 patients in each age group

8.1.1 Visit 1 Screening visit

It is voluntary for the patient to consent to having a blood sample drawn for genotyping, or if performed previously, to have genotype information made available for this trial. Consent for genotyping can be obtained at any time during the main phase of the trial. *Not applicable for Israel.*

- FVIII genotyping. - Any time during the main phase of the trial, if consent is provided. *Not applicable for Israel*

Table 8–1 Visit 1 procedures

Visit 1 assessments to be performed and/or recorded in the electronic case report form (eCRF) • Pharmacogenomic (FVIII genotype) consent and FVIII genotype documentation (if applicable). *Not applicable for Israel*
Blood sampling • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once). *Not applicable for Israel*

8.1.1.1 Visit 1 PK procedures

Assessments to be performed and/or recorded in the eCRF

- Administration of previous FVIII product ~~with patient's usual dose~~. *The dose to be administered is 50 IU/kg BW*

Blood sampling

Blood sampling volumes should be respected, please refer to section 8.4.1.

- FVIII activity post-dose. Should be collected at ~~3~~60min (~~±~~±15min), 6h ±1h, 24h ±2h and 30h ±3h post previous FVIII product dosing. The 30h sample should only be collected from patients weighing ≥20.0 kg due to limit on blood sampling volume.

If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injection. If so, the first portion of blood must be discarded ~~(1 ml in patients < 20 kg of BW; 3-5 ml patients > 20 kg of BW)~~.

~~Blood may not be drawn from port-a-cath or other central venous access devices. Blood may not be drawn from heparinised venous access devices~~

Table 8–2 Visit 2 procedures

Visit 2 assessments to be performed and/or recorded in the eCRF • Confirmation of inclusion and exclusion criteria • Withdrawal criteria (post N8-GP dosing) • PRO questionnaires if not performed at Visit 1 (must be completed prior to N8-GP dosing) • AEs • Concomitant illness • Concomitant medication • *Date and time of last coagulation factor administration* • Physical examination incl. joint assessment • BW • Vital signs pre-dose and 60 min (±15 min) post N8-GP dosing. *For patients participating in PK assessments vital signs must be measured prior to the 60 min sample collection* • Administration of N8-GP. Dose, date and time (stop of injection) to be recorded in the eDiary • Severity rating of bleeding episodes reported between Visit 1 and 2
Blood sampling • FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once). *Not applicable for Israel*

8.1.2.1 Visit 2 PK procedures

Assessments to be performed and/or recorded in the eCRF

- Administration of N8-GP. The dose to be administered is ~~6~~50 U/kg BW

Blood sampling

Blood sampling volumes should be respected, please refer to section 8.4.1.

- FVIII activity post-dose. Should be collected at ~~3~~60min (~~±~~±15min), 6h ±1h, 24h ±2h, 30 ±3h, 72 ±2h and 96 ±2h post N8-GP dosing. The 30h sample should only be collected from patients

weighing ≥20.0 kg due to limit on blood volume. 96 hour sample corresponds with Visit 3 N8-GP pre-dose sample.

If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injection. If so, the first portion of blood must be discarded ~~(1 ml in patients < 20 kg of BW; 3-5 ml patients > 20 kg of BW)~~.

~~Blood may not be drawn from port-a-cath or other central venous access devices. Blood may not be drawn from heparinised venous access devices.~~

8.1.3 Visit 3 Second N8-GP dosing for all patients

Table 8–3 Visit 3 procedures

Blood sampling
• FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once). *Not applicable for Israel*

8.1.4 Visit 4 - 7 N8-GP dosing visits for all patients

Table 8–4 Visit 4 - 7 procedures

Blood sampling
• FVIII genotype (can be collected at any time during the main phase of the trial, if consent is provided. Only to be collected once). *Not applicable for Israel*

8.1.7 Visit 17 – X N8-GP dosing visits for all patients

Table 8-7 Visit 17 – X procedures

IV/WRS
• N8-GP dispensing call for site dosing, only at visit 18, 20, 22,…
• N8-G*P~~O~~* dispensing call for home treatment
• N8-GP drug accountability for all dispensed and returned vials must be recorded in IV/WRS drug accountability

8.2.1 Haemophilia details

- Underlying gene defect (if known and consent provided for disclosure). *Not applicable for Israel*

8.4.2.5 FVIII genotype testing

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

8.4.2.6 FVIII activity analysis

The blood samples should be taken from the contralateral arm as compared to the arm used for FVIII injection within a time period of at least 24 hours post-dosing. If, because of poor venous access, repeated venepuncture is not possible, the blood may be sampled from a venflon or a butterfly on the contralateral arm as compared to the arm used for injection. If so, the first portion of blood must be discarded ~~(1 ml in patients < 20 kg of BW; 3-5 ml in patients > 20 kg of BW)~~.

