

Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

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Novo Nordisk

Protocol

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Author:



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List of Abbreviations

AE	adverse event
ALAT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BU	Bethesda unit
BW	Body weight
CHO	chinese hamster ovary
CL	total clearance
CNS	central nervous system
CRF	case report form
CRO	contract research organisation
CRP	c-reactive protein
CTA	clinical trial application
CTN	clinical trial notification
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
ED	exposure days
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of trial
EQ-5D	Euroqol 5 dimension self-report questionnaire
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPFV	first patient first visit
FVII	coagulation factor seven
FVIII	coagulation factor eight
FVIII:C	factor eight clotting activity
FIX	coagulation factor nine
FU	follow up
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HAEMO-QOL	haemophilia-quality of life
HAEM-A-QOL	haemophilia-adult-quality of life
HEMO-SAT	haemophilia-satisfaction
HE	health economics
HIV	human immunodeficiency virus
HCV	hepatitis C
HCP	host cell proteins
IB	Investigators Brochure

ICH	International Conference on Harmonisation
ICMJE	The International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	immunoglobulin g
IgE	immunoglobulin e
IMP	investigational medicinal product
IRB	Institutional Review Board
i.v.	intravenous
IV/WRS	interactive voice/web response system
LAR	legally acceptable representative
LOCF	last observation carried forward
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MRT	mean residence time
NIMP	non investigational medicinal product
NOAEL	no observed adverse effect level
PCV	packed cell volume
pd-aPCC	plasma derived activated plasma coagulation factor concentrates
pd-PCC	plasma derived plasma poagulation factor concentrates
PK	pharmacokinetic
PRO	patient reported outcome
N8-GP	glycopegylated recombinant coagulation factor VIII (NCC 0129-0000-1003)
PEF	peak expiratory flow
PEG	polyethylene glycol
PTP	previously treated patient
PUP	previously untreated patient
rFVIII	recombinant factor eight
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reactions
t _{1/2}	terminal half life
TGA	thrombin generating assay
TMM	trial materials manual
turoctocog alfa	recombinant coagulation factor VIII
TVP	trial validation plan
V _{ss}	volume of distribution at steady state
WFH	World Federation of Hemophilia
VWF	Von Willebrand Factor

1 Summary

Co-Primary Objectives

- To evaluate the immunogenicity of NNC 0129-0000-1003 (hereafter referred to as N8-GP) in previously treated patients with Haemophilia A
- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis)

Secondary Objectives

- To evaluate the clinical efficacy of N8-GP when treating bleeds in patients with haemophilia A
- To evaluate the safety of N8-GP when used for prevention of bleeds and treatment of bleeds in patients with haemophilia A
- To evaluate PK properties of N8-GP
- To evaluate Patient Reported Outcomes
- To evaluate the health economic impact of N8-GP treatment
- Generation of a population based PK-model for N8-GP

Co-Primary Endpoints

- The Incidence rate of FVIII-inhibitors ≥ 0.6 BU
- Annualised bleeding rate in the prophylaxis arm

Key Secondary Endpoint

- Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure

The endpoints will be analysed based on all available information until the end of trial (EOT) visit and up to approximately 19 months.

Trial design:

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety, pharmacokinetics and clinical efficacy of N8-GP when used for treatment of bleeding episodes and for long-term prophylaxis.

A minimum of 115 patients must complete the trial in 2 treatment arms including at least 10 patients in on-demand treatment and 105 patients in prophylaxis treatment with N8-GP every 4 days. Whether a patient will receive prophylaxis treatment or on-demand treatment is the choice of the patient and Investigator and will be decided at the screening visit.

A minimum of 15 of the patients in the prophylaxis arm must undergo two PK sessions to obtain 13 patients with two PK profiles. In order to ensure recruitment of patients for PK it is planned that the first patients (approximately 10) entering the prophylaxis arm must undergo PK sessions.

Treatment duration is approximately 7-19 months. In the prophylaxis arm, all patients will continue in the trial until the last patient has received at least 50 exposure days (EDs) of N8-GP, thus all patients in the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be above 1 year. The purpose of the on-demand arm is to ensure that sufficient bleed treatment data are collected in the trial. The on-demand patients can switch to prophylaxis treatment after approximately 6 months on-demand treatment if, the prophylaxis arm is still open for enrollment, or continue on-demand treatment until end of trial (EOT).

When this trial is completed, all patients will be offered to continue treatment in the extension trial NN7088-3861 (pathfinder™ 4) provided approval in the respective countries.

If the patients need to undergo surgery during the present trial they can switch into the surgery trial NN7088-3860 (pathfinder™ 3). Upon completion of the surgery the patients can return to the NN7088-3859¹ (pathfinder™ 2) trial.

Please refer to [Figure 3-1](#) for a description of the transfer of patients between trials.

Trial Population:

Approximately 150 previously treated patients (PTPs) with severe (FVIII <1%) haemophilia A in a non-bleeding state will be screened to allow for a minimum of 115 patients to complete 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 <1%, according to medical records)
- Documented history of at least 150 EDs to other FVIII products
- Age \geq 12 years (except for Croatia where the lower age limit will be 18 years)

Key Exclusion Criteria

- Previous participation in this trial defined as withdrawal after administration N8-GP
- Any history of FVIII inhibitors, see section [8.4.4.1](#)
- FVIII inhibitors \geq 0.6 BU/mL at screening

¹ patients that enter the surgery trial as on-demand patients will continue in the pathfinder™2 trial in the on-demand arm

- HIV positive, defined by medical records with CD4+ count $\leq 200/\mu\text{L}$ or a viral load of >400000 copies/mL. If the data is not available in medical records within last 6 months, CD4+ will be measured at the screening visit
- Congenital or acquired coagulation disorders other than haemophilia A
- Previous significant thromboembolic events (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as defined by available medical records
- Platelet count $< 50,000$ platelets/ μL (laboratory value at the screening visit)
- ALAT > 3 times the upper limit of normal reference ranges at central laboratory
- Creatinine level ≥ 1.5 times above upper normal limit (according to central laboratory reference ranges)
- Ongoing immune modulating or chemotherapeutic medication

Safety Assessments

AEs, antibody assessment, haematology, biochemistry and FVIII activity will be measured throughout the trial. Furthermore, Vital signs, physical examination, electrocardiogram (ECG), Urinalysis, viral assessments and lupus anticoagulant will be measured.

Efficacy Assessments

Haemostatic effect of N8-GP when used for treatment of bleeding episodes (excellent, good, moderate, none), number of bleeding episodes per patient, consumption of N8-GP required per bleed and total number of N8-GP injections administered to the patient per bleed during the trial. Furthermore, patient reported outcomes will be assessed.

PK Assessments

The PK sessions with N8-GP will be performed at visit 2a and 7 and the parameters assessed include Incremental recovery, trough level, AUC, Terminal half-life ($t_{1/2}$), Clearance, Mean Residence time (MRT) and V_{ss} (Volume of distribution at steady state). The first sample will be taken within one hour prior to the administration of N8-GP and the last sample will be taken 96 hours after.

Trial Product(s):

The following trial products will be used in the trial:

- N8-GP drug product

N8-GP 2000 U/vial 211 μg /vial drug product is a lyophilised powder in single use vials with a nominal content of 2000 U/vial produced by Novo Nordisk A/S, Denmark. Each vial is to be

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reconstituted with 4.3 mL of 0.9% NaCl. After reconstitution each vial contains 500 U/ml N8-GP at pH 6.9. Sodium Chloride 0.9% solution will be provided by Novo Nordisk.

In the prophylaxis arm, each patient will receive prophylaxis treatment with a N8-GP dose of 50 U/kg body weight (BW) every 4 days. In most cases this will be home treatment with intravenous (i.v.) self-injection by the patient. Patients participating in the on-demand arm and patients in the prophylaxis arm will be treated with 20-75 U/kg BW in case of bleeding episodes.

Patients participating in the PK sessions (visit 2a and 7) will be administered one dose of N8-GP of 50 U/kg BW.

Visit number	1	2a ¹	2b	3	4	5	6	7 ^{1,2}	8	9	10	11	12	13	14	Un- sched- uled visit
Time of visit	2w prior to visit 2a	0	4 days after Visit 2	4w	8w	12w	20w	28w	36w	44w	52w	60w	68w	76w EOT		
Visit window	Weeks +1			±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1		
SUBJECT RELATED INFO/ASSESSMENTS																
Affirmation statement									X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	
End of trial Form								X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	
e-Diary training		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
e-Diary data review			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Home treatment training		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footer	Description
1	Please refer to Table 2-2 for the patients that need to undergo PK
2	Patients in the on-demand arm can switch into prophylaxis treatment after 6 months treatment
3	Confirmation of screening visit 1 in- and exclusion criteria
4	If applicable, i.e. following patient consent and in accordance with local law
5	Only if this visit is EOT visit – dependent on when the patient entered the trial
6	Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment since last visit
7	A wash-out period of minimum 96 hrs is needed before the sample (except visit 1 and visit 2a where wash out is minimum 72 hours)
8	Only in case of an unexpected allergic/anaphylactic reaction
9	Not for patients in the on demand arm
10	Only to be taken if HIV status is positive
11	Only BW will be measured
12	From visit 3-13, only for patients in the prophylaxis arm

Table 2-2 PK Flow Chart for Selected Patients having PK Sampling Performed at Visit 2a and Visit 7

Day(s)	0						1	2	3	4
	Pre-dose	0	30	1 hr	4 hrs	12 hrs				
Nominal Time¹							24 hrs	48 hrs	72 hrs	
Visit Window	-1h ²	± 5 min		± 5 min	± 30 min	± 30 min	+ 8 hrs	+ 8 hrs	+ 8 hrs	+ 8 hrs
Inclusion / Exclusion Criteria	X ³									
Withdrawal Criteria	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration	X									
e-Diary data review	X									
Adverse Events	X	X	X	X	X	X	X	X	X	X
Body measurements (weight)	X									
Physical examination	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
Haematology	X									
Urinalysis	X ⁴									
Biochemistry	X	X	X	X	X	X	X	X	X	X
Coagulation related parameters	X									
FVIII activity	X	X	X	X	X	X	X	X	X	X
N8-GP binding antibodies	X									
FVIII inhibitors	X									
Adm. of N8-GP		X								
N8-GP accountability							X			
TRAINING AND REMINDERS										
Home treatment and e-Diary training							X			
eDiary dispensing							X			
IW/VRS	X									X ⁵
Footer	Description									
1	Time values refer to time elapsed after N8-GP has been administered (completion of the injection)									
2	Time window of 1h pre-dose, only applicable for blood samples. Any other assessments must be performed prior to dosing at the day of dosing.									
3	Confirmation of Screening visit (Visit 1) in- and exclusion criteria (only visit 2a)									
4	Only visit 2a									
5	Only visit 7									

3 Introduction

In this document the Investigator refers to the individual overall responsible for the 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 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 care¹.

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 haemostasis². 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 deformities³. Bleeding episodes may occur in all parts of the body 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. 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 be initially evaluated in PTPs as these patients have been exposed to previous FVIII products and considered to be at a low risk of developing inhibitors and therefore the most suitable for trial population.

Haemophilia A is classified according to the plasma activity of FVIII (FVIII:C), as severe (FVIII:C <1% of normal), moderate (FVIII:C 1-5%) or mild (FVIII:C 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 registers the numbers are about 50 % severe, 20 % moderate and 30 % mild.

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

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 is replacement of the FVIII protein. Currently available FVIII products are all lyophilised products for i.v. infusion and either plasma derived or recombinant. This replacement therapy can be provided either as prophylaxis or as on-demand treatment of bleeding episodes. turoctocog alfa

3.1.2 N8-GP

N8-GP represents a new recombinant FVIII (rFVIII) with a longer half life and clinical areas of interest include the prophylaxis and treatment of bleeding in patients with Haemophilia A without inhibitors, and the prevention of bleeding in surgery undertaken in these patients.

N8-GP is a rFVIII covalently coupled to a single 40K-PEG (polyethylen glycol) 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 native rFVIIIa upon activation by thrombin at the site of injury. In this process, the pegylated activation peptide is released.

Recombinant human FVIII is synthesised at Novo Nordisk A/S in 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.

The No Observed Adverse Effect Level (NOAEL) after multiple dosing with N8-GP in male and female rats and male cynomolgus monkeys was 2500 U/kg.

3.1.3 N8-GP Clinical Data

In accordance with the European Medicines Agency (EMA) Guidelines⁷, the clinical programme for N8-GP was initiated by a pharmacokinetic (PK) trial to document the essential PK characteristics of the product and to achieve initial safety information.

By April 2011, 26 PTPs were dosed with N8-GP in the NN7088-3776 (pathfinderTM 1) trial and had undergone a safety and PK investigation. The phase 1 trial has successfully been concluded with no safety concerns. No FVIII inhibitors were detected and no treatment related SAEs were reported. The half-life was pro-longed with approx 1.6-fold compared to the patients previous FVIII product. For further information on medicinal aspects, non-clinical data and quality of N8-GP, please refer to the Investigator's Brochure (IB)⁸.

3.1.4 Risk and Benefits

N8-GP has a longer half-life and thus the potential to improve the quality of life for the haemophilia A patients by offering a convenient prophylaxis treatment, reducing the burden of frequent infusions.

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 $t_{1/2}$. PEG is allowed in foods and drugs and it is also used in other licensed products. 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 product⁹. Non-clinical and clinical data does 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 a new rFVIII product is the potential risk of the development of neutralising antibodies to FVIII. The N8-GP clinical trial has been designed in order to minimise the risk of inhibitor development. Selection of patients for the clinical trials 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 clinical risk of patients developing antibodies against N8-GP is regarded as low.

Potentially fragile patients where the treatment with N8-GP may present a risk will not be included in the study. Therefore, patients with severe cardiovascular disease, 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, will upon completion of the present trial, be offered to continue treatment with N8-GP in the extension trial (pathfinderTM 4), where patients have the opportunity to continue with N8-GP treatment until commercially availability^b.

3.2 Rationale for the Trial

This trial is part of a clinical development programme that at present includes a completed phase 1 trial (pathfinderTM 1), the present pivotal phase 3a trial (pathfinderTM 2), an extension phase 3b trial (pathfinderTM 4) and a surgery phase 3a trial (pathfinderTM 3). The phase 3 trials are offered as one package to each investigational site to ensure that patients are offered to continue N8-GP until commercially available³ and patients in need of surgery can undergo surgery without having to switch product. The clinical programme is illustrated in [Figure 3-1](#).

^b For UK only: The end of the extension trial will be defined by exact date and not when commercially available

In the preceding phase 1 trial (pathfinder™¹), 26 patients with haemophilia A had one PK session with their current FVIII product followed by one PK session with N8-GP. The trial was completed on 18 April 2011 and the results formed the basis for the doses selected in the present trial.

The rationale for this trial is to investigate the safety and efficacy, including PK and long-term safety of N8-GP in Haemophilia A patients from 12 years of age.

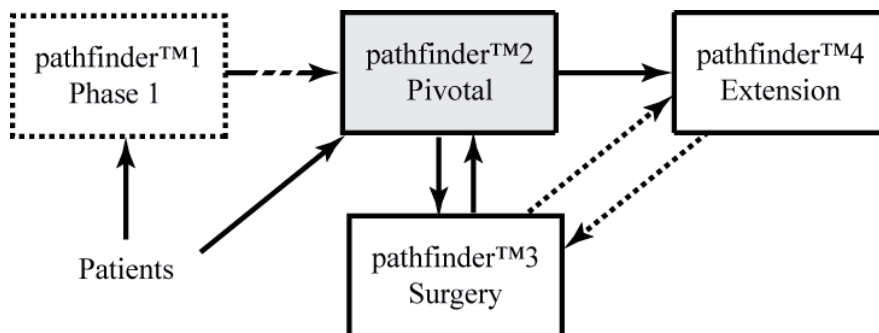


Figure 3-1 Overview of the pathfinder™ clinical trial programme.

Arrows indicate possible transfer of patients between trials. Patients completing the phase 1 trial may also be enrolled in the coming trials if found eligible.

4 Objective(s) and Endpoint(s)

4.1 Objectives

4.1.1 Co-Primary Objectives

- To evaluate the immunogenicity of N8-GP in previously treated patients with Haemophilia A
- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeds during prophylaxis)

4.1.2 Secondary Objectives

- To evaluate the clinical efficacy of N8-GP when treating bleeds in patients with haemophilia A
- To evaluate the safety of N8-GP when used for prevention of bleeds and treatment of bleeds in patients with haemophilia A
- To evaluate PK properties of N8-GP
- To evaluate Patient Reported Outcomes (PRO)
- To evaluate the health economic impact of N8-GP treatment
- Generation of a population based PK-model for N8-GP

4.2 Endpoint(s)

4.2.1 Co-Primary Endpoints

- The incidence rate of FVIII-inhibitors ≥ 0.6 BU
- Annualised bleeding rate in the prophylaxis arm

4.2.2 Secondary Endpoints

4.2.2.1 Confirmatory Secondary Efficacy Endpoint

- The haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.

4.2.2.2 Additional Supportive Efficacy Endpoints

- Consumption of N8-GP (number of infusions and U/kg) per bleed
- Consumption of N8-GP (number of infusions and U/kg per month and per year) during prophylaxis and on-demand treatment
- Haemostatic effect as measured by recovery and trough levels FVIII:C (in all patients in the prophylaxis treatment arm)
- Patient Reported Outcomes and Health Economic Endpoints
 - PRO scores and their changes from baseline to the end of the trial

- Bleed related health economic resource use and patient/caregiver burden

4.2.2.3 Safety Endpoints

- Adverse Events (AEs) and Serious Adverse Events (SAEs) reported during the trial
- Changes in vital signs (BP, pulse, temperature, respiratory rate)

4.2.2.4 Pharmacokinetic Endpoints

- Incremental recovery ([U/mL] / [U/kg])(single dose and steady state)
- Trough level ([U/mL]) (single dose and steady state)
- Area Under the Curve (AUC), (h*U/mL)
- Terminal half-life ($t_{1/2}$), (h)
- Clearance (mL/h/kg)
- Mean Residence time (MRT)
- Vss (Volume of distribution at steady state)

4.2.3 Exploratory Endpoints

- Incidence of binding, non-inhibitory antibodies to N8-GP/ turoctocog alfa

5 Trial Design

5.1 Type of Trial

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety, pharmacokinetics and clinical efficacy of N8-GP when used for treatment of bleeding episodes and for long-term prophylaxis.

A minimum of 115 patients must complete the trial including at least 10 patients in on-demand treatment and 105 patients in prophylaxis treatment with N8-GP every 4 days. In order to ensure recruitment of patients for PK it is planned that the first patients (approximately 10) entering the prophylaxis arm must undergo PK sessions. Whether a patient will receive prophylaxis treatment or on-demand treatment is non randomised and will be the choice of the patient and Investigator. This will be based on medical needs and decided at the Screening visit. For the US, recruitment will open for the on-demand arm before enrolling patients in the prophylaxis arm, whereas both arms will open concurrently at non-US sites. The distribution of patients will be as follows:

- It is expected that approximately 120 patients will be dosed in the prophylaxis arm in order to obtain 105 completed patients on prophylaxis treatment. These patients will receive treatment with 50 U/kg of N8-GP every 4 days during a period of approximately 7-19 months. In case of a bleed the patients will be treated with doses between 20-75 U/kg BW.
- It is expected that approximately 12 patients will be enrolled in the on-demand arm to obtain 10 completed patients who have been treated on-demand with N8-GP during a period of approximately 6 months. In case of a bleed the patients will be treated with doses between 20-75 U/kg BW. When they have completed approximately 6 months on-demand treatment, the on-demand patients will be offered to switch to the prophylaxis arm if, the prophylaxis arm is still open for enrollment, or to continue on-demand treatment until the end of trial.

A minimum of 15 of the patients in the prophylaxis arm must undergo 2 PK sessions to obtain 13 patients with two usable PK profiles each. The first PK session will take place at Visit 2a and the second will take place at Visit 7. When 15 patients have successfully completed the two PK sessions and data is available, no additional patients will be required to undergo PK assessments. Furthermore, recovery and trough levels of FVIII will be followed throughout the trial at all visits for all patients on prophylaxis to evaluate steady-state and indications of inhibitor formation.

Treatment duration is approximately 6 months in the on-demand arm and from approximately 7 (200 days plus screening period of 2-3 weeks) to approximately 19 months in the prophylaxis arm. The maximum treatment period in this trial is 24 months. In the prophylaxis arm, all patients will continue in the trial until the last patient has received at least 50 EDs of N8-GP, thus all patients in

the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be more than 1 year. When this trial is completed, all patients will be offered to continue treatment in the extension trial pathfinderTM 4, if approved by country. As all patients will complete the present trial at the same time (or within a short timeframe) the transition of patients from pathfinderTM 2 to pathfinderTM 4 will be gradual and within a window of approximately 1 month.

Furthermore, if the patients need to undergo surgery during the present trial they can switch into the surgery trial pathfinderTM 3 and upon completion of the surgery they can return to the pathfinderTM 2^c trial. Recruitment into the surgery trial pathfinderTM 3 will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pivotal trial pathfinderTM 2. For US the surgery trial will not be initiated until at least 20 bleeding episodes in at least 10 patients are treated with N8-GP.

The flow of patients between trials is illustrated in [Figure 3-1](#).

The screening period will add approximately 2-3 weeks to each patient's trial participation.

The clinical efficacy assessment for treatment of bleeding episodes will be based on the treatment of all bleeding episodes (spontaneous, traumatic, re-bleed and after minor surgery). Haemostatic effect of N8-GP in treatment of bleeding episodes will be assessed on a four-point scale (excellent, good, moderate and none).

5.2 Rationale for Trial Design

The purpose of the prophylaxis arm is to provide sufficient exposure to N8-GP to evaluate immunogenicity and to provide efficacy data from 50-100 EDs of prophylaxis treatment with N8-GP in at least 105 patients with severe haemophilia A ≥ 12 years. The reason for not having a prophylaxis control is that no FVIII product is globally approved for prophylaxis treatment.

The purpose of the on-demand arm is to ensure that sufficient bleeding treatment data is collected in the trial. Additional safety data will also be generated in these on-demand treated patients. It is not a comparator to the prophylaxis arm. The reason for not having an on-demand control is that most patients are on prophylaxis treatment and it is considered unethical to randomise prophylaxis patients to on-demand treatment. In addition, a comparator arm is not required for registration in the EU.

The purpose of continuing all patients in the prophylaxis arm in the trial until the last patient has completed at least 50 EDs of N8-GP is to ensure that the average exposure to N8-GP will be above 1 year for a considerable portion of the patients.

^c patients that enter the surgery trial as on-demand patients will continue in the pivotal trial in the on-demand arm

The trial is not controlled by a placebo group. It is considered unethical to administer an ineffective treatment to patients with haemophilia. The rationale for choosing a multi-centre design is to ensure a sufficient number of patients with this rare disorder.

For clinical efficacy of N8-GP in the prevention of bleeding episodes, historical data on annualised bleeding frequency during on-demand treatment and prophylaxis will be used for comparison. The historical data derive from a recent review by an independent board of haemophilia treaters within the Swedish Council on Health Technology Assessment, including all published clinical studies on treatment of severe haemophilia A during the last 25 years which were comprised of at least 20 patients¹⁰. The review selected in total 37 separate studies of haemophilia A replacement therapy, seven of which contained data on bleeding frequency in an adult and/or adolescent population¹¹.

5.3 Treatment of Patients

Approximately 150 patients are planned to be screened in order to dose approximately 132 patients in the trial out of which 105 patients are expected to complete the prophylaxis part of the trial and a minimum of 10 patients are expected to complete approximately 6 months in the on-demand part of the trial.

The two initial doses of N8-GP will be administered in a hospital setting in order to observe for adverse reactions. Thereafter, home treatment can be initiated. All patients must previously have received at least 150 doses of FVIII and must be familiar with or instructed in home treatment of both prophylaxis and treatment of bleeding episodes.

A severe bleed should be treated immediately at home and the haemophilia site must be contacted without delay for further instructions and/or transport to the site.

The following medications are not allowed during the course of the trial until after the EOT visit:

- Bypassing products: rFVIIa, pd-PCC and pd-aPCC
- Coagulation Factors containing products: FVIII, FIX and FVII other than N8-GP.
- Anti-coagulants such as Heparin and vitamin-K antagonists. Heparin is allowed for sealing of central venous access ports

5.3.1 Prophylaxis

In the prophylaxis arm, one single bolus dose of 50 U/kg BW of N8-GP is administered intravenously every 4 days (96 hours interval). The dose chosen is based on phase 1 data from the pathfinderTM 1 trial and is chosen to ensure a trough level of >1% FVIII:C activity in the majority of patients in the prophylaxis arm. During treatment a shortening of the dosing interval for prophylaxis to twice weekly may be undertaken at the Investigator's discretion, if deemed necessary for the individual patient (see section [5.3.2](#)). If the dosing regimen is changed to twice weekly, doses should be separated with at least 3 calendar days and no more than 4 calendar days. Other changes

of the dose or dosing interval for prophylaxis are not allowed within the trial. However, extra doses of N8-GP will be administered if a patient experiences a treatment requiring bleeding episode or in case of minor surgery.

5.3.2 Treatment of Bleeding episodes

A treatment requiring bleeding episode is in this trial defined as a bleed that require treatment with a coagulation factor product e.g. N8-GP. If a patient experiences a treatment requiring bleed it must be treated as soon as it is identified (refer to Section [8.2.1](#)). The Investigator must always be contacted in case of a severe bleed and the patient should visit the site within 24 hours.

Mild/moderate bleeding episodes can be treated at home without contacting the site. For definition of the severity of a bleed please refer to section [8.2.1.1](#).

For the treatment of bleeding episodes, doses will be based on World Federation of Haemophilia (WFH) guidelines¹ (see Section [8.2.1](#)). For treatment of a bleed all on demand and prophylaxis patients will be treated with doses between 20-75 U/kg BW (the recommended standard dose will be 50 U/kg). Due to individual patient's bleeding pattern during the trial, an adaptation in dosing regimen to 50 U/kg twice weekly will be permitted at the investigator's discretion. If the dosing regimen is changed to twice weekly, doses should be separated by at least 3 calendar days and no more than 4 calendar days.

The dose for treatment of bleeding episodes is aimed to achieve an expected post injection level of at least 0.50 U/mL of FVIII.

Any dose used for treatment of a known active bleed must be recorded as treatment of bleed and not as prophylaxis treatment. When the bleed has resolved, the patient can resume the prophylaxis treatment.

If a dose for treatment of a bleed is taken, the next prophylaxis dose should follow the original dosing scheme and not be altered by the additional treatment of bleed administration. If a bleed occurs on the same day as the planned prophylaxis, the dose must be registered for the bleed and not as prophylaxis.

Number of doses and frequency of dosing is decided by the Investigator in relation to the particular bleed. The maximum dose to be administered to a patient within 24 hours (hrs) is 200 U/kg BW. The dose is recommended to be divided and only considered under exceptional circumstance such as serious trauma or severe bleeding episodes.

If a haemostatic response cannot be achieved after 48 hours using adequate doses of N8-GP treatment when treating bleeding episodes, another FVIII product may be selected at the discretion of the Investigator. The use of other FVIII products will result in withdrawal of the patient.

An electronic diary (eDiary) will be kept to register all bleeding episodes and their treatment. The investigator must review the eDiary data and rate the bleeding episodes at every visit. If the patient or caregiver is unable to fill in information for severe bleeding episodes in the eDiary or is hospitalised, this information can be entered in the patient's medical record and hereafter in the eCRF by site personnel. The dose, dose interval, number of doses and efficacy of treatment will be registered in the eDiary. The dose level can be decided based on the patient's FVIII recovery or trough data. All phone contacts with the site must be documented by the study personnel.

5.3.3 Patients Participating in PK procedures

Patients will be administered a single i.v. bolus injection of 50 U/kg BW of N8-GP at Visit 2a and at Visit 7. The PK sessions are 4 days long and with multiple site visits. Overnight stay is not required. After completion of the PK sessions the patients will continue treatment in the prophylaxis arm with the next visit in line.

Patients must not have received current FVIII product for at least 4 days prior to the PK session at visit 2a and N8-GP for at least 7 days prior to the PK session at visit 7. The lines/tubes must be flushed immediately after administration of the trial product.

5.3.4 Surgery

Patients in need of major surgery may qualify for the surgical trial (pathfinderTM3) being conducted in parallel to the present pivotal trial. The patient can undergo a surgery when he has received a minimum of 5 N8-GP EDs. If a patient transfers to the surgery trial a surgery transfer visit must be scheduled (see section 8.1.6). Minor surgery can be performed while participating in this trial by administering an additional dose of 50-75 U/kg N8-GP or a dose sufficient to increase the FVIII level to 100% prior to the minor surgery to prevent peri-operative bleeding.

Definition of Minor Surgery

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

5.3.5 Patients Continuing Into Other N8-GP Trials

All patients in the prophylaxis arm will continue in the trial until the last patient initiated in the prophylaxis arm has received at least 50 EDs. After completion of the trial, all patients will be offered to continue prophylaxis or on-demand treatment in the extension trial pathfinderTM4 for up to approximately two years or until N8-GP becomes commercially available^d in the patient's country. As all patients will complete the present trial at the same time the transition of patients from

^d For UK only: The end of the extension trial will be defined by exact date and not when commercially available.

pathfinder[™] 2 to pathfinder[™] 4 will be gradual and within a window of approximately 1 month. Please refer to [Figure 3-1](#) for an overview of the flow of patients between trials in the clinical development programme.

If the N8-GP programme is terminated or if the health 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 trial will be stopped and treatment with N8-GP will be ended. Data collected up to the point where the patient is transferred to the extension trial will be used in the data analysis in the present trial.

5.4 Rationale for Treatment

In the preceding phase 1 trial (pathfinder[™] 1) 26 patients with haemophilia A had one PK session with their current FVIII product followed by one PK session with N8-GP. The trial was completed on 18 April 2011 and the results formed the basis for the doses selected in the present trial.

The phase 1 trial has successfully been concluded with no safety concerns. No FVIII inhibitors were detected and no treatment related SAEs were reported. The half-life was prolonged with approx 1.6-fold compared to the patients previous FVIII product

Lack of compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with factor treatments, and frequent dosing interrupts and restricts daily activities¹². The longer half-life of N8-GP will allow for prophylaxis with fewer injections and presumably better compliance.

6 Trial Population

6.1 Number of Patients to be Studied

Countries planned to participate: Australia, Brazil, Croatia, Denmark, France, Germany, Hungary, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

Planned number of patients to be screened (i.e. documented informed consent) approximately: 150

Planned number of patients to be started on trial product(s) approximately: 132

Planned number of patients to complete the trial: ≥ 115

- Minimum 15 patients must be 12-17 years old at screening
- Minimum 10 patients must be in the on-demand arm
- Minimum 105 patients must be in the prophylaxis arm

Planned number of trial sites (approximately): 55

6.2 Inclusion Criteria

1. Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject.)
2. Male patients with severe congenital haemophilia A (FVIII activity $<1\%$, according to medical records)
3. Documented history of at least 150 exposure days to other FVIII products^e
4. Age ≥ 12 years (except for Croatia where the lower age limit will be 18 years)
5. Body Mass Index (BMI) ≤ 35
6. The patient and/or caregiver is capable of assessing a bleed, capable of home treatment of bleeding episodes and otherwise following the trial procedures

6.3 Exclusion Criteria

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products

^e Prophylaxis, prevention, on-demand and treatment during surgery counts as exposure days.

If not possible to count the actual number of exposures in the medical chart, 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. This statement should be filed either with the patient chart or separately with the Investigator Trial File.

2. Previous participation in this trial defined as withdrawal after administration of N8-GP.
3. The receipt of any investigational drug (with the exception of turoctocog alfa) within 30 days prior to enrolment into the trial (**For Brazil, only:** Participation in a previous clinical trial within one year prior to screening for this trial (Visit 1), unless there is a direct benefit to the research subject, at the investigator discretion).
4. Any history of FVIII inhibitors, see section [8.4.4.1](#)
5. FVIII inhibitors ≥ 0.6 BU/mL at screening
6. HIV positive, defined by medical records with CD4+ count $\leq 200/\mu\text{L}$ or a viral load of >400000 copies/mL If the data is 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 events (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as defined by available medical records
9. Platelet count $< 50,000$ platelets/ μL (laboratory value at the screening visit)
10. ALAT > 3 times above the upper limit of normal reference ranges at central laboratory
11. Creatinine level ≥ 1.5 times above the upper normal limit (according to central laboratory reference ranges)
12. Ongoing immune modulating or chemotherapeutic medication
13. 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
14. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation

For the UK: Patients who are sexually active and have partners who are or could become pregnant must be willing and are required to use a barrier method of contraception (e.g. condom) for the duration of the trial and for 90 days following the last dose of trial medication.

Patients who are non-compliant with any of the eligibility criteria, but included in the trial, should be excluded immediately. If extraordinary circumstances speak in favour of maintaining the subject in the trial then this is only acceptable if justified and approved by the IEC/IRB, and if the regulatory authorities are notified according to local requirements.

6.4 Criteria for rescheduling planned visits

1. Major surgery within one month prior to the first injection of N8-GP and PK evaluation
2. Subjective signs of illness or fever within 48 hours prior to the first injection of N8-GP and to PK sessions
3. In a bleeding state (all visits including PK)
4. Less than 72 hours wash out prior the screening visit 1 and visit 2a (except patients who undergo PK session at visit 2a)

5. Less than 96 hours wash out prior to inhibitor and antibody testing when treated with N8-GP (all patients)
6. 4 days wash out before the 1st PK evaluation and 7 days wash out before the 2nd PK evaluation (Patients undergoing PK evaluation at visit 2a and 7)
7. Mild/moderate bleed within one week or a severe bleed within one month prior to PK evaluation visits

6.5 Withdrawal Criteria

The patient may withdraw at will 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.

A patient must be withdrawn if the following applies:

1. Haemostasis not achievable with N8-GP: The bleed cannot be controlled after 48 hours using adequate doses of N8-GP
2. FVIII inhibitor (≥ 0.6 BU/mL) as confirmed by re-testing by Central Laboratory
3. Allergy/anaphylaxis to the trial product
4. Use of Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma or cryoprecipitate. (**Exception:** current FVIII allowed until 72 hours before Visit 2a)
5. Incapacity or unwillingness to follow the trial procedures

6.6 Patient Replacement

Patients withdrawn from the trial can be replaced until 105 patients in the prophylaxis arm have had at least 50 EDs, and 10 patients have had 20 bleeding episodes in the on-demand and/or the prophylaxis arm.

6.7 Rationale for Trial Population

The present phase 3 trial will enrol patients with haemophilia A aged ≥ 12 years who are likely to benefit from the treatment in the trial. The trial is global and should include different ethnicities. Children in the age groups 12 to 17 years are amongst those who might benefit significantly from prophylaxis treatment. Adherence to current prophylaxis regimens drops dramatically during the teenage years where the compliance rate may be as low as 13%¹². Fewer injections are therefore likely to improve compliance.

The trial population characterised through the inclusion criteria:

- Criterion no. 1 is included in accordance with ICH-GCP
- Criterion no. 2 is included to select patients most likely to benefit from the treatment
- Criterion no. 3 is included for selecting previously FVIII treated patients and is in accordance with the EMA guideline
- Criterion no. 6 is included to ensure compliance with treatment and protocol requirements
- Criteria nos. 2, 3, 4, 5, are included in order to limit to a well characterised patient population

The trial population characterised through the exclusion criteria:

- Criteria nos 1, 4, 5, 6, 8, 9, 10, 11, 12, 13 and 14 are to prevent exposure of potentially fragile patients to a new compound and to prevent exposure of FVIII to patients with FVIII inhibitors
- Criterion no 2 is to ensure that a patient only counts once in the data analyses
- Criteria nos. 3 and 12 are selected to minimise any effect of external compounds on the patient's coagulation and immune system.
- Criteria nos. 7, 9, 10 and 11 are chosen to exclude patients with endogenous abnormalities of the coagulation system other than haemophilia A and to exclude patients with severely impaired liver or kidney function.
- Criterion no. 8 is chosen to minimise the risks of thrombotic manifestations

7 Trial Schedule

Planned duration of recruitment period: 12 months

After a period of 12 weeks, patient recruitment will be competitive between countries and trial sites unless otherwise agreed. If a trial site or country has not enrolled the planned number of patients according to the recruitment strategy, the remaining patients may be reallocated. All Investigators will be notified immediately when the enrolment period comes to an end, after which no patients may be screened unless required due to patient withdrawals.

Planned date for FPFV: 01-Feb-2 012

Planned date for LPLV: 01-Oct-2013

The end of the clinical trial is defined as LPLV.

Planned completion of clinical trial report: within 6 months after LPLV

Protocol information for this trial will be subject to public disclosure at external web sites (www.clinicaltrials.gov and www.novonordisk-trials.com) according to international regulations e.g. the International Committee of Medical Journal Editors (ICMJE)¹³, the Food and Drug Administration Amendments Act (FDAAA)¹⁴ - as reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

8 Methods and Assessments

8.1 Visit Procedures

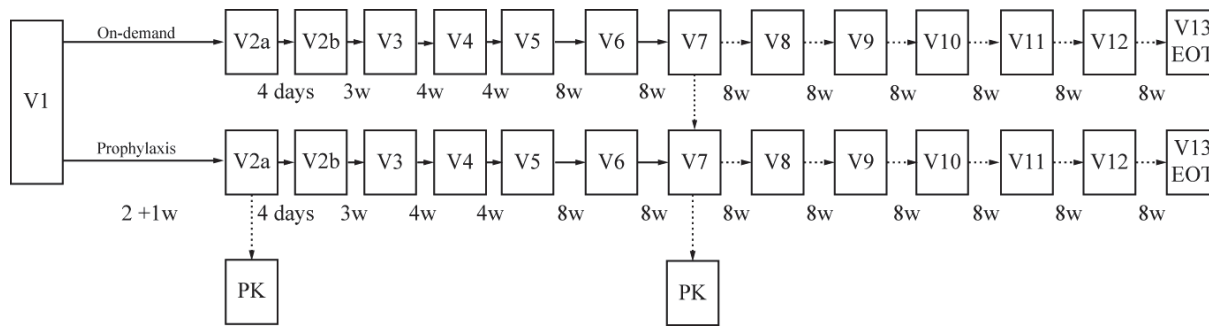


Figure 8-1 Overview of visits and home treatment periods

All patients will complete at least 8 visits depending on when they are enrolled in the trial as the trial will be completed when the last prophylaxis patient has had 50 EDs. The last patient will have EOT visit at visit 7 after having received at least 50 EDs whereas the first patient enrolled in the trial will have the EOT visit at Visit 13. Therefore, the EOT visit can be all visits from visit 7 to visit 13. More visits may be added depending on when the last patient has had at least 50 EDs.

The trial includes the following visits:

- **Visit 1:** Screening visit
- **Visit 2a and 2b:** Visits at the site.
 - All patients will have their first and second dose administered at the site.
 - Patients in the prophylaxis arm undergoing PK evaluation will undergo first PK evaluation at Visit 2a.
- **Visit 3-13:** Visits at the site.
 - Patients in the prophylaxis arm will be dosed during the visits
 - Patients in the prophylaxis arm undergoing PK evaluation will undergo second PK evaluation at Visit 7
 - Patients in the on-demand arm will not be dosed during the visits

Follow-up visit (FU), not shown in [Figure 8-1](#): only for patients withdrawn due to development of FVIII inhibitors

Procedures for the scheduled visits are described in the section below and in the flowcharts (please refer to section 2). If a visit window is exceeded due to a bleed, this will not be considered a protocol deviation.

Trial Participation: It must be stated in the medical record that the patient is participating in the trial. Patients enrolled will also be provided with a card stating that they are participating in the trial, and contact addresses and telephone numbers. The patients should be instructed to carry the card with them at all times and to return the card to the Investigator at the last visit of the patient or destroy the card after the last trial visit.

Screening and Enrolment Log: The Investigator must keep a Subject Identification List and a Subject screening and Enrolment log/ Informed Consent Log (these can be combined in one document).

Informed Consent Procedure: The patient and/or the patient's legally acceptable representative (LAR) will receive verbal and written information about the trial prior to conduct of any trial related procedures/activities. The information will include e.g. descriptions of N8-GP, the procedures involved, the practical consequences of participating, responsibilities and rights while participating in the trial including the possible advantages and disadvantages. Qualified site staff will ensure that patients and caregivers are fully informed both verbally and in writing. Patients and LAR(s) will have the opportunity to ask questions and have ample time to consider participation. If the patient wishes to participate in the trial, the patient and/or the patients LAR(s) will be requested to sign and date the Informed Consent Form. If the patient is a minor, he can in addition sign a child assent form, as per local regulations. When signing consent for this trial the patient and /or the patients LAR(s) should be informed about the surgery and the extension trials as well.