In each assay both an internal N8-GP *product* specific *standard* ~~calibrator~~ and a standard human plasma calibrated against the WHO international FVIII standard are used as assay calibrators, and the FVIII activities of plasma samples and Quality Controls (QCs) are measured against the plasma *standards* ~~calibrators~~ (for measurements performed on previous product only the WHO international FVIII standard is used). The measured FVIII activities are reported in U/mL when obtained using N8-GP calibration and in IU/mL when obtained using the standard human plasma. The potency of the trial products will be measured using the same methods as for FVIII activity.

The PK analysis will be based on FVIII chromogenic data and FVIII one stage clot data. Both analyses will be performed at a laboratory selected by Novo Nordisk. Sites will receive results based on the FVIII chromogenic assay using the N8-GP *product* specific *standard* ~~calibrator~~.

8.4.3 Local laboratory assessments

When FVIII activity measurements are made at local laboratories, clot or chromogenic assays must be used, and an N8-GP *product* specific *standard* ~~calibrator~~ must be used. The N8-GP *product* specific *standard* ~~calibrator~~ will be provided by Novo Nordisk together with a description of how to handle, store and use it.

9.1 Trial products

The reconstituted solution is colourless and clear to almost clear with a pH of 6.9. The reconstituted solution must not be further diluted. It is recommended to use N8-GP immediately after reconstitution. Exposure to direct sunlight and~~/or~~ freezing must be avoided. N8-GP must not be added or mixed with other material (other than NaCl solution).

11.4.1 Reporting of technical complaints

All technical complaints on N8-GP, ~~and~~ NaCl solution *and auxiliary supplies* which occur from the time of first usage of trial supplies until the time of the last usage of trial supplies must be collected and reported to Novo Nordisk.

Technical complaints must be reported on a separate technical complaint form and must be completed for each trial product, ~~and~~ NaCl solution *and auxiliary supplies* listed on the technical complaint form. If the technical complaint involves more than one batch number or DUN, a technical complaint form for each batch number or DUN must be completed.

16.4.3 Pharmacokinetics endpoints on previous FVIII product and N8-GP

- $IR_{~~3~~60min}$

PK will be reported for both previous FVIII product and N8-GP for each assay and each ~~calibrator~~ *standard* used.

Table 16-1 Definition and Calculation of PK Parameters

Parameter	Description	Calculation
$IR_{~~3~~60min}$	Peak level recorded ~~3~~*6*0 min after end of injection, adjusted for dose ([U/mL]/[U/kg])	The incremental recovery is calculated as (FVIII:C activity measured in plasma ~~3~~*6*0 min after dosing - FVIII:C activity measured in plasma immediately before dosing) / (dose injected at time 0 min), where the dose is expressed as U FVIII product per kg BW

T½ (log transformed) will be compared between previous FVIII (international standard) and N8-GP (N8-GP *product* specific *standard* ~~calibrator~~) in an ANOVA model with patient and treatment as systematic effect. The estimated difference with a 2-sided 95% confidence interval will be reported.

FVIII:C activity will be summarised and listed for both previous FVIII *product* and N8-GP ~~and~~ for each assay *and each standard* used.

17.1 Informed consent

FVIII genotype testing/collection of previous genotype documentation

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

Protocol Amendment

no 2
to Protocol, Final version 2.0
dated 02-November 2012

Trial ID:NN7088-3885

A Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Trial phase: 3
Applicable to all countries

Amendment originator:

[redacted]

[redacted]

Table of contents

1 Introduction including rationale for the protocol amendment

In the current version of the NN7088-3885 (pathfinder™5) protocol (section 6.4) it is stated that a patient must be withdrawn if the following applies:

- FVIII inhibitor (≥0.6 BU) as confirmed by re-testing by Central Laboratory

With this current wording, a patient with a low titre inhibitor that does not interfere with prophylaxis or treatment of bleeding episodes with N8-GP must be withdrawn from the trial. This is not in line with current treatment practices in haemophilia A where patients with low titre inhibitors continue treatment with FVIII until the inhibitor interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (Collins et al 2013, BJH). In addition, some low titre inhibitors may be transient, disappearing within 6 months of initial documentation, despite recent antigenic challenge with factor concentrate (Srivistava et al 2012, Haemophilia).