It must be emphasised that any change in a patient's normal treatment routine is a trial-related activity, which is not allowed before the patient has consented to participate in the trial. For example: If a patient is taken off prophylaxis to allow for 72 hours without FVIII treatment before screening and the interval between the patient's normal prophylaxis doses is less than 72 hours, it is a trial related activity. In such case, it is essential that the informed consent procedure is completed prior to the trial related activities undertaken at the screening visit.

For screening failures: Screening failures are defined as patients who have signed the Informed Consent Form, but fail to comply with the inclusion and exclusion criteria or if patients withdraw consent prior to dosing. Data in respect to the screening visit (Visit 1) will be entered in the screening failure form in the electronic case report form (eCRF) preferably 3 days after data are available. A screening failure call must be made in the interactive voice/web response system (IV/WRS). Serious and non-serious AEs from screening failures will be entered by the Investigator in the eCRF, and consequently transferred to the clinical database. When the trial related procedures have been finalised for screening failures, no more AEs should be entered in the eCRF. Follow-up of AEs should be made according to section [12](#).

Screening failures may be re-evaluated for participation in the trial and is allowed once. This will require a renewed informed consent to be obtained from the patient, a new eCRF should be started and the patient should be allocated a new patient number.

For withdrawn patients: Withdrawn patients are defined as patients who meet the withdrawal criteria after dosing, see section [6.5](#). In case a patient is prematurely withdrawn from the trial the Investigator must aim at undertaking procedures for the last visit (EOT visit) as soon as possible, if possible. The primary reason (AE, non-compliance with protocol or other) for discontinuation must be specified in the eCRF. The end-of-trial form must be completed, and final drug accountability must be performed even if the patient is not able to attend. 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 [8.1.4](#).

End of trial visit: The EOT visit can be all visits from visit 7 until visit 13 depending on when the patient is enrolled in the trial. For patients continuing in the extension trial (pathfinder™ 4) the EOT visit will also be Visit 1 in this trial. If a patient is withdrawn prior to completion of the trial, all attempts must be made to schedule an EOT visit for the patient. The EOT form should be signed at the EOT visit. If a patient continues in FU the EOT form will be signed at the FU Visit.

8.1.1 Visit 1 – Screening Visit for All Patients

Before enrolment in the trial and prior to conduct of any trial related procedures/activities the patient and/or the LAR must have signed the informed consent form after having received written and verbal information about the trial.

The Screening visit should be planned taking the patients FVIII dose regimen in consideration since there should be at least 72 hours after the last administration of coagulation factor products.

All screened patients will receive a unique patient number, which will be assigned to the patient throughout the trial.

Prior to any assessments (laboratory and clinical) at Visit 1, baseline PRO data must be collected.

The patient should be registered for screening by the use of IV/IWRS.

At the Screening visit the following assessments will be performed and/or recorded in the eCRF:

- Informed consent form, signed, dated, see section [19.1](#)
- Pharmacogenomic (FVIII genotype) consent (if applicable), see section [8.3.7.5](#)
- Inclusion and exclusion criteria, see section [6.2](#) and [6.3](#)
- PRO questionnaire, see section [8.4.5](#)

- Demography, see section [8.4.1](#)
- Medical history and Concomitant illness, see section [8.4.4](#)
- Haemophilia treatment history and History of Bleeding Episodes, see section [8.4.4.2](#)
- Haemophilia details, see section [8.4.4.2](#) and Inhibitors status, see section [8.4.4.1](#)
- Concomitant medication, see section [11](#)
- Check date and time of last coagulation factor administration (see section [8.4.3](#))
- AEs, see section [12.1](#)
- Body measurements, see section [8.4.2](#)
- Physical examination, see section [8.3.3](#)
- Vital signs, see section [8.3.4](#)
- ECG, see section [8.3.5](#)
- Dispense trial card
- Enrolment session in IV/IWRS, see section [10](#)

Blood sampling/Urinalysis for local laboratory assessments:

- Haematology, see section [8.3.6.1](#)
- Urinalysis with sticks provided by the central laboratory, see section [8.3.6.2](#)

Blood sampling for central laboratory assessments:

- Biochemistry, see section [8.3.7.1](#)
- Coagulation related parameters (Lupus anticoagulant, Von Willebrand Factor, aPTT and INR) see section [8.3.7.2](#)
- FVIII activity (trough level), see section [8.3.7.3](#)
- FVIII inhibitors, see section [8.3.2.2](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)
- Hepatitis, see viral assessments in section [8.3.7.4](#)
- HIV, see viral assessments in section [8.3.7.4](#)
- FVIII genotype (if documentation is not available in the patient chart and as allowed per local law. In addition, the Investigator, patient or LAR has the right to refuse), see section [8.3.7.5](#)

All results necessary for evaluating the inclusion and exclusion criteria, from local and central laboratory analyses must be available before determining whether or not the patient can continue in the trial in accordance with inclusion and exclusion criteria.

Training and Reminders:

- An appointment for Visit 2a, 2-3 weeks after visit 1, should be made
- Patient should continue with current coagulation factor product until 72 hours prior to Visit 2a. If treated with coagulation factors within the last 72 hours the visit should be rescheduled
- Patients in the prophylaxis arm participating in the PK session should be reminded that Visit 2a will require 4 days wash-out and consist of 4 visits to the site during a period of 4 days

Patients will be assigned to on-demand treatment or the prophylaxis arm. The decision to enrol into either the on-demand arm or the prophylaxis arm lies with the patient and Investigator.

8.1.2 Visit Schedule for Patients on Prophylaxis not Undergoing PK Evaluation and for Patients on On-Demand treatment

Visit 2a should take place as soon as possible upon confirmation of eligibility and 2-3 weeks after the Screening visit (Visit 1).

At visit 2a the patients will have their first dose of N8-GP (50 U/kg) BW administered at the site. The second dose (50 U/kg BW) is given at visit 2b 4 days after visit 2a. If a bleeding occurs during this period the patient must come to the site for treatment with N8-GP.

The samples taken post-dose must not be taken from the same vein as previously used for administration of N8-GP.

Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic treatment including doses administered at visits.

At Visit 2a the following assessments will be performed and/or recorded in the eCRF

- Confirmation of inclusion and exclusion criteria, see section [6.2](#) and [6.3](#)
- Withdrawal criteria, see section [6.5](#)
- Concomitant medication, see section [11](#)
- Check date and time of last coagulation factor administration (see section [8.4.3](#))
- AEs: before and after dosing, see section [12.1](#)
- Body measurements (weight only), see section [8.4.2](#)
- Physical examination, see section [8.3.3](#)
- Vital signs (before dosing and 30 min (\pm 10 min) after dosing), see section [8.3.4](#)
- e-Diary training, see section [5.3](#) and [8.4.3](#)
- e-Diary dispensing
- Dispensing of N8-GP in IV/WRS, see section [10](#)
- Administration of first dose of N8-GP (Stop time of injection must be recorded in the eCRF, this corresponds to time “0”)

Blood sampling for local laboratory assessments

- Haematology, see section [8.3.6.1](#)
- Urinalysis with sticks provided by the central laboratory, see section [8.3.6.2](#)

Blood sampling for central laboratory assessments

- Biochemistry, see section [8.3.7.1](#)

- Coagulation related parameters (before dosing and 30 min (± 10 min) after the first dose), see section [8.3.7.2](#)
- FVIII activity (trough and recovery), i.e. before dosing and 30 min (± 5 min) after dosing), see section [8.3.7.3](#)
- FVIII inhibitors, see section [8.3.2.2](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)

At Visit 2b (4 days after first dose) the following assessments will be performed and/or recorded in the eCRF

- Withdrawal criteria, see section [6.5](#)
- Concomitant medication, see section [11](#)
- AEs: before and after dosing, see section [12.1](#)
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section [10](#).
- Dispensing of N8-GP in IV/WRS, see section [10](#)
- Home treatment/e-Diary training, see section [5.3](#) and [8.4.3](#)
- Administration of second dose of N8-GP
- e-Diary data review and rating severity of bleeding episodes, see section [8.2.1](#)

Reminders:

- An appointment for Visit 3 (4 weeks ± 1 week after visit 2a) should be made.
- Withhold N8-GP minimum 96 hours prior to next visit

8.1.2.1 Visit 3-13 for Patients on Prophylaxis not Undergoing PK Evaluation and Patients on On-Demand Treatment

The home treatment period for patients on prophylaxis and on-demand is approximately 4 weeks ± 1 week between Visit 3, 4 and 5 and approximately 8 weeks ± 1 weeks between Visit 6, 7, 8, 9, 10, 11, 12 and 13, see section [Table 2-1](#). At the EOT visit patients will not be dosed at the site.

Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment during the home treatment period since last visit

The samples taken post dose, must not be taken from the same vein as previously used for administration of N8-GP.

The following will be performed and/or recorded in the eCRF:

- Withdrawal criteria, see section [6.5](#)
- PRO questionnaires, EOT visit only, see section [8.4.5](#)
- Concomitant medication, see section [11](#)
- Check date and time of last coagulation factor administration (see section [8.4.3](#))
- AEs: Since previous visit, see section [12.1](#)
- Body measurements (weight only at all visits except EOT visit), see section [8.4.2](#)
- Physical examination (only at visit 5, 9 and EOT visit), see section [8.3.3](#)
- Vital signs, (before dosing), see section [8.3.4](#)
- ECG (only at EOT visit), see section [8.3.5](#)
- e-Diary data review and rate severity of bleeding episodes, see section [8.2.1](#)
- Home treatment/e-Diary training (not at EOT)
- N8-GP administration, not at EOT visit and not for on-demand patients (Stop time of injection must be recorded in the eCRF, this corresponds to time “0”)
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section [10](#)

- Dispensing of N8-GP for clinic dosing/home treatment must be performed via IV/WRS (except at EOT visit), see section [10](#)
- EOT form (at last visit)
- Affirmation statement (at EOT only)
- Completion session in IV/WRS (at EOT only)
- Return eDiary (at EOT only)

Blood sampling for local laboratory assessments:

- Haematology (to be taken within 1 hour prior to dosing), see section [8.3.6.1](#)

Blood sampling for central laboratory assessments:

- Biochemistry, see section [8.3.7.1](#)
- FVIII activity (trough level and recovery), i.e. before dosing and 30 min (± 5 min) after dosing. Recovery not to be done in the on-demand arm and not at EOT visit, see section [8.3.6.3](#)
- FVIII inhibitors, see section [8.3.2.2](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)

Reminders for each visit:

- An appointment for the next visit should be made.
- Withhold N8-GP minimum 96 hours prior to next visit
- For patients continuing in the pathfinderTM 4, the EOT Visit will be the first visit in the extension trial, therefore informed consent must be obtained prior to EOT Visit.

8.1.3 Visit Schedule for Patients on Prophylaxis Undergoing PK Evaluation

The PK procedures will take place at visit 2a and visit 7.

All other visits, i.e. visits 1, 3-6, 8-13 (except for the PK visits) are identical to the visits described in section [8.1.2](#).

After completion of the PK sessions the patients will continue treatment in the prophylaxis arm.

8.1.3.1 Visit 2a for Patients on Prophylaxis Undergoing PK Evaluation

Visit 2a should take place as soon as possible upon confirmation of eligibility 2-3 weeks after the screening visit (Visit 1). Overnight stay is not required during the PK evaluation.

At visit 2a the patients will receive their first dose of N8-GP (50 U/kg BW) at the site and nine PK samples will be taken during the following 4 days.

The additional assessments and blood samples for PK patients are outlined in the flowchart in [Table 2-2](#).

Samples taken pre-dose may be taken from the same arm as the one used for N8-GP administration.

The samples taken 30 min post dose must not be taken from the same vein as previously used for administration of N8-GP. The lines/tubes must be flushed immediately after administration of the trial product.

The following will be performed and/or recorded in the eCRF:

Assessments to be made before the PK session at the day of dosing

- Confirmation of inclusion and exclusion criteria, see section [6.2](#) and [6.3](#)
- Withdrawal criteria, see section [6.5](#)
- Concomitant medication at all time points during PK, see section [11](#)
- Check date and time of last coagulation factor administration (see section [8.4.3](#))
- AEs, see section [12.1](#)
- Body measurements (weight only), see section [8.4.2](#)
- Physical examination, see section [8.3.3](#)
- Vital signs, see section [8.3.4](#)
- e-Diary dispensing

Blood sampling for local laboratory assessments to be taken within 1 hour prior to dosing:

- Haematology, see section [8.3.6.1](#)
- Urinalysis with sticks provided by the central laboratory, see section [8.3.6.2](#)

Blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- Biochemistry, see section [8.3.7.1](#)
- Coagulation related parameters (aPPT and INR) (before dosing and 30 min (± 10 min) after the first dose) see section [8.3.7.2](#)
- FVIII activity (trough level), see section [8.3.7.3](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)
- FVIII inhibitors, see section [8.3.2.2](#)

First N8-GP administration

- Dispensing of N8-GP for PK evaluation in IV/WRS
- Patients will receive 50 U/kg BW of N8-GP (Stop time of injection must be recorded in the eCRF, this corresponds to time "0")

The following will be performed and/or recorded in the eCRF for the PK session:

- FVIII activity: 30 min (± 5 min), 1 hr (± 5 min), 4 hours (± 30 min), 12 hours (± 30 min.), 24 hours (+ 8 hours), 48 hours (+ 8 hours), 72 hours (+ 8 hours) and 96 hours (+ 8 hours) after dosing, see section [8.3.7.3](#)
- AEs, within 1 hour before dosing, 30 min (± 5 min), 1 hr (± 5 min), 4 hours (± 30 min), 12 hours (± 30 min) 24 hours (+ 8 hours), 48 hours (+ 8 hours), 72 hours (+ 8 hours) and 96 hours (+ 8 hours) after dosing, see section [12.1](#)
- Vital signs: within 1 hour before dosing and 30 minutes (± 5 min) and 96 hours (+ 8 hours) after dosing, see section [8.3.4](#)

Laboratory assessments are to be analysed at central Laboratory

Training

- e-Diary training, see [5.3](#) and [8.4.3](#)

8.1.3.2 Visit 2b for Patients on Prophylaxis Undergoing PK Evaluation

The second dose of N8-GP will be administered at the site after the last PK sample is taken.

Four days after first dose the following assessments will be performed and/or recorded in the eCRF

- Withdrawal criteria, see section [6.5](#)
- AEs: before and after dosing, see section [12.1](#)
- e-Diary data review and rate severity of bleeding episodes [8.2.1](#)
- Home treatment/e-Diary training, see section [5.3](#) and [8.4.3](#)
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section [10](#).

- Dispensing of N8-GP in IV/WRS, see section [10](#)
- Administration of second dose of N8-GP

Reminders:

- An appointment for Visit 3 (4 weeks \pm 1 week after) should be made.
- Withhold N8-GP minimum 96 hours prior to next visit
- The patients who underwent a PK evaluation at Visit 2a must undergo an additional PK evaluation at Visit 7.

8.1.3.3 Visit 7 for Patients on Prophylaxis Undergoing PK Evaluation

Patients who underwent a PK evaluation at Visit 2a must undergo an additional PK evaluation at Visit 7. If the patient received N8-GP within the last 7 days prior to Visit 7, the visit should be rescheduled. Overnight stay is not required during the PK evaluation.

Samples taken pre-dose may be taken from the same arm as the one used for N8-GP administration.

The samples taken 30 min post dose must not be taken from the same vein as previously used for administration of N8-GP. The lines/tubes must be flushed immediately after administration of the trial product.

The following will be performed and/or recorded in the eCRF:

Assessments to be made before the PK session at the day of dosing

- Withdrawal criteria, see section [6.5](#)
- Concomitant medication, see section [11](#)
- Check date and time of last coagulation factor administration (see section [8.4.3](#))
- AEs, since previous visits, see section [12.1](#)
- Body measurements (weight only), see section [8.4.2](#)
- Physical examination, see section [8.3.3](#)
- Vital signs, see section [8.3.4](#)

Blood sampling for local laboratory assessments to be taken within 1 hour prior to dosing:

- Haematology, see section [8.3.6.1](#)
- Urinalysis with sticks provided by the central laboratory, see section [8.3.6.2](#)

Blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- Biochemistry, see section [8.3.7.1](#)
- Coagulation related parameters, see section [8.3.7.2](#)
- FVIII activity (trough level), see section [8.3.7.3](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)
- FVIII inhibitors, see section [8.3.2.2](#)

N8-GP administration

- Dispensing of N8-GP for PK evaluation in IV/WRS
- Patients will receive 50 U/kg BW of N8-GP (Stop time of injection must be recorded in the eCRF, this corresponds to time “0”)

The following will be performed and/or recorded in the eCRF for the PK session:

- FVIII activity: 30 min (± 5 min), 1 hr (± 5 min), 4 hours (± 30 min), 12 hours (± 30 min.), 24 hours (+ 8 hours), 48 hours (+ 8 hours), 72 hours (+ 8 hours) and 96 hours (+ 8 hours) after dosing, see section [8.3.7.3](#)
- AEs, within 1 hour before dosing, 30 min (± 5 min), 1 hr (± 5 min), 4 hours (± 30 min), 12 hours (± 30 min), 24 hours (+ 8 hours), 48 hours (+ 8 hours), 72 hours (+ 8 hours) and 96 hours (+ 8 hours) after dosing, see section [12.1](#)
- Vital signs: within 1 hour before dosing, 30 minutes (± 5 min) and 96 hours (+ 8 hours) after dosing, see section [8.3.4](#)

Laboratory assessments are to be analysed at Central Laboratory.

Training/review

- e-Diary data review and rating of severity of bleeding episodes, see section [8.2.1](#)
- Home treatment/e-Diary training, see section [5.3](#) and [8.4.3](#)

IV/WRS

- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in the IV/WRS, see section [10](#)
- Dispensing of N8-GP for home treatment must be performed via IV/WRS, see section [10](#)

Reminders:

- An appointment for Visit 8 (8 weeks ± 1 week later) should be made.
- Withhold N8-GP minimum 96 hours prior to next visit

8.1.4 Follow-up visit (only for patients withdrawn due to development of FVIII inhibitors)

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 \pm 2 weeks) after the EOT Visit the patient must attend a FU Visit, please see Section [8.3.6](#). 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 \pm 2 week as long as clinically warranted up until 3 months after confirmation of the FVIII inhibitor.

The following will be performed and/or recorded in the eCRF:

- Follow up on any AEs according to section [12.1](#)
- Vital signs, see section [8.3.4](#)
- Bleeding episodes since last visit
- Affirmation statement
- EOT form

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see section [8.3.2.2](#)

8.1.5 **Unscheduled Visits**

It is possible to perform Unscheduled visits during the trial. The Unscheduled visit can be performed any time after enrolment and until the EOT visits as either a telephone visit or a site visit. Patients can attend an unscheduled visit due to a bleeding episode, suspicion of inhibitor development, any AE, sampling for laboratory test etc.

Visits/contacts to the site for the purpose of non-trial related activities do not need to be reported as an Unscheduled visit.

The following can be performed/reported at an Unscheduled visit:

- Withdrawal criteria, see section [6.5](#)
- Concomitant medication, see section [11](#)
- Bleeding episodes including date, severity and location see section [8.2.1](#)
- E-Diary compliance review, see section [8.2.1](#)
- AEs: Since previous visit, see section [12.1](#)
- Dispensing of N8-GP for dosing/home treatment must be performed via IV/WRS, see section [10](#)
- Body measurements, see section [8.4.2](#)
- Physical examination, see section [8.3.3](#)
- Vital signs, see section [8.3.4](#)
- ECG, see section [8.3.5](#)
- Biochemistry, see section [8.3.7.1](#)
- Haematology, see section [8.3.6.1](#)
- HIV (viral assessments), see section [8.3.7.4](#)
- Hepatitis (viral assessments), see section [8.3.7.4](#)
- Coagulation-related parameters, see section [8.3.7.2](#)
- FVIII activity (trough level and recovery), see section [8.3.7.3](#)
- FVIII inhibitors, see section [8.3.2.2](#)
- N8-GP binding antibodies, see section [8.3.2.1](#)
- IgE, IgG, see section [8.3.2.3](#)
- N8-GP administration, not for on-demand patients
- Home treatment/E-Diary training, see section [5.3](#) and [8.4.3](#)
- Drug accountability of N8-GP, see section [10](#)
- Surgery transfer session

8.1.6 Transfer of Patients due to Major Surgeries

In case major surgery is needed the patients should be transferred to the pathfinder™ 3 trial. To enable patients to be transferred the following assessments have to be performed:

- To ensure that N8-GP is available for the surgery, notify the IVRS system at least 14 days prior to a planned surgery by using the IVRS “Dispensing session”. This can be done both at planned and unscheduled visits.
- At the day of transferring to the pathfinder™ 3 trial the IVRS ”surgery transfer session” should be used in order to transfer the patient into pathfinder™ 3
- Drug accountability – the patient must return and account for all drug dispensed in the current trial before entering pathfinder™ 3
- After completion of pathfinder™ 3 trial an IVRS ”surgery transfer session” should be performed in order to transfer the patient into pathfinder™ 2
- Fill in the Surgery transfer form in the e-CRF

Upon completion of pathfinder™ 3, patients will return to pathfinder™ 2, re-entering the prophylactic or on-demand treatment arm as per their prior participation in the trial. The patient will return to the next visit in line in Pathfinder™ 2 and the visit assessment performed at the EOT visit in pathfinder™ 3 will be used.