Therefore the withdrawal criteria section 6.4 of the protocol will be amended to allow patients with a low titre inhibitor (≤ 5 BU), that does not result in clinically ineffective treatment with N8-GP, to continue in the trial. Furthermore section 8.1.9 and 8.4.2.7 are updated to reflect this change of process.

Throughout the protocol the reference unit for Inhibitors has been aligned to BU.

Furthermore a few other updates have been performed concurrently:

- Lupus Anticoagulant has been added to table 2.1 Flow chart main phase and table 2.2 Flow Chart extension phase, at the inhibitor follow up visit
- Minor update to section 5.1 to allow for patients to continue in the extension phase as soon as 25 patients for each cohort have completed the main phase.
- Section 6.1 has been updated to reflect actual participating countries.
- Section 8.4.2.6 FVIII results to investigators changed to one-stage clotting assay to align across N8-GP project.

- Section 8.4.2.7 has been updated to include an assay to analyse for antibodies towards PEG.
- Section 8.4.2.8 has been updated to clarify that FVIII activity should be analysed in case of severe allergic reaction.
- Section 9.3 updated to allow labelling by third party vendors.
- Section 11 added suspected transmission of infectious agents to the SAE definition.
- Section 13 - Extended the window for monitoring during the extension phase to reflect the visit scheduled.
- Section 16.4.2 clarified that multiple bleeding from the same event or time point will be counted as one bleeding episode.
- Minor updates to section 16.5 Interim Analysis.

In this protocol amendment:

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

2 Changes

Protocol originator:

Name: [redacted]

List of abbreviations:

…

MAA Marketing Authorization Application

…

NDA New Drug Application

2 Flow chart

Table 2 1 Flow chart for the main phase

Lupus anticoagulant included at inhibitor follow up visit

Visit purpose	Screen[1]	1st dose	2nd dose	N8-GP dosing visits				End of main phase	Inhibitor follow-up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	
Time of visit (weeks)	-4w	0	4 days	6w	11w	16w	21w	26w	
Visit window	±2w[2]		-1 day[3]	±1w	±1w	±1w	±1w	±1w	
PATIENT RELATED INFO/ASSESSMENTS									
Informed consent	X								
In/exclusion criteria	X	X							
Pharmacogenomic (FVIII genotype) consent and documentation (if applicable)[4]	X								
Withdrawal criteria		X	X	X	X	X	X	X	
PRO questionnaires	X[5]							X	
Concomitant illness	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X
Demography	X								
Haemophilia details	X								

Visit purpose	Screen[1]	1st dose	2nd dose	N8-GP dosing visits				End of main phase	Inhibitor follow-up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	
Time of visit (weeks)	-4w	0	4 days	6w	11w	16w	21w	26w	
Visit window	±2w[2]		-1 day[3]	±1w	±1w	±1w	±1w	±1w	
Haemophilia treatment history	X								
History of bleeding episodes	X								
History of surgery	X								
Medical history[6, 7, 15, 17]	X								
Joint status at screening	X								
Date and time of last coagulation factor administration	X[8]	X							X
eDiary data review		X	X	X	X	X	X	X	
Bleeding episodes (severity rating)		X	X	X	X	X	X	X	X
ADVERSE EVENTS and CLINICAL ASSESSMENTS									
Adverse events	X	X	X	X	X	X	X	X	X[9]
Body measurements - Height - Body weight	 X X	 X		 X	 X	 X	 X	 X X	
Physical examination	X	X		X		X		X	
Vital signs		X[10]	X[10]					X	X
LABORATORY ASSESSMENTS									
Haematology	X		X		X			X	
Biochemistry	X		X		X			X	
Antibodies - FVIII inhibitors - N8-GP binding antibodies	 X X	 X X		 X X	 X X	 X X	 X X	 X X	 X X
PK sampling (FVIII)[11]	X	X							
FVIII activity - FVIII trough level - FVIII recovery	 X	 X X[12]	 X X	 X X	 X X	 X X	 X X	 X X[13]	X[14] X[14]
Hepatitis screen	X[15]								
HIV - HIV antigen/antibody screen test - CD4+ T cells	 X[15] X[16]								
Lupus anticoagulant	X[6]								*X*
von Willebrand factor (vWF)	X[17]				X[17]				
FVIII genotype testing (if applicable)[4]	X[18]								