8.2 Efficacy Assessments

8.2.1 Bleeding Episodes

During the entire trial period all treatment requiring bleeding episodes will be entered by the patient or caregiver in the patient’s eDiary. In case a patient is unable to enter a bleeding episode in the eDiary or hospitalised the Investigator will have to report it in the eCRF as an unscheduled visit, please refer to section [8.1.5](#).

If a patient experience a 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 bleed is mild/moderate, the treatment responsibility is with the patient, patient’s caregiver(s) and/or Investigator. For severe bleeding episodes, the treatment responsibility is always with the Investigator and the patient should contact the site and come to an unscheduled visit. Treatment of severe bleeding episodes should be initiated as soon as possible by the patient or caregiver, before coming to the site. It is the responsibility of the Investigator to assess the severity of the bleeding episodes and to ensure that all data is recorded correctly in the patient’s eDiary.

Joint bleeds are either categorised as target joint or non-target joint bleeds. Target joints are defined as 3 or more bleeding episodes in the same joint within 6 months. When there has been no bleed in this same joint for 12 months, such a joint is no longer considered a target joint.

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

- Prophylaxis or treatment of bleed
- Date and time of onset of bleed
- Location of the bleed
- Cause of bleed (spontaneous, traumatic, minor surgery)
- Haemostatic drug used for
- Pain relieving medication
- Dose(s) and Time(s) of administration
- Other therapy used (compression, ice or other)
- Stop of bleed (date and time)
- Categorisation of the bleeding episode (mild/moderate or severe), in the eCRF
- Clinical evaluation of the haemostatic response (excellent, good, moderate or none)
- Bleed related days away from work or school
- Bleed related days using mobility aids

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.

8.2.1.1 Definition of Severity of Bleeding episodes

- **Mild/Moderate:** Bleeding episodes that are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds
- **Severe:** All intracranial, retroperitoneal, iliopsoas and neck bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe. These bleeding episodes must be treated immediately or at the local emergency room and the trial personnel must be contacted. The details of severe bleeding episodes must be entered in the eDiary or if the patient is unable to fill in the e-Diary or hospitalized, the Investigator or trial personnel can enter the data in the eCRF as an unscheduled visit. Traumatic bleeds at other locations than described above can always be considered severe at the investigators discretion.

8.2.1.2 Definition of Haemostatic Response:

- **Excellent:** abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single infusion.
- **Good:** definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after one infusion, but possibly requiring more than one infusion for complete resolution
- **Moderate:** probable or slight beneficial effect within approximately 8 hours after the first infusion; usually requiring more than one infusion
- **None:** no improvement, or worsening of symptoms

Classification of a bleeding episode

- Spontaneous, traumatic, re-bleed, minor surgery

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

8.3 Safety Assessments

8.3.1 Adverse Events

Monitoring of AEs will be performed from the first trial related activity (screening) to the EOT visit, according to the procedures described in section [12](#).

For recording of bleeding episodes, please refer to sections [8.2.1](#) and [12.1.3](#).

8.3.2 Antibody Assessments

Blood samples for assessment of antibody formation against N8-GP will be drawn at the screening visit, pre-dose of N8-GP administration at all visits (except visit 2b) and at the follow-up visit approximately one month after the End of Trial visit. Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment during the home treatment period since last visit. The samples will be analysed both using the Bethesda assay identifying inhibitory antibodies towards FVIII and using an assay capable of identifying the occurrence of any antibodies towards both rFVIII and N8-GP.

8.3.2.1 N8-GP antibody assay

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

The presence of N8-GP binding antibodies will be determined by a radioimmunoassay and is 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 a 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 will 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 96 hours wash out is not sufficient to avoid drug interference in the inhibitor assay.

8.3.2.2 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 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 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 has inhibitor (≥ 0.6 BU/mL) if the patient has been tested positive for inhibitors at two consecutive test samples performed at the central laboratory preferably with no more than 2 weeks between the tests.

A follow-Up Visit must be scheduled 1 month after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted up to 3 months after the EOT Visit.

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. A positive inhibitor test must be reported as a MESI (please refer to section [12.1.2](#))

Blood samples for measurement of inhibitors towards FVIII will be analysed according to the Nijmegen modification of the Bethesda assay¹⁵. Any sampling for the inhibitor test must be performed at least 96 hours after last administration of N8-GP to allow for maximum wash-out of the drug.

An inhibitor test with a result ≥ 0.6 BU/ml will be considered as a positive inhibitor test. A patient is verified inhibitor positive if two independent samples from same patient are inhibitor positive (≥ 0.6 BU) – and the patient should discontinue the trial including an EOT Visit and FU Visits.

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

If more than two patients are verified inhibitor positive an unscheduled Safety Committee Meeting will be called by Global Safety – and a decision whether to continue, modify or stop the trial will be made, see Section [12.5.3](#).

8.3.2.3 Antibody Assessments in case of Allergic/Anaphylactic Reaction

Any patient who experiences an unexpected allergic/anaphylactic reaction will be assessed for inhibitors and antibodies against drug product content, such as IgG/IgE against N8-GP and Host Cell Proteins (HCP). Additional blood samples may be requested for this purpose. If it is deemed necessary, the same analyses will be performed for all patients enrolled in the trial using available blood samples.

8.3.3 Physical Examination

The physical examinations will be performed according to local procedure and will 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

Any changes in the examination between the visits which fulfil the criteria of an AE must be recorded as such (see section [12](#)).

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

8.3.4 Vital Signs

Before measurement of vital signs the patient must rest comfortably for at least three 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.

Vitals signs include assessment of:

- Body temperature (according to local standard practice)
- Pulse
- Blood pressure
- Respiratory rate (resp./min)

Elevated BP is defined as a systolic BP >160 mmHg or a diastolic BP >95 mmHg. Decreased BP is defined as a systolic BP <90 mmHg or a decrease from pre-dose of more than 30 mmHg.

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.

8.3.5 ECG

ECG must be performed at Screening (Visit 1) and EOT visit. ECGs will be performed using a 12-lead Electro Cardiogram. For the ECG recording the patients must be resting and in a horizontal position. Any irregularities observed during the ECG e.g. cough, should either induce a re-run of the ECG and/or be annotated in the eCRF page with description of the occurrence. Print-outs must include date, time, patient's identification, and initials of the Investigator, and at least 2 complexes for each lead and a single rhythm strip of 6 beats. Electronic capture of these measurements may also be performed.

The interpretation of result must follow the categories "normal", "abnormal, not clinically significant" or "abnormal, clinically significant". The evaluation should be made by the Investigator or delegated to a cardiologist.

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

8.3.6 Local Laboratory Tests

The local laboratory will analyse and report all laboratory safety tests related to haematology and urinalysis performed in this trial. Laboratory results from the local laboratory will be reported in the eCRF.

An investigator must sign, date and categorise the local laboratory results. Categorisation will be either "normal", "out of normal range, not clinically significant" or "out of normal range, clinically significant". Clinically significant findings must be recorded as Concomitant Illness (blood samples during visit 1) or as an AE (blood samples taken at visit 2-13 incl. unscheduled visits).

Abnormalities should only be recorded as AEs if not present or worsened from baseline/previous assessments. Laboratory results should be signed and dated. Local laboratory result (reports) are

considering source data and should be kept in the patient file for source data verification (carried out by the monitor).

The administration of N8-GP will be performed after collection of all blood samples for the laboratory tests, except the recovery samples which must be collected 30 minutes after administration of N8-GP.

Storage, handling, and disposition of samples analysed at local laboratories, will be performed according to local laboratory procedures. It will be possible for the site to report in other predefined units than listed below.

The local laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the trial database or the eCRF, but may be reported to the investigator according to specifications in the laboratory standard operating procedures and requirements. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

8.3.6.1 Haematology

- Platelet count (thrombocytes) ($\times 10^9/L$)
- Haemoglobin (mmol/L)
- Red cell count (erythrocytes) ($\times 10^{12}/L$)
- Mean corpuscular volume (MCV) (fL)
- Packed cell volume (haematocrit) (PCV) (%)
- White cell count (leucocytes) ($\times 10^9/L$)
- Differential white cell count (%)
 - Lymphocytes
 - Monocytes
 - Neutrophils
 - Eosinophils
 - Basophils

8.3.6.2 Urinalysis

Qualitative examination (stick):

- pH
- Proteins
- Glucose
- Bilirubin
- Blood

Urinalysis will be performed locally with sticks provided by the central laboratory and should be recorded directly in the eCRF. Results from the urinalysis other than pH, proteins, glucose, bilirubin and blood should not be reported to Novo Nordisk.

Clinical significant findings must be recorded as concomitant illness at screening and as AEs at the following visits if it is new finding or a change relative to a previous visit.

8.3.6.3 FVIII activity (local laboratory)

- FVIII:C (U/mL)

The patient is enrolled in the trial based on the FVIII activity reported in the medical records.

The Investigator can at any time during the trial perform FVIII activity at his/her discretion. When FVIII activity measurements are made clot or chromogenic assays must be used. Moreover, a reference standard provided by Novo Nordisk should also be analysed when running the assay. The reference standard will be provided by Novo Nordisk together with a description of how to handle, store and use it.

8.3.7 Central Laboratory Assessments

A Central Laboratory will analyse and report all laboratory safety tests performed in this trial related to coagulation parameters, biochemistry, viral assessments, and FVIII inhibitor assessments. Laboratory data from the Central Laboratory will be reported to Novo Nordisk electronically. Laboratory data will be reported to Novo Nordisk in a manner that anonymity of patients will be maintained. Central Laboratory data will be reported to the investigators by fax or e-mail. Upon review of the central laboratory results the investigator must sign and date the laboratory reports.

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

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

The central laboratory is requested only to report the analyses dictated by this protocol.

The central laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses. Such data will not be transferred to the trial database or the eCRF, but may be reported to the investigator according to specifications in the

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

8.3.7.1 Biochemistry

- Sodium (mmol/L)
- Potassium (mmol/L)
- Total calcium (mmol/L)
- Chloride (mmol/L)
- Creatinine (micromol/L)
- Urea (mmol/L)
- Albumin (g/L)
- Total Proteins (g/L)
- Total bilirubin (micromol/L)
- Cholesterol (mmol/L)
- Aspartate aminotransferase (AST) (IU/L)
- Alanine aminotransferase (ALT) (IU/L)
- Gamma glutamyltransferase (GGT) (IU/L)
- Alkaline phosphatase (IU/L)
- C-reactive protein (CRP) (mg/L)

8.3.7.2 Coagulation related Parameters

- aPTT (activated partial thromboplastin time) (s)
- INR (prothrombin time) (sec, INR)
- Lupus anticoagulant
- Von Willebrand's factor

8.3.7.3 FVIII Activity (central laboratory)

The analysis of plasma FVIII activity will be performed at laboratory selected by Novo Nordisk by three different assays (see below). Blood samples for analysis of FVIII activity will be collected from all patients in the prophylaxis arms at the dosing visits pre-dosing (trough level)^f and 30 minutes post-dosing (FVIII recovery)^g. For patients on prophylaxis undergoing PK evaluation (at Visit 2a and Visit 7), additional samples will be taken post-dose (30 min, 1, 4, 12, 24, 48, 72 and 96 hours post). Exact date and time of sampling must be documented. The sampling time points are relative to completion of N8-GP administration.

^f The trough level is defined as the lowest level of FVIII measured immediately prior to dosing and reported as (U/mL).

^g Incremental recovery is the FVIII level 30 minutes after trial product administration relative to the dose administered and will be reported as [U/mL]/[U/kg]

For on-demand patients only one sample will be taken at each visit for analysis of plasma FVIII activity. The primary analysis of PK will be based on the chromogenic method; however, the samples will also be assayed using a modified one-stage clotting assay.

One-stage clot activity assay

The one-stage bioassay (FVIII:C assay, clot assay) measures the activity of the compound in a specific process (clot formation). The FVIII:C assay is a modified one-stage clotting assay (modified aPTT assay) calibrated with an internal N8-GP reference standard for N8-GP and/or with an international standard.

Chromogenic activity assay

A bioassay (FVIII:C chromogenic assay), which measures the activity of the compound with a two-stage method. The FVIII:C is determined by measuring the FVIIIa/FIXa-mediated FX activation with a chromogenic FXa substrate. It is a validated assay calibrated with an internal N8-GP reference standard for N8-GP and/or with an international plasma standard.

Exploratory assays for measuring N8-GP activity

A non validated exploratory Thrombin generation assay (TGA) and/or other assays can be applied for measuring activity of N8-GP and analysed by the end of the trial. The results from these assays will be reported separately.

8.3.7.4 Viral assessments (HIV, Hepatitis B and C)

Viral assessments should be performed if status is unknown or the investigator considers there is an indication to test.

- Surface antigen of hepatitis B (HBsAg)
- Anti-HCV antibodies (Hepatitis C)
- HIV 1 & 2 antibodies (If known to be HIV positive, last CD4+ T cell count and date of test. If the CD4+ T cell count test is more than 6 months old, a new test must be taken and send to the central laboratory before determining whether or not the patient is eligible in accordance with inclusion and exclusion criteria)
- Viral load

8.3.7.5 FVIII genotype testing (Not applicable to Brazil)

At visit 1, all patients/LARs will be asked about documentation of previous FVIII genotype tests. If not available or if it needs to be re-tested FVIII genotype testing will be offered at visit 1. Investigator and patients/LARs have the right to refuse to provide patient's FVIII genotype documentation or to refuse genotyping.

Applicable for Japan and Taiwan only: If documentation of the patients' genotype already exists, the patients are offered to provide their data for the trial. Only FVIII genotype is analyzed by using

DNA, isolated from patients' leucocytes at the laboratory in Germany. No further analysis will be carried out for other genotype. Samples will be disposed appropriately after the test. All test results are kept strictly confidential in sufficient consideration of individual information.

8.4 Other Assessments

The following assessments should preferably be performed prior to blood sampling and prior to administration of N8-GP unless it is clearly stated otherwise. All assessments should be recorded in the eCRF unless stated otherwise.

8.4.1 Demographic data

Collected as allowed per local law

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

8.4.2 Body Measurements

All body measurements (weight, height and BMI) will be performed at Visit 1. On all other visits only weight will be measured. The weight measured at the respective visits should be the weight used for calculation of the dose administered.

- Weight, wearing light clothing only (kg/pounds) and without shoes
- Height, without shoes (cm/inches), (visit 1 only)
- BMI calculation (kg/m^2) (visit 1 only)

8.4.3 eDiaries

eDiaries will be used in this trial. The patient should bring the eDiary to every visit to the site.

The following data will, as a minimum, be captured by the patient or the caregiver in the e-Diary:

- Treatment
 - FVIII product used
 - Prophylaxis or treatment of bleed
 - Dose level
 - Date and time of dose administration
- Bleeding episodes
 - Onset of bleed (date and time)
 - Haemostatic drug used for treatment (dose and time of administration)
 - Pain relieving medication
 - Cause of bleed (spontaneous, traumatic, minor surgery)
 - Location of bleed
 - Other therapy used (compression, ice or other)

- Evaluation of haemostatic response (excellent, good, moderate, none)
- Stop of bleed (date and time)
- Bleed related days away from work or school
- Bleed related days using mobility aids

The Investigator must carefully instruct the patient in how to evaluate a bleeding episode, the haemostatic response after treatment and how to complete the eDiary.

The entries made by the patient in the eDiary will be reviewed by the Investigator together with the patient and/or 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.

It is the investigator responsibility to rate the severity of all reported bleeding episodes in the eCRF.

Trial product administration performed at the site should also be entered in the eDiary by the patient.

8.4.4 Medical History/Concomitant Illness

Complete medical history is to be obtained during the screening procedure. If a diagnosis is unknown the description of symptoms will be recorded. Onset date including year for all illnesses within the last two years should be recorded.

The following organ systems should be assessed and included from medical record:

- Central and peripheral nervous systems
- Eyes-ears-nose-throat
- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal-genitourinary
- Endocrine-metabolic
- Musculo-skeletal
- Dermatologic
- Haematopoietical-lymphatic including blood type parameter (0 type or non-0) as allowed by local law and if available
- Immunological

Conditions related to the following items should be assessed:

- Allergies, including any drug allergies or sensitivities
- Psychiatric disorders
- Abuse of drug, alcohol or any substance

Haemophilia Details (including history)

- Diagnosis of haemophilia A (date)
- Other coagulation related diseases
- Classification of haemophilia A (severe form requested in this trial) and FVIII:C activity level (%) from medical history
- Underlying gene defect (if known)
- Clinical suspicion of inhibitors data from medical history
- Number of inhibitor tests and/or FVIII:C recovery tests within the last 8 years
- History of switching FVIII products (type of products (from/ to) and age at switching) if available
- Relatives with haemophilia A (yes/no)
 - If yes – specify any relatives with haemophilia A and inhibitors (as recalled by patient)

8.4.4.1 Documentation of Inhibitor Status

A positive 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 must include the following:

- two inhibitor test result should be documented within the period since diagnosis, *not necessary within the last 8 years*
- FVIII recovery test performed at least every third year during the last 8 years + evaluation of the bleeding history AND/OR negative inhibitor testing at least every third year during the last 8 years.

8.4.4.2 Bleeding Treatment History including History of Bleeding Episodes

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

- Number of months on prophylaxis
- Dose and frequency of dosing
- Recombinant or plasma FVIII product
- Number of bleeding episodes within the last 12 months (number of treatment requiring bleeding episodes)
- Estimated amount and number of doses used to treat a bleed
- Bleeding pattern prior to prophylaxis therapy was initiated

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

- Number of bleeding episodes within the last 12 months (number of treatment requiring bleeding episodes)
- Recombinant or plasma FVIII product

- Estimated amount and number of doses used to treat a bleed

For all patients the following should be recorded

- **History of Surgery** (Surgeries within the last 5 years)
 - Date of surgery
 - Indication (surgery)
 - Recombinant or plasma FVIII product
- Number of EDs prior to trial entry: must be at least 150 days (yes/no)
- Vaccinations in the last 12 months
- Planned vaccinations in the next 12 months from time of screening visit (should be recorded as concomitant medication at the time of vaccination)

8.4.5 PRO Questionnaires and Health Economics

PROs will be collected at screening visit (Visit 1) and at EOT visit for all patients. The questionnaires should preferably be completed prior to any other trial related activities during the two visits. Health economic data will be collected after treatment starts in connection with bleeding episodes.

Several questionnaires will be used to assess disease and age-group specific quality of life and treatment satisfaction from the screening and EOT Visits.

The following questionnaires should be completed by the patients and, where relevant, also by the parent/LAR:

For trial patients aged 12-16:

HAEMO-QOL: Questionnaire for children/adolescents (8-12 years, 13-16 years)

EQ-5D: Questionnaire (13 years and above)

HAEMO-QOL: Parents proxy; Questionnaire for parents/LARs of Children/adolescents (8-12 years, 13-16 years)

HEMO-SAT(P): Parents proxy; Questionnaire for parents/LARs of adolescents (13-16 years)

For trial patients aged 17 and above:

HAEM-A-QOL: Questionnaire for adults aged 17 and above

HEMO-SAT(A): Questionnaire for adults aged 17 and above

EQ-5D: Questionnaire (13 years and above)

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

To characterise the impact of on-demand and prophylaxis treatment on health economics aspects, the following data will be collected as part of the patient eDiaries:

- Number of days not able to attend school or work if related to bleeding episodes or sequelae of bleeding episodes
- Number of days requiring use of mobility aids (cane, crutches, wheelchair) if related to bleeding episodes or sequelae of bleeding episodes

Furthermore, the following will be recorded in the eCRF:

- Number of hospital admissions and hospitalisation days due to a bleeding episode or sequelae of bleeding episodes
- Visits to an emergency room if related to a bleeding episode or sequelae of bleeding episodes

8.5 Patient Compliance

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

Failure of compliance with scheduled visits and trial product administration may result in withdrawal in accordance with the protocol withdrawal criteria.

Compliance with the N8-GP treatment should be addressed at each visit. In the prophylaxis treatment, 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 96 hours dose intervals mentioned above, but the dose is administered on the correct day, this is not considered a protocol deviation.

8.5.1 Definition of Treatment Compliance

Good compliance: If the prophylaxis infusions of N8-GP is $50 \text{ U/kg BW} \pm 5 \text{ U/kg BW}$ for at least 80% of the prophylaxis infusions and the time interval between two prophylaxis infusions is 4 days for at least 80% of the time.

Less compliance: If the prophylaxis infusions of N8-GP is outside $50 \text{ U/kg BW} \pm 5 \text{ U/kg BW}$ for more than 20% of the prophylaxis infusions or if there is more or less than 4 days between two prophylaxis dosis for more than 20% of the time.

9 Trial Supplies

9.1 Trial Product(s)

The following trial products will be supplied by Novo Nordisk:

- N8-GP 2000 U/vial 211µg/vial as a sterile, freeze-dried powder in a 2-8 °C (36-46°F) stable formulation single use vial of 2000 U/vial to be reconstituted with 4.3 mL of 0.9% Sodium Chloride (NaCl) for i.v. injection.

N8-GP 2000 U/vial 211µg/vial powder must be reconstituted prior to administration. After reconstitution with 4.3 mL Sodium Chloride 0.9% solution each 2000 U vial contains 500 U/mL of N8-GP (4 mL can be withdrawn from the vial). Sodium Chloride 0.9% 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.

Detailed instructions regarding reconstitution of N8-GP will be provided in the Trial Materials Manual (TMM). The reconstitution 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 content of several vials may be combined in one syringe. N8-GP must not be added to or mixed with other material (other than NaCl).

9.2 Trial Product Administration

The trial product should be administered as a slow bolus i.v. injection over approximately 2 mins (from start to completion of injection) for all trial product administrations.

These administrations will primarily be performed at home. All patients and/or caregivers will be instructed by the Investigator how to handle home administration before the first dose administration at home.

9.3 Packaging and Labelling of Trial Product(s)

Novo Nordisk A/S will label and pack the trial product.

N8-GP drug product and sodium chloride will be provided in separate boxes. All trial products will be packed open labelled.

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

Labelling will be in accordance with GCP Annex 13¹⁶, local law and trial requirements.

The details of the packaging and labelling of N8-GP drug product will be provided in the TMM supplied by Clinical Supplies Coordination, Novo Nordisk A/S.

9.4 Storage, Handling, Accountability and Destruction of Trial Product(s)

N8-GP 2000 U/vial 211µg/vial must be stored at 2-8 °C, protected from light. It is recommended to use the trial product immediately following reconstitution. If not used immediately, the reconstituted product can be stored for up to 4 hours at room temperature (below 30°C) or 24 hours at 2–8°C. Exposure to direct sunlight as well as freezing must be avoided after reconstitution. As for other parenteral preparations, the product should be inspected visually for particulate matter and discoloration prior to administration and discarded if either is present.

The Investigator must ensure the availability of proper storage conditions at site and monitor, record and evaluate the temperature. The storage facilities must be checked frequently using a calibrated temperature logging device. A temperature log for temperature recording (actual, min., and max. temperature on working days) must be kept at the Investigator site. The Investigator must contact the Monitor in case of deviation from the acceptable temperature range.

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 temperatures must be logged

The site must carefully instruct the patient in how to store the trial product at home and to read the labels with special attention to storage conditions.

Dispensing and Drug Accountability

The IV/WRS will allocate the 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.

- No trial product should be dispensed to any person not enrolled in the trial
- Unused trial product must be stored separately from used trial product
- All vials (used, partially used, unused, returned, and lost/damaged)(except NaCl vials) must be recorded in the IV/WRS drug accountability module

The Investigator or delegated person e.g. trial nurse will perform drug accountability in the IV/WRS Drug Accountability module.

Drug accountability must be performed for all delivered trial products (except NaCl). Trial product will be dispensed at dispensing or assessments visits as appropriate.

All used, partly used and unused trial products returned by the patient must be stored separately from non-allocated trial products. 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.

The TMM detailing the handling of the trial materials will be provided by Novo Nordisk.

For Japan only: Responsibility for storage and drug accountability of the trial products at the study site rests with the head of the study site. The head of the study site should assign some or all of the responsibilities for accountability of the trial products at the sites 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 study 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 adapters etc.

10 Interactive Voice/Web Response System (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time via the internet. Some sessions may be available through a toll-free telephone number. Accessibility 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,
- dispensing of trial product,
- controlling of expiry date of trial product,
- ordering of trial product,
- drug accountability
- screening failure data
- Completion of the trial and
- withdrawal information
- surgery transfer session

Since drug will not be shipped to the site before screening, the investigator should be encouraged to perform screening call in the IV/WRS immediately upon screening of the patient, otherwise the drug may not be available for visit 2.

An IV/WRS site user Guide will be provided to the site.

11 Concomitant Illnesses and Concomitant Medication

Definitions:

Concomitant illness: any illness that is present at the start of the trial (i.e. at the first visit or re-entering from pathfinder™3).

Concomitant medication: any medication, other than the trial product(s), that is taken during the trial, including the screening periods.

Details of all concomitant illnesses and medication must be recorded at trial entry (i.e. at the first visit or re-entering from pathfinder™3). Any changes in concomitant medication must be recorded at each visit. If a change is due to an AE then this must be recorded and reported according to section [12](#). If the change influences the subject's eligibility to continue in the trial then the Monitor must be informed.

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

Prohibited Medication

The following medications are **not** allowed during the course of the trial until after the EOT visit.

- Bypassing products: activated recombinant factor VII (rFVIIa), plasma-derived prothrombin complex concentrates (pd-PCC) and plasma-derived activated prothrombin complex concentrates (pd-aPCC)
- Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma or cryoprecipitate. (**Exception:** current FVIII allowed until 72 hours before Visit 2a)
- Anti-coagulants such as Heparin and vitamin-K antagonists. Heparin is allowed for sealing of central venous access ports according to local practice

12 Adverse Events and Pregnancies

12.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical 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 medicinal product, whether or not considered related to the medicinal product.

Note: This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

An AE can also be a clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity, and is of a severity that requires active management (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

A worsening in concomitant illness must be recorded as an AE. A worsening of an ongoing AE should be reported on a new AE form by making a new assessment for seriousness and/or severity.

The following should not be recorded as AEs:

- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures. These should be recorded as medical history/concomitant illness.

Serious Adverse Event (SAE):

A SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience ^{a)}
- In-patient hospitalisation or prolongation of existing hospitalisation ^{b)}
- A persistent or significant disability/incapacity ^{c)}
- A congenital anomaly/birth defect
- Important medical events ^{d)} that may not result in death, be life-threatening ^{a)} or require hospitalisation may be considered a SAE when, based upon 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.

- 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 were more severe.
- b) The term “hospitalisation” describes a period of at least 24 hours. Over-night stay for observation, treatment at emergency room or treatment on an out-subject basis does not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious.
Hospitalisations for administrative, trial related and social purposes do not constitute hospitalisations as defined by the seriousness criteria, and should therefore not be reported as such. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs.
- c) The term “disability/incapacity” means that following the event the patient or clinical investigation patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.
- d) The term “important medical events” means events which may jeopardise the subject or require intervention to prevent a seriousness criterion. It can be AEs which suggest a significant hazard or puts the subject or clinical investigation subject at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.

Non-Serious Adverse Event:

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

Severity Assessment Definitions:

- Mild – No or transient symptoms, no interference with the subject’s daily activities
- Moderate – Marked symptoms, moderate interference with the subject’s daily activities
- Severe – Considerable interference with the subject’s daily activities, unacceptable.

Relationship to Trial Product N8-GP Assessment Definitions:

- Probable – Good reasons 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.

Outcome Categories and Definitions:

- Recovered – Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering – The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae – As a result of the AE the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). If the sequelae meet seriousness criteria the AE must be reported as serious.
- Not recovered
- Fatal
- Unknown – This term should only be used in cases where the subject is lost to follow-up.

12.1.1 Technical Complaint

A technical complaint is any written, electronic, or oral communication that alleges defects on trial products - listed as trial supplies in this protocol (section 9). The technical complaint may be associated with an AE, but does not concern the AE itself.

A technical complaint may for example concern:

- the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- the packaging material (e.g. leakage, cracks, problems with rubber membrane in the cartridge or errors in labelling text)

12.1.2 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 following the same reporting requirements and timelines for SAEs (see SAE sections) irrespective of if the MESI fulfils a SAE criterion.

The following events are defined as MESIs in this trial;

1. Medication error
 - Administration of wrong drug
 - wrong route of administration such as intramuscular instead of intravenous
 - Administration of an accidental overdose, ie dose which may lead to significant health consequence as judged by the investigator irrespective of whether a SAE criterion is met.
 - Administration of a high dose with the intention to cause harm

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 ($BU \geq 0.6/mL$) at two consecutive tests - sampled preferably within 2 weeks - this should be reported by the investigator as a MESI

3. Allergic reaction including Anaphylactic reaction as defined by Sampson et al 2006¹⁷ (see below). Allergic reactions included 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 as described by Sampson et al.¹⁷. All hypersensitivity reactions reported as MESI will be followed up with a hypersensitivity follow up form..

4. Thromboembolic events

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

5. Other events for expedited reporting

- Suspected transmission of an infectious agent via a trial product

Complete the AE form in the eCRF. If for any reason the EDC application is unavailable, then fax, telephone or email Novo Nordisk. Complete the safety information forms on paper CRFs. Forward a copy electronically in PDF format by fax or courier to Novo Nordisk.

Clinical Criteria for Diagnosing Anaphylaxis (Sampson et al. 2006¹⁷)

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

- Persistent gastrointestinal symptoms (eg, 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)
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline PEF, BP.

Definition of an Acute, Evolving, or Recent Myocardial Infarction

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

1. Typical rise and gradual fall in Troponin T or more rapid rise and fall in Creatine Kinase, Muscle and Brain of biochemical markers of myocardial necrosis with at least one of the following:
 - Ischaemic symptoms
 - Development of pathologic Q waves on the ECG
 - ECG changes indicative of ischaemia (ST segment elevation or depression)
 - Coronary artery intervention (e.g. angioplasty)
2. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria 1 and 2 below are fulfilled):
 - Increase in Troponin T above the "diagnostic" limit: i.e. > 0.03 µg/L
 - New ST-segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)
 - ST-segment depression and or T-wave inversion in two or more contiguous leads ≥ 0.1 mV

Definition of Pulmonary Embolism

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

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

Definition of Cerebral Thrombosis/Infarction:

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

- Computerised tomography
- Magnetic Resonance scan
- Magnetic Resonance Angiogram

- Cerebral angiography

Deep Vein Thrombosis

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

Definition of Other Clinically Significant Thromboembolic Events

Clinically significant signs or suspicion of a thromboembolic event, e.g. visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis.

Thrombophlebitis is not considered a clinically significant thromboembolic event unless evaluated by the Investigator as related to trial product.

Peripheral Artery Occlusion

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

12.1.3 Disease-related Bleeding

Disease-related bleeding episodes evaluated by the Investigator as part of the underlying disease should not be reported as AEs or SAEs unless evaluated by the Investigator as related to trial product.

In case of fatal outcome, the bleeding episode must be reported as a SAE. All bleeding episodes and other symptoms related to the underlying disease will be captured in the eCRF/eDiary.

12.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported for all medicinal products.

At each contact with the trial site (visit or telephone, excluding the follow up visits due to inhibitor development, where the patient is not seeing the Investigator or his staff e.g. visit to the laboratory) the patient must be asked about AEs, 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 recorded by the Investigator and evaluated. Novo Nordisk' assessment of expectedness is done according to the reference documents:

- Investigator's Brochure, N8-GP⁸

The Investigator should record the diagnosis, if available. If no diagnosis is available then the Investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the Investigator on the standard AE form. If more than one sign or symptom is to be reported, use a separate AE form for each sign and symptom. For serious AEs, the safety information form must also be completed. If several signs or symptoms occur as part of the same clinical picture only one set of safety information pages need be used to describe these SAEs.

MESIs must always be reported to the department responsible for global product safety on the AE form and the safety information form, irrespective of seriousness within the same timelines as for SAEs.

The Investigator must report initial information on all SAEs and MESIs to Novo Nordisk within **24 hours** of obtaining knowledge about the event.

The Investigator must complete and forward electronically in pdf format/fax copies to Novo Nordisk:

- AE form in the eCRF **within 24 hours**
- safety information form on the paper CRFs **within 5 calendar days**

of obtaining knowledge about the SAE.

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

Novo Nordisk must inform the regulatory authorities and IECs/IRBs in accordance with the local requirements in force and ICH GCP¹⁸.

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

For Japan only: Novo Nordisk must inform the health authorities and the relevant parties of SAE information in accordance with the Japanese requirements in force and ICH GCP¹⁹.

Investigators will be notified of trial-related SAEs in accordance with the local requirements in force and ICH GCP²⁰.

12.2.1 Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the Investigator should ensure that adequate medical care is provided to the subject for any AE, including clinically significant

laboratory values related to the trial. The Investigator should inform the subject when medical care is needed for AE(s) of which the Investigator becomes aware.

The follow up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Follow-up information (corrections, new or additional information) should be reported **within 24 hours** of obtaining knowledge of the information for SAEs, and if previously non-serious AEs become SAEs.

All non-serious AEs classified as severe or possibly/probably related to the trial product must be followed until the subject has "recovered" or "recovered with sequelae", and all queries have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (i.e. subject dies from another AE) can be closed with an outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the subject has completed the post-trial follow-up period and is expected by the Investigator to recover.

All other 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 post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. AEs ongoing at time of death (i.e. subject dies from another AE) can be closed with an outcome of "recovering" or "not recovered".

The Investigator must ensure that the worst case severity and seriousness is kept consistent.

The Investigator must record follow-up information on non-serious AEs by updating the AE form in the eCRF. The follow-up information should only include new (updated and/or additional) information that reflects the situation at the time of the Investigator's signature.

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days, unless otherwise specified. The Investigator must forward follow-up information on SAEs and MESIs within 5 calendar days of obtaining the information. This must be done by updating the AE form in the eCRF and/or completing a new safety information form marked follow-up on paper

CRF and forwarding these to Novo Nordisk. If for any reason the EDC application is unavailable, then fax, telephone or e-mail to Novo Nordisk.

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 or cancer or AEs ongoing at time of death (i.e. the subject dies from another AE) can be closed with the outcome of "recovered" or "not recovered". Cases can be closed with an outcome of "recovering" when the subject has completed the trial and is expected by the Investigator to recover.

After access to update the AE form in EDC is removed the Investigator must record any SAE and MESI follow-up information, if required, on the paper CRFs provided at trial closure.

Details on how to handle AEs that were not Recovered/Recovering in the pathfinder™3 Surgery Trial when patients are included in the pathfinder™2 Trial

An AE (including SAEs and MESIs), that is not recovered/recovering in the Surgical Trial pathfinder™3 when the patient is enrolled into the present trial (pathfinder™2), will be followed up in the preceding Surgical Trial (pathfinder™3) and entered by the Investigator as concomitant illness in the present trial.

Non-serious AEs that are reported as not related and not severe in the Surgery Trial will not be followed-up when enrolling into the pathfinder™2 trial. Details on how to handle unresolved non-serious AEs when patients are transfer from the pathfinder™3 (Surgery Trial) into the present trial (pathfinder™2) are described below and in [Table 12-1](#).

A not recovered AE from the preceding Surgery Trial which has worsened during participation in the pathfinder™2 must be entered as an AE in the present pathfinder™2 by the Investigator.

Table 12-1 Handling of Not Recovered Non-Serious AEs from pathfinder™3

Severity		Outcome Categories		Relationship		AE follow-up in: NN7088-60 (Surgery)	AE in NN7088-3859 (Present)	Concomitant illness in NN7088-3859 (Present)
Mild/ Moderate	Severe	Recovered/ Recovered with sequelae/ Fatal/ Unknown	Not recovered/ Recovering	Probable/ Possible	Unlikely			
X			X	X		Yes	No*	Yes
	X		X	X		Yes	No*	Yes
X			X		X	No	No*	No
	X		X		X	Yes	No*	Yes

* Unless worsened during participation in pathfinder™2 (Present Trial)

12.3 Technical Complaints and Technical Complaint Samples

12.3.1 Collection and Reporting of Technical Complaints

All technical complaints, as defined in Section [12.1.1](#) - occurring from the time of first and until 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:

- AE(s), SAE(s) and/or MESI(s)

The AE(s), SAE(s) and MESI(s) related to technical complaint(s) must be reported by the investigator following the same reporting requirements and timelines as for other AEs, SAEs and MESIs (see section [12.2](#)).

Technical complaints must be reported on the technical complaint form by the Investigator, as described in the following:

One technical complaint form must be completed for each trial product, non investigational medicinal product (NIMP) or auxiliary supply. If the technical complaint involves more than one batch number, a technical complaint form for each batch number must be completed.

The Investigator must fax the technical complaint form to *Customer Complaint Center, Novo Nordisk, fax: +45 44 42 13 70*, within the following timelines of the trial site obtaining knowledge of the technical complaint:

- technical complaint assessed as related to a **SAE and/or MESI within 24 hours**
- all other technical complaints within **5 calendar days**

12.3.2 Collection, Storage and Shipment of Technical Complaint Samples

The Investigator must collect the technical complaint sample. If the technical complaint sample is not collected, the investigator must specify why it was not collected on the technical complaint form.

The **technical complaint sample and a paper copy of the technical complaint form** must be sent to Novo Nordisk within **5 calendar days** of receiving the technical complaint sample at trial site by using the following address:

- Novo Nordisk A/S,
Att.: Customer Complaint Center,
Krogshøj 55,
DK-2880 Bagsværd,
Denmark

The investigator must ensure that the technical complaint sample is labelled with the batch number and, if available, the DUN number.

Storage and shipment of the technical complaint sample should be done in accordance with the conditions described for the product (see section [9](#)). For further details on the shipment conditions of technical complaint samples please contact the monitor.

12.3.3 Pregnancies in Partners of Trial Patients

In the case of an AE (with a causal relationship evaluated as possible or probable by the Investigator) in the foetus, newborn infant(s) or infant(s)/toddler(s) of a trial subject's partner, who is potentially exposed to the trial product via the trial subject, the pregnancy and the AE should be reported on pregnancy form A and B and AE and Safety information forms as appropriate. This information can only be requested after informed consent from the partner.

12.4 Precautions

As with any protein injected i.v., hypersensitivity reactions may occur. The possible events include rash, pruritus, fever, nausea, headache, vomiting and changes in BP.

If any of these events are suspected further FVIII administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines.

12.5 Safety Committee(s)

12.5.1 Internal Novo Nordisk Safety Committee

Novo Nordisk will constitute an internal Safety Committee to perform ongoing safety surveillance of N8-GP.

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

12.5.2 Data Monitoring Committee

As this is an open label trial, the patient group is not particularly vulnerable, and the investigational drug is not expected to show toxicity, no data monitoring committee (DMC) will be established for this trial. Rather, an internal Novo Nordisk Safety Committee will be established with the overall responsibility of overseeing the safety of the patients enrolled in the trial.

12.5.3 Stopping Rules

Any event occurring after administration of N8-GP fulfilling the SAE/MESI criteria must be reported to Novo Nordisk within 24 hours. If the stopping criteria mentioned below is fulfilled, enrolment of additional patients will be put on hold. All Investigators will be informed in writing. An unscheduled Safety Committee meeting will be called for to decide whether or not the trial can continue with or without modifications. During the evaluation of the stopping rules the trial will be on hold meaning no new patients 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 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 phase III trials being put on hold:

- Inhibitor formation (Bethesda Unit (BU) of ≥ 0.6 BU) 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

13 Case Report Forms

Novo Nordisk will provide a system for electronic data capture (EDC). 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.