Visit purpose	Screen[1]	1st dose	2nd dose	N8-GP dosing visits				End of main phase	Inhibitor follow-up
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	
Time of visit (weeks)	-4w	0	4 days	6w	11w	16w	21w	26w	
Visit window	±2w[2]		-1 day[3]	±1w	±1w	±1w	±1w	±1w	
TRIAL MATERIAL									
Administration of previous FVIII product (if applicable)	X[19]								
Administration of N8-GP		X	X	X	X	X	X	X[13]	
N8-GP dispensing		X	X	X	X	X	X	X[13]	
Drug accountability		X	X	X	X	X	X	X	
IV/WRS call	X	X	X	X	X	X	X	X	
TRAINING AND REMINDERS									
Trial card dispensing	X								
Patient information packs	X								
Home treatment training			X	X[20]					
eDiary dispensing and training	X	X[20]							
Washout requirements prior to next visit	X	X	X	X	X	X	X	X[13]	

Table 2 2 Flow chart for the extension phase

Lupus anticoagulant included at inhibitor follow up visit

Visit purpose	N8-GP dosing visits						EOT extension	Inhibitor follow-up
Visit number	V9, V10, V11	V12	V13, V14, V15	V16	V17, V19, V21,...[1]	V18, V20, V22,..[1]		
Time of visit (months)[2]	+3m +6m +9m	+12m	+15m +18m +21m	+24m	+27m +33m +39m +…	+30m +36m +42m +…	Min 4 days after last dose	
Visit window	±2w	±2w	±2w	±2w	±2w	±2w		
PATIENT RELATED INFO/ASSESSMENT								
Withdrawal criteria	X	X	X	X	X	X	X	
PRO questionnaires		X		X		X[3, 4]	X[4]	
Concomitant illness	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration								X
eDiary data review	X	X	X	X	X	X	X	

Visit purpose	N8-GP dosing visits						EOT extension	Inhibitor follow-up
Visit number	V9, V10, V11	V12	V13, V14, V15	V16	V17, V19, V21,...[1]	V18, V20, V22,..[1]		
Time of visit (months)[2]	+3m +6m +9m	+12m	+15m +18m +21m	+24m	+27m +33m +39m +…	+30m +36m +42m +…	Min 4 days after last dose	
Visit window	±2w	±2w	±2w	±2w	±2w	±2w		
Bleeding episodes (severity rating)	X	X	X	X	X	X	X	X
ADVERSE EVENTS and CLINICAL ASSESSMENTS								
Adverse events	X	X	X	X	X	X	X	X[5]
Body measurements: Height Body Weight	 X	X X	 X	X X	 X	X[6] X	X X	
Physical examination	X	X	X	X	X	X	X	
Vital signs							X	X
LABORATORY ASSESSMENTS								
Haematology	X[7]	X	X[7]	X		X	X	
Biochemistry	X[7]	X	X[7]	X		X	X	
Antibodies: FVIII inhibitors N8-GP binding antibodies	X X	X X	X X	X X		X X	X X	X X
FVIII activity: FVIII trough level FVIII recovery	X X	X X	X X	X X		X X	X	X[8] X[8]
Lupus anticoagulant								*X*
TRIAL MATERIAL								
Administration of N8-GP	X	X	X	X		X		
N8-GP dispensing	X	X	X	X	X	X		
Drug accountability	X	X	X	X	X	X	X	
IV/WRS call	X	X	X	X	X	X	X	
REMINDERS								
Washout requirements prior to next visit	X	X	X	X	X			
eDiary collection							X	

Table 2-1 Flow chart for PK assessments

Only applicable for the subset of patients participating in PK assessments. All time points are relative to completion of injection of FVIII product. Please refer to section 8.1.1.1 and 8.1.2.1

	Nominal time			Dosing	Parameters		
	hours	min	Sample window (min)		PK sample	Vital signs	Adverse events
VISIT 1[1]							
Day1	-01		*+60~~55~~*		X		X
	00	00		X[3]			
	01	00	±15		X		
	06		±60		X		
Day 2	24		±120		X		X
	30[2]		±180		X		
VISIT 2							
Day1	-01		*+60~~55~~*		X	X	X
	00	00		X[4]			
	01	00	±15		X	X[5]	
	06		±60		X		
Day2	24		±120		X		X
	30[2]		±180		X		
Day 4	72		±120		X		X
Day 5	96		±120		X		X

5.1 Type of trial

…

After approximately 25 patients in each of the two age groups (0-5 and 6-11 years) have completed the main phase, any patients who have not yet completed the main phase will be offered continued treatment in the extension phase. The patient's next ~~scheduled~~ visit will then be visit 8 (end of main phase*), which should be scheduled to take place as soon as possible. .*

See table 5-1: text added

6.1 Number of patients

…

Countries planned to participate: ~~Australia, Brazil~~, Canada, France, Germany, Greece, Israel, Italy, Japan, *Lithuania* ~~Macedonia~~, Malaysia, ~~Poland~~, Portugal, ~~South Korea, Spain~~, Switzerland, Turkey, Ukraine, United Kingdom and United States

6.4 Withdrawal criteria

...

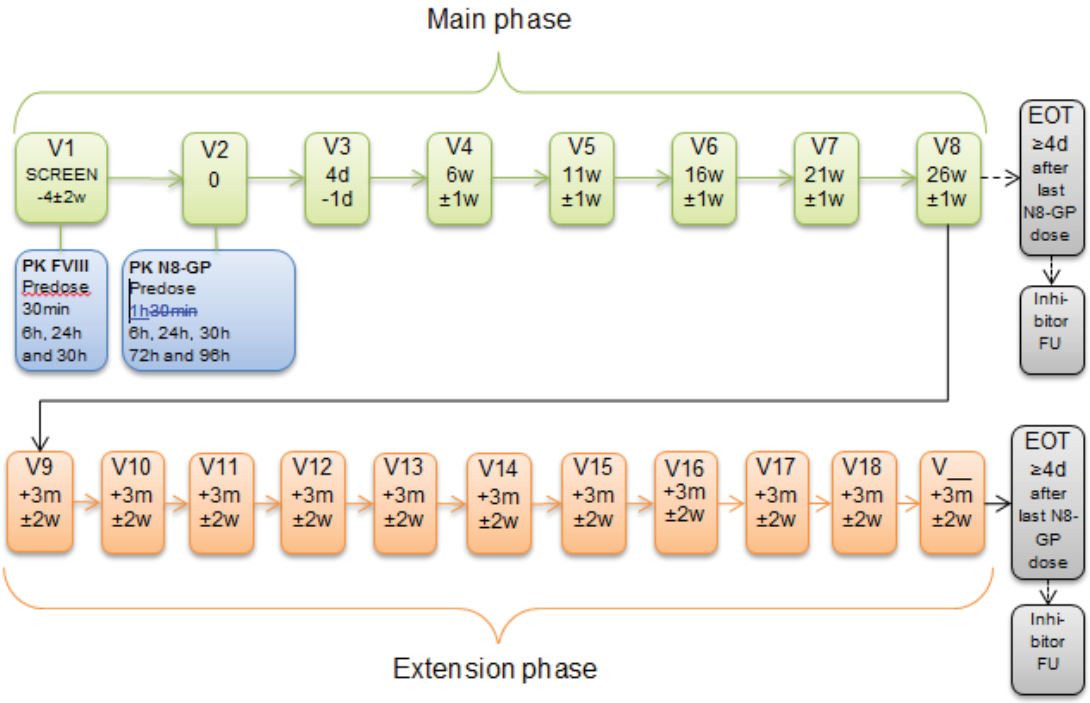
1. FVIII inhibitor (*>5 BU*~~≥0.6 BU~~) as confirmed by re-testing by Central Laboratory

…

7. Incapacity or unwillingness to follow trial procedures

8.FVIII inhibitor (≥0.6 and ≤ 5 BU) as confirmed by re-testing by Central Laboratory that makes treatment (prophylaxis and/or treatment of bleeding episodes) with N8-GP clinically ineffective

8.1 Visit procedures…



The extension phase consists of the following visits:

…

Inhibitor follow-up (FU) visit: Conditional inhibitor follow-up visits, which must be conducted if patient is withdrawn due to FVIII inhibitor (> *5*≥BU~~0.6 BU~~) development.

8.1.5 Visit 8 End of main phase

For patients NOT continuing in the extension phase

This is the last scheduled visit; unless the patient has developed an inhibitor *with titre >5 BU*, which would require further follow-up (see section 8.1.9). In addition to procedures listed in Table 8 5 the following procedures should be performed .

8.1.9 Inhibitor follow-up visit

In case of withdrawal due to FVIII inhibitor development *that makes prophylaxis treatment with N8-GP clinically ineffective or inhibitor titre >5 BU*, the patient should be scheduled for an EOT Visit as soon as possible and within 1 week after a positive inhibitor test ~~is confirmed via re-testing~~, preferably prior to initiation of treatment with another FVIII product. One month (4 weeks ± 2 weeks) after the EOT Visit the patient must attend a FU Visit, please see section 8.4.2.7. At each FU Visit, it will be evaluated if further FU Visits are required. The additional FU Visits will be arranged at intervals of 4 weeks ± 2 week as long as clinically warranted.