13.1 Rules for Completing eCRFs

Ensure that all relevant questions are answered, and that no empty data blocks exist.

If a test/assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable) indicate this according to the data entry instructions.

The Investigator must ensure that all information derived from source documentation is consistent with the source information. By signing the case book electronically, the Investigator confirms that the information is complete and correct.

13.2 Corrections to eCRFs

Corrections to the CRF data will be made by the Investigator or the Investigator's authorised staff. An audit trail will be maintained in the EDC application containing as a minimum: 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 of the Investigator's signature on the case book then the case book must be signed again by the Investigator.

13.3 eCRF Flow

The Investigator must ensure that data is recorded in the CRFs as soon as possible after the visit (preferably within 3 days). When data is entered it will be available to Novo Nordisk for data verification activities.

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 EDC has been removed. This data will be retained by the site.

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

13.4 eDiary

Novo Nordisk will provide patients with an eDiary for electronic recording of details of their bleeding episodes, see section 8.4.3. The eDiary and related support services will be supplied by a vendor that will be working under the direction and supervision of Novo Nordisk.

At Visit 2a, the patients will be provided with the eDiary and trained in the use hereof. The eDiary will be returned by the patient at the EOT visit.

Data will be entered by the patient or caregiver in the eDiary device. All data entered will be automatically transferred from the device to the 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 of need for corrections to the transferred data, 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.

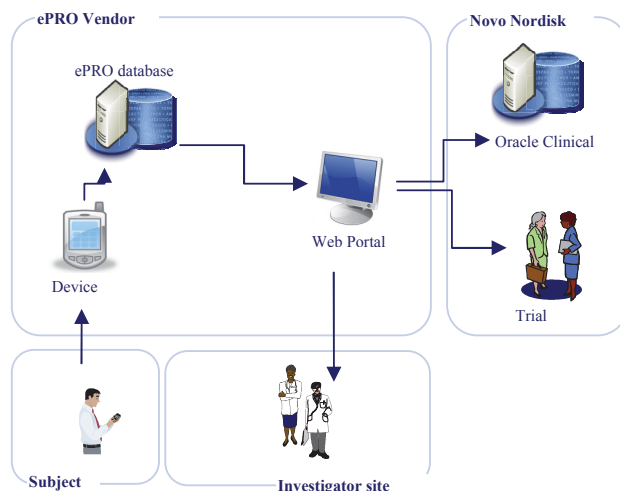


Figure 13-1 eDiary Data Flow

14 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. The intervals between visits must 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. In addition the Monitor should be available for discussions e.g. by telephone.

For Screening Failures: Data in respect to the Screening visit must be entered in the eCRF within preferably 3 days after data are available. The Screening Failure Form must be completed. These data 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.

It must be possible to verify data in the eCRF against source documents.

eDiaries will be provided by PHT. Information on treatment and bleeding episodes will be collected in the eDiaries (please refer to section [8.4.3](#)).

The completed Diaries are considered source data. The patient will only be identified by patient number. The Monitor will verify and ensure that the eCRFs and diaries are completed.

For all data recorded the source document must be defined in a source document agreement at each site.

15 Data Management

Data management is the responsibility of Novo Nordisk Headquarters. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or external clinical research organisation (CRO).

Appropriate measures such as encryption of data files will be used to assure confidentiality of subject data when it is transmitted over open networks.

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

The central and local laboratories will provide laboratory reports to the Investigator. The laboratory report must be signed and dated by the Investigator and stored at the trial site as source data.

Data will be entered and delivered in an Oracle Clinical file and loaded into Oracle Clinical.

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

16 Computerised Systems

Novo Nordisk will capture and process clinical data using computerised systems which are described in NN 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.

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

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection). 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 50 years or as required by local data retention laws for trial data.

17 Evaluability of Patients for Analysis

17.1 Safety Analysis Set

The Safety Analysis Set consists of all patients exposed to N8-GP. The analyses of the safety endpoints will be based on the Safety Analysis Set and all available information until the last visit.

17.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all patients exposed to N8-GP. The efficacy analysis and the PK analysis will be based on the FAS and all available information until EOT visit.

Handling of Exceptional PK Outlier Data

Exceptional outlier pharmacokinetic profiles and/or individual plasma concentrations may be excluded when analysing pharmacokinetic endpoints based on the FAS. If exceptional outlier data are identified, a sensitivity analysis including the outlier data will be conducted.

Unless otherwise stated, analysis results obtained from FAS excluding exceptional outliers will be presented with reference to the “Full Analysis Set excluding outliers”. The results of the sensitivity analysis including the exceptional outliers will refer to “Full Analysis Set incl. all data”.

17.3 Documentation of Analysis Sets

The decision to exclude data points from analysis of PK endpoints based on the Full Analysis Set will be made from a review prior to Database Lock. It will be the joint responsibility of the Clinical Pharmacology Scientist and the Trial Statistician.

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. The documentation will be stored together with the remaining trial documentation. This will also be described in the CTR.

18 Statistical Considerations

18.1 Sample Size Calculation

The study has two co-primary endpoints that both need to succeed for the study to succeed. The two endpoints can reasonably be considered approximately independent and combined power then becomes the product of the individual power for each co-primary endpoint.

Co-Primary Endpoint: Incidence Rate of Inhibitory Antibodies against FVIII Defined as Titre ≥ 0.6 BU/mL

Given the rarity of the disease, a sample size of 105 patients treated for a minimum of 50 exposure days will allow for a reasonable evaluation of inhibitor formation in this pivotal trial.

The aim is to demonstrate that the upper confidence limit for the inhibitor rate is below 6.8%. In practical terms this will happen if 2 or less inhibitors are observed in the planned 105 patients with 50 exposure days (3 or less if the trial should end with 127 patients with 50 EDs). If the true inhibitor rate of N8-GP is 1% then the chance/power to achieve a maximum 2 inhibitor out of 132 patients entered into the trial will be 85%.

Co-Primary Endpoint: Annualised bleeding rate in the prophylaxis arm

The clinical efficacy of N8-GP in long term bleeding prophylaxis will be evaluated based on all the prophylaxis period data. This will give different period lengths for the different patients but on average it is expected to give about 12 month prophylaxis treatment per patient (~7 months for the last recruited patients and ~17-19 months for the first recruited patients). Prophylactic effect will be concluded if the upper 97.5% confidence limit for the annualised bleeding frequency is < 8.5 . The model will be a Poisson regression allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom (i.e. Scale=Pearson in SAS)) and using log observation time as offset to account for the differing treatment lengths. Based on an approximation to the normal distribution and assuming that the patients bleed 6.8 times per year and an over-dispersion of 5 (so variance 34) 120 patients entered on prophylaxis will give a power of 89%.

The following table shows the power for various relevant assumptions of bleeding rates and over-dispersions (OD).

True rate	OD	Prophylaxis power
6.8	5	89%
6.5	5	97%
6	5	99.9%
6.8	4	83%
6.8	6	95%

Combined power

With 85% power for the first co-primary endpoint and 89% power for the second co-primary endpoint the combined power for the study with the given sample size is expected to be about $85\% \times 89\% = 76\%$.

Confirmatory Secondary Endpoint: Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.

Clinical efficacy of haemostasis (treatment of bleeding episodes) of N8-GP will be demonstrated by showing that the success rate (with success defined as scoring excellent or good and failure as scoring none or moderate) on the four point scale for haemostatic response is acceptably close to 80% (defined as statistically significantly larger than 65%).

Operationally the null-hypothesis will be rejected and a success rate acceptably close to 80% is considered confirmed if the lower bound of the 1-sided 97.5% confidence interval for the rate is above 65%. By assuming that the observations are independent, the power may be calculated exact using the binomial distribution. The power will depend on the number of bleeding episodes actually observed. It is expected that more than 200 bleeding episodes will occur in the trial in the on-demand arm and the prophylaxis arms combined. Assuming a true response rate of 80% the power for this endpoint is greater than 95%. Correlation between observations corresponding to the same patient may reduce this power but is not expected to affect it too much.

18.2 Statistical Methods

18.2.1 General Considerations

Novo Nordisk A/S will be responsible for the statistical analysis. All tests will be performed as 1-sided tests on 2.5% significance level.

18.2.2 Primary Endpoint(s)

The study has two co-primary endpoints that both have to succeed.

Incidence Rate of Inhibitory Antibodies against FVIII defined as Titre ≥ 0.6 BU/ml.

The rate of neutralising antibodies will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the inhibitor rate the nominator will include all patients with neutralising antibodies while the denominator will include all patients with a minimum of 50 exposures plus any patients with less than 50 exposures but with neutralising inhibitors. Adequate safety with regard to neutralising

inhibitors will be concluded if the upper 1-sided 97.5% confidence limit is below 6.8% roughly corresponding to the upper 97.5% confidence limit if 2 inhibitors out of 105 patients are observed (3 or less if the study should get 127 or more patients with 50 exposure days).

In terms of actual observed number of neutralising antibodies the consequence of this is that with the planned trial size of 105 patients with 50 or more exposure days 2 or less patients with a neutralising antibody will be considered acceptable, whereas 3 or more neutralising antibodies will be considered unacceptable. Should the study end up with 127 or more patients with 50 exposure days 3 or less inhibitors would be acceptable

Number of bleeding episodes (total bleeding episodes assessed as Annualised Bleeding Rate) per patient in the prophylaxis arm

A review of historical data has found that haemophilia A patients on on-demand treatment on average bleed 24 times per year while they bleed 6.8 times per year when treated on prophylaxis.

Historical Control for Hypothesis Test for Prophylaxis

Based on the studies referenced below, Novo Nordisk suggests that representative numbers for mean annual bleeding rate (ABR) in severe haemophilia patients is 24 bleeds/year for patients treated on-demand and 6.8 for patients on prophylactic treatment.

Novo Nordisk has based the estimate of historical annual bleeding rate on a systematic review of the treatment of Haemophilia A and B and von Willebrand disease, performed by the Swedish Council on Health Technology Assessment.

The referenced report is based on review of 3710 abstracts in total, covering treatment of Hemophilia A, B or von Willebrand disease. Articles were then selected for full review according to specific criteria such as administration of recombinant or plasma-derived Factor concentrate, outcome (eg number of bleeding episodes, inhibitor development or quality-of-life measurements), and number of patients included. For hemophilia A, only studies comprising 20 patients or more were selected. The main objectives of the SBU review is to evaluate the short- and long-term effects with different treatment strategies with coagulation factor concentrates in Hemophilia A and B and von Willebrand disease.

In the search, SBU identified 37 references dealing with “replacement therapy with factor concentrates in treating severe, moderate, and mild hemophilia A”. All these references identified by SBU were reviewed as full length articles at Novo Nordisk, and only the original papers with a mean total ABR reported (or at least possible to calculate) in patients with an endogenous FVIII:C activity <2% were included in our analysis.

Table 18-1 Historical mean total annual bleeding rate in Haemophilia A patients with an endogenous FVIII:C activity <2%

SBU Ref No	Reference	On-demand (mean ABR)	Number of patients	Prophylaxis (mean ABR)	Number of patients
4	<i>Courter, 2001</i> ²¹	18	27	4	27
5	<i>Lusher, 2003</i> ²²	23	85	10	85
5	<i>Lusher, 2003</i> ²²	N.R.	N.R.	6	45
9	<i>Tarantino, 2004</i> ²³	N.R.	N.R.	6.3	107
10	<i>Nemes, 2007</i> ²⁴	N.R.	N.R.	4.9	49
11	<i>Recht, 2009</i> ²⁵	N.R.	N.R.	3.9	94
15	<i>Abshire, 2000</i> ¹¹	34	38	8.3	27
17	<i>Smith, 2005</i> ^{*26}	N.R.	N.R.	10.3	32
18	<i>Manco-Johnson, 2007</i> ⁴	18	33	3.3	32
25	<i>Schwartz, 1990</i> ^{**27}	19	56	N.R.	N.R.
	Weighted Mean	24	179	6.8	394

ABR = Annual Bleeding Rate. N.R. = not reported. Studies in *italics* have not included adults. No = Reference number in SBU report, chapter 3.1.1. * 5/32 are moderate Hemophilia A, **4/56 are moderate Hemophilia A

In the studies, the mean ABR in patients on prophylaxis is consistently lower than in patients treated on-demand, as expected. The studies have ABR in the range of 18 – 34 and 3.3 – 10, for on-demand and prophylaxis treatment, respectively, and include different numbers of subjects. To arrive at a representative ABR number from the various studies, we weighted the estimates from each study based on the number of subjects included.

As the proposed trial with N8-GP will only include patients aged 12 years and above, we further suggest to exclude 3 of the 9 historical studies^{21, 22, 4} that only include children below age 6, in order to better reflect the study population. The historical mean ABR for on-demand and prophylaxis in haemophilia A with <2% will then be estimated at 24 and 6.8, respectively. However, if also the studies including children below 6 years of age are included, the estimated ABR for on-demand and prophylaxis are 23 and 6.4, respectively. The 2% cut off is often used in clinical studies and will give a conservative estimate of the ABR in the study population in the proposed trial with a cut off of <1%.

Prophylactic effect of N8-GP will be concluded if the bleeding rate is significantly below 50% of the historical on-demand bleeding rate (i.e. significantly lower than 12) as well as within 25% of the historical prophylaxis bleeding rates (i.e. significantly lower than $6.8 * 1.25 = 8.5$). Since both must be met in practice it must be shown that the bleeding rate is significantly lower than 8.5.

Let AR be the observed yearly bleeding rate. The null-hypothesis will be tested against the alternative hypothesis as given by:

$H_0: AR \geq 8.5$ against $H_A: AR < 8.5$

The endpoint will be analysed by a Poisson regression model on number of bleeding episodes per patient allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom (i.e. Scale=Pscale in SAS)) and using log planned observation duration as an offset. Estimates of the annualised bleeding rates will be provided with 95% confidence intervals.

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 this method is considered to give too uncertain LOCF values, hence imputation will not be attempted for such patients and such patients will only contribute with the observed bleeding episodes and observation time.

Sensitivity analyses:

Analysis without imputation to planned trial duration

The primary prophylaxis analysis will be repeated but without imputing number of bleeding episodes from early withdrawals. Instead only the observed bleeding episodes will be counted and the offset will be actual observation duration rather than planned.

Analysis of 12 months data from patients that could have had 12 months prophylaxis

Since patients will stay in the trial until the same end date some patients will get only about 7 months prophylactic treatment while others may get as much as 19 months. To investigate if the varying durations have any impact on the results a sensitivity analysis will be performed looking only at 12 months data from patients with planned trial duration of 12 or more months. Otherwise this analysis will be performed similarly to the primary analysis.

To investigate the effect over time the bleeding rates per month will be calculated and summarised numerically and graphically. For months after month 7 not all patients will be available since the last patients recruited will only receive about 7 months treatment. This may create an apparent time effect really caused by fewer and fewer patients being available. This will be investigated by also

summarising by month only for the first 12 months data from patients that could have received 12 months treatment (i.e. patients recruited earlier than 12 months before LPLV).

Similarly the bleeding rate by calendar month will be calculated and presented. If there is a calendar effect it is conceivable that it would be reversed in the southern hemisphere compared to the northern. For that reason by calendar month summaries will as best possible be presented by northern hemisphere, tropical region and southern hemisphere separately.

18.2.3 Confirmatory Secondary Endpoints

Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.

In order to protect against false significances this endpoint will only be analysed as a confirmatory secondary endpoint if the analyses of the co-primary endpoints are both successful. Otherwise this endpoint will be analysed only as a supportive secondary endpoint.

This is assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and none). Excellent and good counts as success and moderate and none as failure. In addition any bleeding episodes with missing response information will be counted as failures.

A success rate of 80% is considered the goal. Due to variation it is not certain that N8-GP will achieve an observed 80% success rate in this trial even if the true success rate is 80%. For that reason it will be demonstrated that the success rate for N8-GP is at most 15% (absolute) worse than 80%.

Let R be the observed success rate. The null-hypothesis will be tested against the alternative hypothesis as given by:

$H_0: R \leq 65\%$ against $H_A: R > 65\%$

Specifically this will be done by a logistic regression. The analysis will be performed by use of Proc Genmod in SAS. Correlation within patients will be taken into account using a Generalized Estimation Equations approach with a working correlation matrix with a compound symmetry structure. Adequate efficacy will be concluded if the 1-sided lower 97.5% confidence limit for the success rate is above 65%.

Response as measured by the four point scale will also be summarised and listed. Bleeding episodes will come both from the on-demand periods and from prophylaxis periods. This will be analysed together in the statistical analysis but will also be summarised by treatment regimen.

Sensitivity analysis

A sensitivity analysis will be performed similar to the primary analysis but only analysing bleeding episodes with recorded responses (i.e. not counting any bleeding episodes with missing response as failures).

18.2.4 Supportive Secondary Endpoints

18.2.4.1 The Number of Injections of N8-GP required per Bleed

This endpoint will be summarised and listed.

18.2.4.2 Amount of N8-GP required per Bleed

Amount of N8-GP required per bleed (U/kg BW/bleeding episode) will be summarised and listed

18.2.4.3 PK Endpoints

- Incremental recovery, ($[U/mL] / [U/kg]$) (single dose and steady state)
- Trough level, (U/mL) (single dose and steady state)
- AUC, (h*U/mL)
- Terminal half-life ($t_{1/2}$), (h)
- Clearance (mL/h/kg)
- Mean Residence time (MRT) (h)
- Vss (Volume of distribution at steady state) (mL)

Single dose PK will be based on the subgroup of patients with full PK sessions at visits 2 and 7. Steady state PK will be based on the periodic recovery and trough measurements on all patients from visits 3 to 13:

Single dose PK

The PK parameters will be calculated using plasma concentration obtained from chromogenic assay and clot assay. The PK parameters will be derived according to a non-compartmental method, as described in [Table 18-2](#). The actual time points will be used in the calculations.

If any profiles and/or individual plasma concentrations are excluded from the primary pharmacokinetic analysis, a sensitivity pharmacokinetic analysis will also be performed and reported based on all observed data. The primary pharmacokinetic analysis is based on the full analysis set excluding outliers.

Specifically which data points and profiles that will be excluded will be defined prior to database lock. It should exclude profiles with pre-dosing activity > 5% (possibly indicating inadequate washout) and profiles that are not indicative of a normal i.v. short infusion administration (e.g. clearly increasing plasma concentrations initially). If a patient is treated with an additional dose

during the PK session, the plasma concentrations after the occurrence will then be excluded. Furthermore, if the profile shows indications of an additional dose (e.g. clearly increased plasma concentration), the plasma concentrations after the occurrence will then also be excluded.

All pharmacokinetic endpoints will be modelled and analysed by an ANOVA on the log transformed parameter by visit. Estimates of each endpoint with 95% confidence intervals will be provided back-transformed to the natural scale.

All PK profiles will be presented graphically by subject and by visit.

Furthermore, the mean PK endpoints will be summarised and individual PK endpoints will be listed.

Table 18-2 Definition and Calculation of PK Parameters

Parameter	Description	Calculation
Incremental Recovery	Dose-normalised activity recorded 30 min after end of infusion and reported as [U/mL]/[U/kg]. Expected to be the highest dose-normalised activity observed.	The incremental recovery is calculated by dividing the FVIII activity (U/mL) measured in plasma 30 min after dosing by the dose injected at time 0 expressed as U/kg BW
Trough level	Activity recorded immediately before next dose is given and reported as [U/mL]. Expected to be the lowest dose-normalised activity observed.	
$t_{1/2}$	Terminal half-life	$t_{1/2} = \ln(2) / \lambda_z$, where λ_z is the terminal elimination rate. The terminal elimination rate will be estimated using linear regression on the terminal part of the log(activity) versus time profile
CL	Total plasma clearance of drug after intravenous administration	$CL = \text{Dose} / \text{AUC}$
AUC	Area under the activity versus time profile from time zero to infinity. Measure of total plasma exposure.	$\text{AUC} = \text{AUC}_{(0-t)} + C_{(t)} / \lambda_z$, where $C_{(t)}$ is the last measurable activity.

18.3 Safety Endpoints

Treatment emergent AEs (TEAEs defined as AEs occurring after dosing with trial product) and treatment emergent SAEs (TESAEs) will be summarised by frequency of events and frequency of

patients with any event. Similar summaries cross-classified by severity and by causal relation to trial product will be made.

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

HCP-antibodies will be listed.

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

18.4 Interim Analysis

In order to obtain regulatory permission to start surgery treatment in the US, prophylaxis treatment in the US and paediatric trial in the EU lists of acute treatment responses will be prepared at certain time-points. They will include patient details as well as dose given and response to treatment.

18.5 Sequential Safety Analysis/Safety Monitoring

Not applicable (NA).

18.6 Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

NA.

18.7 PK and/or PD Modelling

The relationship between plasma concentration and bleeding frequency will be investigated.

Based on each individuals PK assessments (full PK from some patients but only recovery and troughs for most patients) the time to 5%, 3% and 1% FVIII activity after each dose given will be calculated and the bleeding rates for each period (>5%, 3-5%, 1-3% and <1%) will be calculated and listed and summarised.

A statistical comparison will be made between the bleeding rates above and below 1% FVIII activity. This will be done based on a Poisson regression with patient above or below 1% activity as fixed effects. The model will allow for over-dispersion (estimated using Pearsons chi-square divided by the degrees of freedom) and will use log duration (above 1% activity and below 1% activity respectively) as offset. For computational reasons only patients with at least one bleeding episode will be included and similarly only patients with at least 2 weeks cumulative time under 1% activity and 2 weeks cumulative time over 1% activity will be included.

The following PK parameters will be estimated using a one-compartment population PK model:

- CL_{70kg} (L/h) Population median clearance in a patient of weight 70 kg
- V_{70kg} (L) Population median volume of distribution in a patient of weight 70 kg
- $\beta_{CL,BW}$ Allometric exponent for relation between median CL and BW
- $\beta_{V,BW}$ Allometric exponent for relation between median V and BW

Extrapolated population PK parameters:

- $C_{max,SS}$ Predicted maximal plasma level of FVIII activity in steady state
- AUC_{τ} Predicted total exposure to FVIII activity during a single dosing interval in steady state

PK and possible PK/PD modelling are considered exploratory analyses that may not be reported in the CTR. The PK assay results to be used for modelling are chromogenic FVIII activities measured against N8-GP reference material.

Population PK modelling will be done as a combined analysis with data from the first human dose trial pathfinderTM 1 with the main scope of assessing the influence of demographic covariates such as BW 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 clearance 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 prophylaxis dosing regimes for patients of BW 10 kg, 25 kg, 50 kg, 70 kg and 100 kg and of any race sufficiently well represented in the trial to allow for assessment (min. 20 PK samples from min. 5 different patients).

18.8 Health Economics and/or Patient Reported Outcome

PROs will be assessed through PRO questionnaires at screening visit (Visit 1) and EOT visit for patients in the on-demand arm for patients in the prophylaxis arm.

The main PRO endpoint will be subgroup total scores. Changes in scores over time of the main PRO endpoints at Visit 1 to EOT visit will be explored and presented graphically. Evaluations of PRO data will alone be based on descriptive statistics, i.e. summary tables, listings and figures.

HE calculations will be performed separately by the Novo Nordisk HE department. Novo Nordisk A/S will be responsible for the statistical analysis.

19 Ethics

The trial will be conducted in compliance with ICH GCP²⁸, applicable regulatory requirements, and in accordance with the Declaration of Helsinki²⁹.

When a patient's participation in the trial ends due to completion of the trial, the patient will be offered to continue in the extension trial (NN7088-3861) upon consent. No patient will consent to a trial in the N8-GP clinical programme before all required IRB/IEC and regulatory approvals have been obtained for the trial. If the patient does not wish to continue in the extension trial (NN7088-3861), the patient will consult with the Investigator to decide on the best available treatment.

19.1 Informed Consent Form for Trial Patients

In seeking and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s), and adhere to the ICH GCP³⁰ and the requirements in the Declaration of Helsinki²⁹.

Prior to any trial-related activity, the Investigator must give the subject and/or the subject's legally acceptable representative (LAR) oral and written information about the trial in a form that the subject or the subject's LAR can read and understand. This includes the use of impartial witness where required.

A voluntary, signed and personally dated, including time, informed consent form will be obtained from the patient prior to any trial-related activity.

The responsibility for seeking informed consent must remain with the Investigator or an adequately medically qualified person delegated by the Investigator. The written informed consent must be signed and personally dated, including time, 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 subject and/or the subject's LAR in a timely manner, and a revised written informed consent must be obtained.

A separate signed and dated informed consent must be obtained from the patient's partner when collecting data from the patient's partner, if the patient's partner becomes pregnant during the trial.

FVIII Genotype Testing / Collection of Previous Genotype Documentation (Not applicable to Brazil)

Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient should give their consent before the data is collected for trial purpose. Prior to any trial-related activity, the Investigator must provide the patient the

possibility to abstain from the genetic testing/collection of previous documentation but still be able to participate in the trial.

19.2 Data Handling

If the patient or the patient's LAR withdraws the previously given informed consent or if the patient dies or if the patient is lost to follow up then the patient's data will be handled as follows:

- Data collected will be retained by Novo Nordisk and entered into the database
- Safety events will be reported to the department responsible for global product safety, Novo Nordisk/regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local law and IRB/IEC procedures.

19.3 Institutional Review Boards/Independent Ethics Committee

Prior to commencement of the trial the protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the subject, subject recruitment procedures (incl. advertisement), if any, IB, available safety information, information about payments and compensation available to patients if not mentioned in the patient information, the Investigator's current curriculum vitae and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify the trial identification number, version, EudraCT no., title and/or the date of the documents that have been submitted to the IRB/IEC. Written approval/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: unexpected SAEs where a causal relationship cannot be ruled out, substantial protocol amendments to the protocol, 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/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.

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19.4 Regulatory Authorities

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

For Japan only: Regulatory authorities will receive the clinical trial notification (CTN), notifications of protocol amendments, reports on SAEs, and the clinical trial reports according to the national requirements.

20 Premature Termination of the Trial/Trial Site

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

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and assure appropriate therapy and follow-up. Furthermore, the Investigator and/or Novo Nordisk should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If after the termination of the trial the risk/benefit analysis has changed, the new evaluation should be provided to the IEC/IRB in case it will have an impact on the planned follow-up of the patients who have participated in the trial. If so, the actions needed to protect the patients should be described.

21 Protocol Compliance

Deviations from the protocol should be avoided.

If deviations occur then the Investigator must inform the Monitor, and the implications of the deviation must be reviewed and discussed.

Protocol deviations must be documented stating the reason, date, the action(s) taken, and the impact for the patients and/or the trial except for protocol deviations where no corrections are required as described in the trial specific validation checks in the approved TVP. The Investigator must approve these as outlined in the TVP.

The documentation for the protocol deviations must be kept in the Investigator's trial file and Novo Nordisk's trial master file.

21.1 Audits and Inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk internal Quality Audit System or an inspection from domestic or foreign regulatory authorities. The Investigator and the site staff as well as Novo Nordisk clinical 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 relevant to the conduct of the clinical trial at the site.

22 Critical Documents

Before the Investigator starts the trial (i.e. the site has green light for screening patients), the following documents must be available to Novo Nordisk:

- regulatory approval and/or notification as required
- curricula vitae of Investigator and Sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document)
- signed receipt of IB
- signed and dated agreement on the final protocol
- signed and dated agreement on any substantial protocol amendment(s), if applicable
- approval/favourable opinion from IEC/IRB clearly identifying the documents reviewed: the protocol, any substantial protocol amendments, subject information/informed consent form and any other written information to be provided to the subject, subject recruitment procedures
- copy of IEC/IRB approved subject information/informed consent form/any other written information/advertisement
- list of IEC/IRB members/constitution
- financial agreement(s)
- laboratory reference ranges
- laboratory certification/QA scheme/other documentation
- laboratory methods
- Verification under disclosures per CFR of Financial Conflict of Interest¹¹.

For US:

- Signed and dated FDA form 1572 for each US Investigator (and individual US clinical trial staff if directly involved in the treatment or evaluation of research making a direct and significant contribution to the data).

Protocol NN7088-3859 (US sites):

- Intended for US sites
- Conducted under the IND
- All US investigators will sign FDA Form 1572

Protocol NN7088-3859 (sites outside the US):

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

23 Responsibilities

All staff (Novo Nordisk, site, lab, CRO etc.) must conduct the trial in compliance with ICH GCP³¹, applicable regulatory requirements, and in accordance with the Declaration of Helsinki²⁹.

The Investigator is accountable for the conduct of the trial. If any tasks are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties.

A qualified physician, who is an Investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions.

The Investigator will follow the instructions from Novo Nordisk when processing 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.

In case the Investigator is not able to fulfil the role as Investigator (e.g. retirement), a new Investigator must be appointed in collaboration with Novo Nordisk.

Upon request from Novo Nordisk, the Investigator will provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that such technical and organisational safety measures have been taken.

Plasma samples will be analysed by either central laboratories selected by Novo Nordisk or at Novo Nordisk A/S.

24 Reports and Publications

The information obtained during the conduct of this trial is considered confidential, and can 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 a member of the Advisory Board and Investigator in this trial.

24.1 Communication and Publication

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 by other means.

Novo Nordisk reserves the right to not release data until specified milestones, e.g. when the clinical trial report is available. This includes the right to not release interim results of clinical trials, because the release of such information can invalidate the results of the entire trial.

At the end of the trial, one or more manuscripts for publication will be prepared collaboratively between Investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for less than 60 days to protect intellectual property.

24.1.1 Authorship

Authorship of publications should be in accordance with guidelines from The International Committee of Medical Journal Editors' Uniform Requirements (sometimes referred to as the Vancouver Criteria³²).

24.1.2 Publications

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

In all cases, the trial results shall be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the trial. All Authors will be given the

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relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the Investigators' and Novo Nordisk's opinions shall 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 must acknowledge all trial sites.

Novo Nordisk maintains the right to be informed of any Investigator plans for publication 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 prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

24.1.3 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 Novo Nordisk's 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.

24.2 Investigator Access to Data and Review of Results

As owners of the trial database, Novo Nordisk has discretion to determine who will have access to the database. Generally, trial databases are only made available to regulatory authorities.

Individual Investigator(s) will have their own research participants' data, and will be provided with the randomisation code after results are available.

25 Retention of Clinical Trial Documentation

Subject notes 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 after trial completion, Novo Nordisk can refer the Investigator to an independent archiving provider who has a system in place that allows only the Investigator to access the files.

The Investigator must be able to get hold of his/her trial documents without involving Novo Nordisk in any way.

Clinical trial documentation must be retained until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP.

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

Novo Nordisk will maintain Novo Nordisk's documentation pertaining to the trial as long as the product is on the market plus 20 years. The files from the Investigator site/institution will be retained 15 years after the completion of the trial, or longer if required by national regulations.

26 Indemnity Statement

Novo Nordisk carries product liability for its products and liability 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 country 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 or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research.

Only applicable to The Netherlands: Novo Nordisk accepts liability in accordance with: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Patients Act, 1 March 2006).

Besluit van 23 juni 2003, houdende regels inzake de verplichte verzekering bij medischwetenschappelijk onderzoek met mensen (Decree of 23 June 2003, containing rules for compulsory insurance in medical research involving human patients (Medical Research (Human Patients) Compulsory Insurance Decree).”

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NNC 0129-0000-1003
NN7088-3859 Ext 2 final
Clinical Trial Report
Appendix 16.1.1

~~CONFIDENTIAL~~

Date:
Version:
Status:

01 May 2019
1.0
Final

Novo Nordisk

Global and country key Novo Nordisk staff

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

Content: Global key staff and Country key staff

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date: 24 October 2011
Version: 1.0
Status: Final
Page: 1 of 4

Novo Nordisk

Substantial Protocol Amendment

no. 1-NL

to Protocol, final version 1.0

dated 30 September 2011

Trial ID: NN7088-3859

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to The Netherlands

Amendment originator:



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Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	24 October 2011	Novo Nordisk
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1 Introduction including rationale for the substantial protocol amendment

In this substantial protocol amendment:

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

The reason for this amendment is to change the inclusion criterion 4 regarding age in order to include only adult patients in the trial in the Netherlands.

In the original protocol previously treated patients aged 12 and older were included.

2 Changes

1 Summary

Key Inclusion Criteria

- Age ≥ 12 years (except for Croatia *and The Netherlands* where the lower age limit will be 18 years)

6 Trial Population

6.2 Inclusion Criteria

4. Age ≥ 12 years (except for Croatia *and The Netherlands* where the lower age limit will be 18 years)

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date: 09 December 2011
Version: 1.0
Status: Final
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Novo Nordisk

Substantial Protocol Amendment

no 2

to Protocol, Final version 1.0, dated 30-Sep-2011 and Sample Subject
Information Informed Consent Form, Final version 1.0, dated 30-Sep-2011

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003
when Administered for Treatment and Prophylaxis of
Bleeding in Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

This global substantial amendment is being issued primarily as a response to a Voluntary Harmonised Procedure (VHP) assessment, which involve the CTA submission of the NN7088-3859 (pathfinder™ 2) and NN7088-3860 (pathfinder™ 3) protocol in 8 European countries.

The following changes have been made to the protocol:

- VHP recommend a more detailed guidance on the treatment of bleeds. Therefore section 5.3.2 has been updated accordingly
- VHP recommend a more clear guidance for the required observation period for adverse reactions in connection to administration of the two first doses of N8-GP. This has been added in the relevant sections
- Anti-coagulants and heparin have been added in section 6.5 as prohibited medication to the protocols withdrawal criteria to make this more consistent.
- VPH expressed concerns regarding the blood volume planned to be collected during scheduled visits - especially for adolescents participating in the PK evaluation. This has been clarified in the protocol. Due to the total amount of blood volume planned to be drawn at the screening visit, the genotype blood sampling has been moved to visit 3. Moreover inclusion criterion no 4 has been adjusted only to enroll patients with body weight ≥ 35 kg. This is to ensure that the blood volume collected from the patients for all tests do not exceed 1% of the whole blood volume at any single collection and 3% of the whole blood volume in 28 days. Please refer to section 6.2.
- As N8-GP is not considered to be mutagenic or considered toxic to the reproductive system, no contraception is considered required by males exposed to N8-GP who are sexually active. Therefore the UK requirement on contraception has been deleted in Section 6.3.
- Planned number of sites has been updated to reflect the current plan for number of sites in the trial
- In section 8.4.4.2 (Hemophilia Treatment History including History of Bleeding Episodes), one additional question has been added to collect number of months for patients on on-demand treatment. This will ensure alignment with the historical data collected for the patients currently on prophylaxis treatment. Furthermore one question has been updated to make it more specific with regards to collecting number of bleeding episodes prior to initiation of prophylaxis treatment
- In section 19.1 collection of time in the consent form has been deleted. This is not required as the patients will be informed about the trial at least 14 days prior to the first dosing visit,.
- The flow charts (Table 2-1 and Table 2-2) have been updated to reflect the changes to the protocol and to correct inconsistencies
- One additional country added to the list of countries (section 6.1)
- Mandatory safety text has been updated due to updates in the Novo Nordisk protocol template (section 12.1)
- Some inconsistencies and minor corrections have been updated in the protocol

The following updates have been made to the Sample Subject Information Informed Consent Forms:

- An error in the title of the subject information consent form has been corrected in all forms in order to be consistent with the protocol title
- Genotype sampling has been moved to visit 3 and correct ml for this sample have been added, number of sites have been updated, one additional country has been added, total blood volume collection has been updated and observation time for adverse reactions for the first two doses of N8-GP has been updated to reflect the amendment changes
- Precautionary advice in connection to the reconstitution of trial product has been added for clarification

Minor typographical changes not affecting the content of text, e.g. grammatical and spelling errors, will not be disclosed in the following sections.

Any new text in this amendment is written in *“Italic”*. Any text deleted from the protocol is written with a ~~strike through~~.

The Protocol version 2 incorporates all changes.

The Sample Subject Information Informed Consent form version 2.0, the The Sample Subject Information Informed Consent form for minor version 2.0, the Sample Subject Information Informed Consent form without PK version 2.0 and Sample Subject Information Informed Consent form for partners version 2.0 incorporates all changes described above.

2 Changes to Protocol

List of Abbreviations

...

pd-PCC plasma derived plasma procoagulation factor concentrates

1 Summary

...

Key Inclusion Criteria

- Age >12 years and *body weight* ≥ 35 kg (except for Croatia and The Netherlands where the lower age limit will be 18 years)

2 Flow Chart

The Flow Chart table 2-1 has been updated with the following:

- Genotype testing has been moved from visit 1 to visit 3
- The possibility of measuring ECG has been added to unscheduled visit
- Date and time of last coagulation factor administration not to be recorded at visit 2b
- HCP to be measured at unscheduled visits in case of an allergic reaction

The Flow Chart table 2-2 has been updated with the following:

- Coagulation related parameters (aPTT, INR) to be sampled 30 \pm 5 min post dose
- Bleeding episodes severity to be rated during PK session at visit 7

Footer added for Date and time of last coagulation factor administration

⁶ Wash-out is 4 days prior to visit 2a and 7 days prior to visit 7

Table 2-1 footer:

Footer	Description
1	Please refer to Table 2-2 for the patients that need to undergo PK
2	Patients in the on-demand arm can switch into prophylaxis treatment after 6 months treatment
3	Confirmation of screening visit 1 in- and exclusion criteria
4	If applicable, i.e. following patient consent and in accordance with local law
5	Only if this visit is EOT visit – dependent on when the patient entered the trial <i>To be measured before dosing and 30 min (± 10min) after dosing.</i>
6	Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment since last visit
7	A wash-out period of minimum 96 hrs is needed before the sample (except visit 1 and visit 2a where wash out is minimum 72 hours)
8	Only in case of an unexpected allergic/anaphylactic reaction
9	Trough to be sampled before dosing and recovery to be sampled 30 min (± 5min) after dosing Not for patients in the on-demand arm
10	Only to be taken if HIV status is positive
11	From visit 2a -13 only BW will be measured
12	From visit 3-12 ³ , only for patients in the prophylaxis arm <i>Assessments to be performed at the EOT visit. The EOT visit can be any visit from visit 7 to visit 13 depending on when the patient entered the trial. This current trial will be terminated when the last patient has received 50 exposure days.</i>
13	

3 Introduction

3.1 Basic Information

3.1.1 Haemophilia A

...

This replacement therapy can be provided either as prophylaxis or as on-demand treatment of bleeding episodes. ~~turætoeog-alfa~~

5 Trial Design

...

5.3 Treatment of Patients

...

The two initial doses of N8-GP will be administered in a hospital setting in order to observe for adverse reactions. *The patient must be observed for at least 1hr after dosing.*

5.3.2 Treatment of Bleeding episodes

A treatment requiring bleeding episode is in this trial defined as a bleed that require treatment with a coagulation factor product e.g. N8-GP. If a patient experiences a treatment requiring bleed it must be treated as soon as it is identified (~~refer to Section 8.2.1~~).

...

~~For the treatment of bleeding episodes, doses will be based on World Federation of Haemophilia (WFH) guidelines¹ (see Section 8.2.1). For treatment of a bleed, all on demand and prophylaxis patients will be treated with doses between 20-75 U/kg BW (the recommended standard dose will be 50 U/kg). to achieve a desired dose level based on the severity and location of the bleeding episode. Each unit of N8-GP will raise the FVIII level with approximately 2%. For recommended dose levels see table 1. Further guidance on the treatment of bleeds may be found in WFH guideline¹.~~

The dosage is calculated by multiplying the patient's weight in kilograms by the factor level desired multiplied by 0.5. This will indicate the number of N8-GP units required.

Example: 50 kg x 40 (% level desired) x 0.5 = 1 000 units of N8-GP.

Table 2–1 Guide for dosing in bleeding episodes

Type of haemorrhage	Desired level	Recommended dose
Joint, muscle (except iliopsoas)	40% - 60%	20 - 30 U per kg
CNS/head, Throat and neck, Gastrointestinal, Iliopsoas	80% - 100%	40 – 50 U per kg

Based on recommendations WFH guidelines.

The effect of initial N8-GP dose on the clinical symptoms should be closely monitored and the need for a second dose should be evaluated within 8 hours after the initial N8-GP dose. If further doses are considered necessary to treat the bleeding episode, the patient is recommended to contact the investigator.

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

Age and body weight are markedly correlated in children and adolescents. As the dosing of N8-GP takes body weight into account no further adjustment is needed in the adolescents included in this trial.

Due to individual patient's bleeding pattern during the trial, an adaptation in dosing regimen to 50 U/kg twice weekly will be permitted at the investigator's discretion. If the dosing regimen is changed to twice weekly, doses should be separated by at least 3 calendar days and no more than 4 calendar days.