Table 8 9 Inhibitor follow-up visit procedures

The following will be performed and/or recorded in the eCRF • Concomitant medication • Date and time of last coagulation factor administration • Vital signs • Bleeding episodes since last visit • Inhibitor related AE
Blood sampling • FVIII inhibitor • N8-GP binding antibodies • FVIII activity and FVIII recovery, if applicable • *Lupus anticoagulant*

8.2.1.1 Documentation of inhibitor status

A positive historical inhibitor test excludes the patient. The historical laboratory cut-off value (assay sensitivity or lower limit of quantification) for a positive Bethesda inhibitor titre must not be higher than 1.0 BU.~~/mL~~.

8.4.2 Central laboratory assessment

…

All remaining central laboratory blood samples will be destroyed after finalisation of the clinical trial report, except for antibody samples. ~~The antibody samples may be stored for possible future testing at least until evaluation of the clinical trial by regulatory authorities.~~

Antibody samples including blood samples from patients who are suspected of inhibitors or who have developed inhibitors may be stored for possible future testing at least until evaluation of the clinical trial data by the Regulatory Authorities.

8.4.2.1 Haematology

- Platelet count (thrombocytes) ($x10^9$/L)
- Haemoglobin (mmol/L)
- Red blood cell count (erythrocytes) ($x10^{12}$/L)
- Mean corpuscular volume (MCV) (fL)
- Packed cell volume (haematocrit) (PCV) (%)
- White blood cell count (leucocytes) ($x10^9$/L)
- Differential white blood cell count (% *and*~~or~~ $x10^9$/L)

- Lymphocytes
- Monocytes
- Neutrophils
- Eosinophils
- Basophils…

8.4.2.6 FVIII activity analysis

…

The PK analysis will be based on FVIII chromogenic data and FVIII one stage clot data. Both analyses will be performed at a laboratory selected by Novo Nordisk. Sites will receive results based on the FVIII *one-stage clotting assay* ~~chromogenic assay~~ using the N8-GP product specific standard.

8.4.2.7 Antibody and inhibitor assessments

N8-GP antibody assay

…

Levels of N8-GP binding antibodies will be compared to pre-dose samples throughout the trial. If an inhibitor negative patient develops N8-GP binding antibodies and the ~~incremental~~ recovery value at that visit is less than 60% of screening value, a new inhibitor sample 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 can continue in the trial.

This algorithm will not apply for those who enter the trial with positive N8-GP binding antibodies and will not be triggered more than twice for an individual patient. Furthermore, a 7 days wash-out period will only be applied if the 84 hours wash-out is insufficient to avoid drug interference in the Bethesda inhibitor assay.

If sufficient sample material is available the samples collected for N8-GP binding analysis will be analysed for PEG binding antibodies. The samples to be tested are samples collected before treatment with N8-GP, approximately every 3 months in main phase and every year in extension phase. The analysis of PEG antibodies will be based on a validated assay

.N8-GP binding antibody including PEG antibody results will be reported to site at EOM and EOT.

FVIII inhibitors

All patients will be examined for the development of FVIII inhibitors at scheduled visits. A positive inhibitor test is defined as ≥0.6 BU~~/ml~~. If FVIII inhibitor development is suspected (increased number of spontaneous bleeding episodes, bleeding episodes difficult to treat, recovery and trough levels below expected values) during the course of the trial, additional inhibitor tests can be taken at Unscheduled Visits. All inhibitor tests must be analysed by the Central Laboratory.

In the event that a *previously inhibitor negative* patient has a positive inhibitor test (≥0.6 BU~~/ml~~), the patient must attend an Unscheduled Visit as soon as possible or within 1 week after the result is available to take a confirmatory inhibitor test on a separately drawn sample. *In addition the following tests should be performed: N8-GP binding antibody, FVIII trough, FVIII recovery and lupus anticoagulant. These* ~~this second~~ sample*s* should preferably be taken prior to any change of treatment *and after 84 hours wash-out period. A 7 days wash out period may be applied if the 84 hours wash out is not sufficient to avoid drug interference in the inhibitor assay.*

If the second (confirmatory) inhibitor test is also positive, the patient must be withdrawn if:

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

by discontinuing trial product and attending the EOT Visit as soon as possible and preferable within 1 week after the result is available.

~~*At this Unscheduled Visit, a recovery test must also be performed. If the second inhibitor test is also positive, the patient must be withdrawn by discontinuing trial product and attending the EOT Visit within 1 week after the result is available.*~~

If the second (confirmatory) inhibitor test is positive and ≤ 5 BU and the Investigator judges that the inhibitor does not clinically interfere with N8-GP treatment (prophylaxis or treatment of bleeding episodes) the patients may stay in the trial on per-protocol treatment.

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

For withdrawn patients: A follow-Up Visit must be scheduled 4 weeks ±2 weeks after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted (see section 8.1.9).

~~In case of inhibitor development the patient will be withdrawn from the trial. A follow-Up Visit must be scheduled 4 weeks ±2 weeks after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted (see section 8.1.9).~~

For patients continuing in pathfinder™5 with inhibitor (≥0.6 and ≤ 5 BU): the patient must follow per-protocol treatment schedule and the scheduled visits as described in Flowchart Table 2- 1 and Table 2-2. Additional visits can be scheduled if closer monitoring is needed. Closer monitoring is highly recommended but this decision will be at Investigator's discretion. In the event of a concern about reduced treatment efficacy a PK session is recommended to be performed. The PK can be evaluated after a wash out period of at least 84 hours. Blood sampling during the PK profile session can be performed at the following time points: pre-dose, 1hr (± 15 min), 6hrs (± 60min), 24hrs (± 2 hrs), 30hrs (+ 20 hrs) and 72hrs (± 2 hrs).

A confirmed positive inhibitor is considered to have disappeared if the inhibitor titre is <0.6 BU/mL on 2 consecutive inhibitor tests (performed at 2 consecutive visits) and the FVIII recovery is ≥66% of expected values. A patient with repeated positive inhibitor test result will count only once in the determination of the inhibitor incidence rate. Patients who develop an inhibitor should be classified as high responders (peak inhibitor titre > 5 BU), low responders (peak inhibitor titre ≤5 BU), and whether the inhibitor is transient (disappearing (inhibitor titre <0.6 BU) on ≥ 2 consecutive measurements) spontaneously within 6 months without a change in treatment regimen), or not.

A patient is considered to have developed an inhibitor if two separate samples from the same patient have been tested positive (≥0.6 BU/~~ml~~) for inhibitors at the central laboratory preferably with no more than 2 weeks between the tests. The patient may discontinue the trial including an EOT Visit and FU Visits or remain in pathfinder™5 as described above.

…

8.4.2.8 Antibody assessments in case of severe allergic reaction/anaphylaxis

If a patient experiences a severe allergic reaction/anaphylaxis, extra blood samples should be taken as soon as convenient, and not later than within 2 months after the event (please refer to the laboratory manual). The blood samples must be analysed for *FVIII activity*, inhibitors and antibodies against trial product content (e.g. IgG/IgE and host cell proteins). Patients developing anaphylaxis should be carefully investigated and followed-up for inhibitor development.

…

9.3 Labelling

Novo Nordisk will label and pack the trial product. *Third party vendors may be employed.* Labelling will be in accordance with Annex 1320, local law and trial requirements.

…

11 Adverse events and technical complaints

Serious Adverse Event

An 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 this definition.[d] *Suspicion of transmission of infectious agents via the trial product and formation of inhibitory antibodies must always be considered a SAE.*

…

11.1.2 Medical event of special interest

…

2. Inhibitor formation against FVIII

Blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk and if positive (BU ≥0.6~~6/mL~~)) should be reported as a MESI. A patient is only considered to be inhibitor positive if the inhibitor test is positive (BU ≥0.6~~/mL~~) at two consecutive tests - sampled preferably within 2 weeks. The result of the second test should be reported as follow-up on the MESI reported after the first test no matter if it is positive or negative.

11.6.1.1 Stopping rules

…

The following will result in enrolment in the N8-GP phase III trials being put on hold:

Inhibitor formation (Bethesda Unit of ≥0.6 BU~~/ml~~) in more than 2 patients. A patient has inhibitor formation if the patient has been tested positive for inhibitors at two consecutive tests from the central laboratory.

…

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 visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The monitor should visit a site soon after a patient has been screened. After that the intervals between visits should not exceed 12 weeks *during the main phase. During the extension phase the interval must not exceed 16 weeks, as long as the site has active patients*. .

…**16.4.2 Efficacy endpoints**

…

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

This endpoint will be summarised and listed.

In addition success will be defined as a response of Good or Excellent while failure will be defined as Moderate, None or Missing. Success/failure will be summarised both in total and by location of bleed, by cause of bleed and by country. The haemostatic effect as success/failure will also be summarised without missing included.

- Number of bleeding episodes during prophylactic treatment with N8-GP (annualised bleeding rate)

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

The annualised bleeding rate (ABR) of treatment requiring bleeding episodes will be estimated by a Poisson regression model with log (prophylaxis duration) as offset and estimating over-dispersion by Pearsons scale. The estimated ABR will be presented together with a 2-sided 95% confidence interval. *A sensitivity analysis based on a negative binomial regression model with number of bleeding episodes requiring treatment as the outcome variable, and adjusting for exposure time will also be performed*.

…

16.5 Interim analysis

All data from the main phase of the trial will be analysed and reported before the extension phase is completed. All main conclusions from the trial will be based on this reporting. An interim analysis may be performed on the extension phase to report all available data at the time of finalisation of the main phase. *Additional updates, including more data from the extension phase may be made prior to submission of the initial MAA and NDA.*

A partial data base lock will be performed including data from the main phase of the trial, *and additional partial data base lock including data from the extension phase will be performed if needed,* followed by full data base lock at end of trial.

…

Protocol Amendment

no 3
to Protocol, final version 3
dated 03 February 2014

Trial ID: NN7088-3885

Multinational, Open-Label, Non-Controlled Trial on Safety, Efficacy and Pharmacokinetics of NNC 0129-0000-1003 in Previously Treated Paediatric Patients with Severe Haemophilia A

Trial phase 3

Applicable to all countries

Amendment originator:

[redacted]

Table of contents

Page

1 Introduction including rationale for the protocol amendment

This amendment is implemented following a request from the VHP (Participating Member States: France, Portugal and United Kingdom) involved in pathfinder^{TM}5.
The VHP requested that patients with low titre inhibitors that continue on N8-GP treatment are systematically followed and therefore monthly visits have been included in the protocol. In addition, it was agreed with the VHP that the Novo Nordisk safety committee should be consulted by the investigator to determine the best management of individual patients with low titre inhibitors.

Section 8.1.10 updated to include follow up visits for low titre inhibitor patients.

Section 8.4.2.7 updated to include Novo Nordisk safety committee to be consulted by the investigator to determine the best management of individual patients with low titre inhibitors.

In this protocol amendment:

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

2 Changes

… before the text to indicate that the change occur later in the section

8.1.10 Unscheduled visit

Unscheduled visits can be introduced if required by patients or trial site. An unscheduled visit can be performed any time after enrolment and until the EOT visit, either as a telephone visit or a site visit. Patients can attend an unscheduled visit due to a (severe) bleeding episode, suspicion of inhibitor development, any AE, ~~or~~ sampling for laboratory tests ~~ect~~ *or follow-up for patients with low inhibitor titre who continue N8-GP treatment etc.*

8.4.2.7 Antibody and inhibitor assessments

FVIII inhibitors

…If the second (confirmatory) inhibitor test is positive *the investigator should make a recommendation to Novo Nordisk on whether or not to continue the patient in the trial. The investigator's recommendation should be evaluated by the Novo Nordisk safety committee in order to determine the best management of individual patient in this context.* ~~and ≤ 5 BU and the Investigator judges that the inhibitor does not clinically interfere with N8-GP treatment (prophylaxis or treatment of bleeding episodes) the patients may stay in the trial on per-protocol treatment.~~ For withdrawn patients: A follow-Up Visit must be scheduled 4 weeks ±2 weeks after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted (see section 8.1.9.)

For patients continuing in pathfinder^{TM}5 with inhibitor (≥0.6 and ≤ 5 BU): the patient must follow per-protocol treatment schedule and the scheduled visits as described in Flowchart Table 2- 1 and Table 2-2. *Patients with low titre inhibitors should attend an unscheduled visit monthly. The following tests should be performed: Inhibitor, FVIII activity trough and recovery. It is recommended to sample Lupus if blood sampling recommendations are not exceeded, please refer to section 8.1.10..* ~~Additional visits can be scheduled if closer monitoring is needed. Closer monitoring is highly recommended but this decision will be at Investigator's discretion.~~ In the event of a concern about reduced treatment efficacy a PK session is recommended to be performed. The PK can be evaluated after a wash out period of at least 84 hours. Blood sampling during the PK profile session can be performed at the following time points: pre-dose, 1hr (± 15 min), 6hrs (± 60min), 24hrs (± 2 hrs), 30hrs (+ 20 hrs) and 72hrs (± 2 hrs).