~~The dose for treatment of bleeding episodes is aimed to achieve an expected post injection level of at least 0.50 U/mL of FVIII.~~

Any dose used for treatment of a known active bleed must be recorded as treatment of bleed and not as prophylaxis treatment. When the bleed has resolved, the patient can resume the prophylaxis treatment.

If a dose for treatment of a bleed is taken, the next prophylaxis dose should follow the original dosing scheme and not be altered by the additional treatment of bleed administration. If a bleed occurs on the same day as the planned prophylaxis, the dose must be registered for the bleed and not as prophylaxis.

~~Number of doses and frequency of dosing is decided by the Investigator in relation to the particular bleed. The maximum dose to be administered to a patient within 24 hours (hrs) is 200 U/kg BW. The dose is recommended to be divided and only considered under exceptional circumstance such as serious trauma or severe bleeding episodes.~~

6 Trial Population

6.1 Number of Patients to be Studied

Countries planned to participate: Australia, Brazil, Croatia, Denmark, France, Germany, Hungary, Italy, Japan, Korea, Malaysia, Netherlands, Norway, *Russia*, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

...

Planned number of trial sites (approximately): ~~5575~~

6.2 Inclusion Criteria

...

4. Age ≥ 12 years *and* body weight ≥ 35 kg (except for Croatia *and* The Netherlands where the lower age limit will be 18 years)

6.3 Exclusion Criteria

...

~~For the UK: Patients who are sexually active and have partners who are or could become pregnant must be willing and are required to use a barrier method of contraception (e.g. condom) for the duration of the trial and for 90 days following the last dose of trial medication.~~

6.5 Withdrawal Criteria

...

6. *Use of Anti-coagulants such as Heparin and vitamin-K antagonists (Heparin is allowed for sealing of central venous access ports according to local practice)*

6.7 Rationale for Trial Population

...

The trial population characterised through the inclusion criteria:

- Criterion no. 1 is included in accordance with ICH-GCP
- Criterion no. 2 is included to select patients most likely to benefit from the treatment
- Criterion no. 3 is included for selecting previously FVIII treated patients and is in accordance with the EMA guideline
- *Criterion no 4 Weight is applied in order to ensure that the blood volume collected from the patients for all tests should not exceed 1% of the whole blood volume at any single time and 3% of whole blood volume in 28 days. This requirement is in line with European regulatory requirements) and FDA requirements*

8 Methods and Assessments

8.1.1 Visit 1 – Screening Visit for All Patients

...

At the Screening visit the following assessments will be performed and/or recorded in the eCRF:

...

- *History of surgery, see section 8.4.4.2*
- *FVIII genotype documentation, if applicable, see section 8.3.7.5*

...

Blood sampling for central laboratory assessments:

...

- ~~FVIII genotype (if documentation is not available in the patient chart and as allowed per local law. In addition, the Investigator, patient or LAR has the right to refuse), see section 8.3.7.5~~

8.1.2 Visit Schedule for Patients on Prophylaxis not Undergoing PK Evaluation and for Patients on On-Demand treatment

...

Visit 2a should take place as soon as possible upon confirmation of eligibility and 2-3 weeks after the Screening visit (Visit 1).

At visit 2a the patients will have their first dose of N8-GP (50 U/kg) BW administered at the site. The second dose (50 U/kg BW) is given at visit 2b 4 days after visit 2a.

After each of the 2 initial doses of N8-GP, patients must be observed for adverse reactions for at least 1hr after dosing.

...

At Visit 2a the following assessments will be performed and/or recorded in the eCRF

- Confirmation of inclusion and exclusion criteria, see section 6.2 and 6.3
- Withdrawal criteria, see section 6.5
- Concomitant medication, see section 11
- Check date and time of last coagulation factor administration (~~see section 8.4.3~~)

...

- Administration of first dose of N8-GP (Stop time of injection must be recorded in the eCRF, this corresponds to time "0". *Moreover patients must be observed for at least 1 hr after administration for adverse reactions*)

...

Blood sampling for central laboratory assessments

- Biochemistry, see section 8.3.7.1
- Coagulation related parameters, *aPTT and INR* before dosing and 30 min (± 10 min) after ~~the first dosing~~ *injection*, see section 8.3.7.2

...

At Visit 2b (4 days after first dose) the following assessments will be performed and/or recorded in the eCRF

...

- Administration of second dose of N8-GP (*patients to be observed for at least 1 hr after administration for adverse reactions*)

...

The following will be performed and/or recorded in the eCRF:

...

- Body measurements (weight only ~~at all visits except EOT visit~~), see section 8.4.2

...

Blood sampling for central laboratory assessments:

- Biochemistry, see section 8.3.7.1
- FVIII activity (trough level and recovery), i.e. before dosing and 30 min (± 5 min) after dosing
8.3.7.3. Recovery not to be done in the on-demand arm and not at EOT visit, see section ~~8.3.6.3~~
- FVIII inhibitors, see section 8.3.2.2
- N8-GP binding antibodies, see section 8.3.2.1
- *FVIII genotype (only visit 3). If documentation is not available in the patient chart and as allowed per local law. In addition, the Investigator, patient or LAR has the right to refuse, see section 8.3.7.5*

8.1.3.1 Visit 2a for Patients on Prophylaxis Undergoing PK Evaluation

...

Blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- Biochemistry, see section 8.3.7.1
- Coagulation related parameters, aPPT and INR before dosing and 30 min (± 10 min) after ~~the first dosing~~ see section 8.3.7.2

...

First N8-GP administration

- Dispensing of N8-GP for PK evaluation in IV/WRS

Patients will receive 50 U/kg BW of N8-GP (Stop time of injection must be recorded in the eCRF, this corresponds to time "0". *Moreover patients must be observed for at least 1 hr after administration for adverse reactions*)

8.1.3.2 Visit 2b for Patients on Prophylaxis Undergoing PK Evaluation

Four days after first dose the following assessments will be performed and/or recorded in the eCRF

...

- Administration of second dose of N8-GP (*patients must be observed for at least 1 hr after administration for adverse reactions*)

Reminders:

- An appointment for Visit 3, 4 weeks \pm 1 week after *visit 2a* should be made.

8.1.3.3 Visit 7 for Patients on Prophylaxis Undergoing PK Evaluation

...

Blood sampling for local laboratory assessments to be taken within 1 hour prior to dosing:

- Haematology, see section 8.3.6.1
- ~~Urinalysis with sticks provided by the central laboratory, see section 8.3.6.2~~

Blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- Biochemistry, see section 8.3.7.1
- *Coagulation related parameters, aPPT and INR before dosing and 30 min (\pm 10 min) after dosing, see section 8.3.7.2*

...

Reminders:

- An appointment for Visit 8, 36-~~(8 weeks \pm 1~~ *after visit 2a*~~week later~~) should be made.
Withhold N8-GP minimum 96 hours prior to next visit

8.4.1 Follow-up visit (only for patients withdrawn due to development of FVIII inhibitors)

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 \pm 2 weeks) after the EOT Visit the patient must attend a FU Visit, please see Section ~~8.3.6~~ 8.3.2.2

8.1.5 Unscheduled Visits

...

- IgE, IgG, HCP see section 8.3.2.3
- N8-GP administration, ~~not for on-demand patients~~

8.2 Efficacy Assessments

...

- *Health Economic questions, see section 8.4.5*

8.2.1 Bleeding Episodes

...

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

...

- ~~Haemostatic drug used for~~
- Pain relieving medication
- Dose(s) and Time(s) of administration
- Other therapy used (compression, ice or other)
- Stop of bleed (date and time)
- Categorisation of the bleeding episode (mild/moderate or severe), in the eCRF
- Clinical evaluation of the haemostatic response (excellent, good, moderate or none)
- ~~Bleed related days away from work or school~~

~~Bleed related days using mobility aids~~

8.4.2 Body Measurements

All body measurements (weight, height and BMI) will be performed at Visit 1. On all other visits only weight will be measured. The weight measured at the respective visits should be ~~the weight~~ used for calculating ~~the amount on~~ of N8-GP to be dispensed and the dose of N8-GP to be administered.

- Weight (*registered with one decimal*), wearing light clothing only (kg/pounds) and without shoes
- Height, without shoes (cm/inches), visit 1 only
- BMI calculation (kg/m^2), visit 1 only

8.4.3 eDiaries

eDiaries will be used in this trial. The patient should bring the eDiary to every visit to the site.

The following data will, as a minimum, be captured by the patient or the caregiver in the e-Diary:

- Treatment
- FVIII product used

...

- ~~Bleed related days away from work or school~~
- ~~Bleed related days using mobility aids~~
- *Health Economic questions, see section 8.4.5*

8.4.4.2 ~~Bleeding~~ Haemophilia Treatment History including History of Bleeding Episodes

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

...

- ~~Number of Bleeding pattern episodes within the last 12 months prior to initiation of prophylaxis therapy was initiated~~

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

Number of months on on-demand

12 Adverse Events and Pregnancies

12.1 Definitions

...

b) The term “hospitalisation” ~~describes a period of at least 24 hours. Over night stay for observation, treatment at emergency room or treatment on an out subject basis does not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious.~~

~~Hospitalisations for administrative, trial related and social purposes do not constitute hospitalisations as defined by the seriousness criteria, and should therefore not be reported as such. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs. is used when a subject is:~~

- *Admitted to a hospital/in-subject (irrespective of the duration of physical stay), or*
- *Not admitted to a hospital/not in-subject, but stays at the hospital for treatment or observation for more than 24 hrs.*

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 neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

19 Ethics

...

19.1 Informed Consent Form for Trial Patients

...

A voluntary, signed and personally dated, ~~including time~~, informed consent form will be obtained from the patient prior to any trial-related activity.

The responsibility for seeking informed consent must remain with the Investigator or an adequately medically qualified person delegated by the Investigator. The written informed consent must be signed and personally dated, ~~including time~~, by the person who seeks the informed consent.

22 Critical Documents

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	09 December 2011	Novo Nordisk
Version:	1.0	
Status:	Final	
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...

For US sites:

~~Signed and dated FDA form 1572 must be completed and signed for by each US Investigator (and individual US clinical trial staff if directly involved in the treatment or evaluation of research making a direct and significant contribution to the data).~~

24 Reports and Publications

...

24.2 Investigator Access to Data and Review of Results

As owners of the trial database, Novo Nordisk has discretion to determine who will have access to the database. Generally, trial databases are only made available to regulatory authorities.

~~Individual Investigator(s) will have their own research participants' data, and will be provided with the randomisation code after results are available.~~

3 Changes to Sample Subject Information Informed Consent forms

Changes that concerns the following Sample Subject Information Informed Consent forms:

Sample Subject Information Informed Consent form
Sample Subject Information Informed Consent form for minor
Sample Subject Information Informed Consent form without PK
Sample Subject Information Informed Consent form for partners

Front page, title of protocol:

A Multi-National Trial Evaluating Safety and Efficacy Including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for *Treatment and* Prophylaxis of Bleeding in Patients with Haemophilia A

Changes to Sample Subject Information Informed Consent form, Sample Subject Information Informed Consent without PK and Sample Subject Information Informed Consent form for minor:

1 Information about the Trial and the Trial Product

1.3 Procedures during the trial conduct

...

Visits and tests during the trial

Tests to be performed	Visit 1	Visit 2a <i>14-21days after visit 1</i>	Visit 2b <i>4 days after visit 2a</i>	Visit 3-5 <i>Every 4 weeks</i>	Visit 6-12 <i>Every 8 weeks</i>	Last trial visit <i>Any time between 6-19 month after visit 1</i>
Blood sample for genotyping, if consented to	✗			<i>X (only at visit 3)</i>		

Changes to Sample Subject Information Informed Consent form and Sample Subject Information Informed Consent without PK:

1 Information about the Trial and the Trial Product

1.1 Why are we conducting this trial?

...

We expect that 132 patients worldwide will be enrolled in this trial in approximately 5575 haemophilia centres. The planned participating countries are: Australia, Brazil, Croatia, Denmark, France, Germany, Hungary, Italy, Japan, Korea, Malaysia, Netherlands, Norway, *Russia*, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

1.3 Procedures during the trial conduct

...

You are also separately asked to give your consent for a blood sample (56 ml) to perform genotype testing.

First doses with N8-GP

...

The first dose of N8-GP will take place approximately 14-21 days after your first visit and the second dose will take place four days after the first dose. These first ~~two~~ doses are not dependent on bleeding episodes but are done as prophylactic treatment to ensure that the new drug is safe for you to take. *You will need to stay at the clinic one hour after you have received the first two doses with N8-GP to be observed for any possible adverse reactions.*

1.4 How to handle trial medication, N8-GP

The clinic will supply you with the required amount of trial medication, solvent for reconstitution and infusion sets. If you are treated prophylactically every 4th day, we recommend you take N8-GP in the morning at approximately the same time. The trial medication must be stored refrigerated and handled as described in the medication label and in the instructions provided. When reconstituted *N8-GP is a clear /almost clear colourless solution Please note that you must not use the solution if there are any solid particles to be seen.*

1.9 Withdrawal from the Trial

...

In case you are withdrawn due to inhibitor development we will ask you to come to an end of trial visit one week after detection of the inhibitor and for follow up visits monthly ~~at least monthly in the following three months~~ *up to three months after the end of trial visit.*

Changes to Sample Subject Information Informed Consent form

2 Information about the Risks/Benefits

The total estimated ml of blood that will be taken from you during this trial will be approximately ~~280360~~ ml which is approximately the same as one unit of blood. If you participate in the

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

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pharmacokinetic part the total estimated blood volume will be approximately ~~320~~⁴²⁰ ml during the trial.

Changes to Sample Subject Information Informed Consent form without PK

2 Information about the Risks/Benefits

The total estimated ml of blood that will be taken from you during this trial will be approximately ~~280~~³⁶⁰ ml which is approximately the same as one unit of blood.

Substantial protocol amendment
Trial No.: NN7088-3859
UTN: 01111-1119-7416
Eudra CT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date: 03 January 2012
Version: 1.0
Status: Final
Page: 1 / 4

Novo Nordisk

Substantial Protocol Amendment no 3
to Protocol Attachment II-TR specific, Final version 1.0, dated 17 Oct 2011

Trial ID : NN7088-3859

**A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics,
of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of
Bleeding in Patients with Haemophilia A**

Trial Phase: 3

Author:



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Substantial protocol amendment
Trial No: : NN7088-3859
UTN: 01111-1119-7416
Eudra CT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	03 January 2012	Novo Nordisk
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1 Introduction including rationale for the substantial protocol amendment

In this substantial Subject Information/Informed Consent amendment:

Any new text is written in italic.

Any text deleted from the protocol is written with a strike through..

2 Changes

The following changes to Attachment II to NN7088-3859:



Principle Investigator:	Title:
	Name:
	Surname
	Tel:
	Fax:
	Mobile
	E-mail:



Investigator:

Title/
qualification:
Name:
Surname:

Tel:

Fax:

Mobile:

E-mail:



Substantial Protocol Amendment no. 4-ES
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date: 26 January 2012
Version: 1.0
Status: Final
Page: 1 of 4

Novo Nordisk

Substantial Protocol Amendment

no 4-ES

to Protocol, final version 1.0

dated 30-Sep-2011

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003
when Administered for Treatment and Prophylaxis of
Bleeding in Patients with Haemophilia A**

Trial phase: 3

Applicable to Spain

Amendment originator:



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Substantial Protocol Amendment no. 4-ES
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	26 January 2012	Novo Nordisk
Version:	1.0	
Status:	Final	
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1 Introduction including rationale for the substantial protocol amendment

This local substantial amendment is being issued to include a new site in Spain [REDACTED]
[REDACTED]

The Substantial Amendment No. 4-ES to the protocol will be submitted to the Ethic Committees for approval, before its implementation. According to local regulation, the amendment information will be notified to Competent Authority along with the Ethics Committees opinion.

Any new text in this amendment is written in “*Italic*”. Any text deleted from the protocol is written with a ~~strike through~~.

The Attachment II– Spain List of Key Staff and Relevant Departments version 2/ES incorporates all changes.

2 Changes

Attachment II – Spain List of Key Staff and Relevant Departments

~~Investigator:~~ Name:
*National Coordinating
Investigator:*

Investigator: Name:

Title:

Address:

Tel:

Local laboratory(ies): Name:

Address:

Tel:



Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date: 3 February 2012
Version: 1.0
Status: Final
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Novo Nordisk

Substantial Protocol Amendment-Local France

N° 5-FR

to Protocol, Final version 1.0, dated 30-Sep-2011, and Global substantial amendment N°2, dated 9-Dec-2011

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003
when Administered for Treatment and Prophylaxis of
Bleeding in Patients with Haemophilia A**

Trial phase: 3

Applicable to France

Amendment originator:



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Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	3 February 2012	Novo Nordisk
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1 Introduction including rationale for the substantial protocol amendment

This local substantial amendment is being issued following Ethics Committee decision: due to absence of data from clinical trials in adult population, patients below 18 years of age cannot be included in this trial.

The following change has been made to the protocol:

- Inclusion criterion N° 4 has been modified to exclude patients of age < 18 years in France.

Any new text in this amendment is written in "*Italic*". Any text deleted from the protocol is written with a ~~strike through~~.

2 Changes to Protocol

1 Summary

Key Inclusion Criteria

- Age >12 years and body weight ≥ 35 kg (except for Croatia ~~and~~, The Netherlands *and France* where the lower age limit will be 18 years)

6 Trial Population

6.2 Inclusion Criteria

...

4. Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia, ~~and~~ The Netherlands *and France* where the lower age limit will be 18 years)

Substantial Protocol Amendment

no 6

to Final Protocol, version 2, dated 09 December 2011

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003
when Administered for Treatment and Prophylaxis of
Bleeding in Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

This global substantial protocol amendment is being issued primarily as a response to a Special Protocol Assessment (SPA) request sent to the US FDA in connection with submission of the NN7088-3859 protocol in the United States and includes the following:

Section 18:

- Annualised bleeding rate in prophylaxis arm. The calculation of annualised bleeding rate for withdrawals has been changed. Imputation will also be performed for withdrawals within the first month. An annualised bleeding rate of 24 will be used for imputation for all patients withdrawing in the first month, including those with zero bleeds
- Sample size calculations have been changed. For the inhibitor test a true inhibitor rate of 0.5% instead of 1% is now assumed. This is based on the experience with clinical trials with turoctocog alfa. For the prophylaxis test, the impact on the power of the change in imputation rule for early withdrawals without bleeding episodes is accounted for
- An interim analysis has been added in order to evaluate the over-dispersion (only) once approximately 90 patients have entered into the prophylaxis arm. If the estimated over-dispersion is greater than 6 then the planned sample size will be adjusted up to include 160 prophylaxis patients instead of 120 patients. The planned sample size will not be increased without issuing a further amendment
- Additional sensitivity analyses have been added both for haemostatic response and for annualised bleeding rate
- Other editorial adjustments have been made to the statistical section of the protocol (section 18) to better align with the wording of the protocol endpoints in section 4 of the protocol.

In connection with this protocol amendment other clarifications to the protocol have been made:

- Sections 1 and 6: France has been added to the list of countries that will not allow adolescents to participate in the trial
- Section 1: Clarification of the definition Exposure Days (ED) has been added
- Sections 5, 6 and 11: Changes to these sections have been made in order to allow patients to use their current FVIII product in case they need to treat a bleeding episode immediately at home in the period between the first two doses of N8-GP (visit 2a and visit 2b). The changes have been made in consideration of patients' safety
- Sections 5: The conditions for starting up pathfinder^{TM3} (NN7088-3860) has been aligned with the conditions stated in the pathfinder^{TM3} protocol
- Sections 5 and 8: Symptoms that can relate to stop of a bleeding episode have been added. This in order to guide investigators and patients on how to determine the stop time of a bleeding episode

- Sections 5 and 6: Guidance for rescheduling of PK sessions in case of a bleeding episode during a PK sampling session has been added
- Section 5: Requirement for documentation of investigators review of the patient's eDiary at every visit has been added
- Section 8: text regarding Documentation of Inhibitor Status clarified
- Section 8: Clarifications have been made to the viral assessments.
- Section 8: Recording the urine analysis results has been changed from recording the results directly into the eCRF to recording this on the laboratory requisition form. This has been changed to reflect the current trial set up
- Section 8: Time point for genotype testing has been corrected from visit 1 to visit 3 in order to align with the rest of the protocol
- Section 8: The first two doses of N8-GP administrated at the hospital will be documented in the e-CRF and *not* in the eDiary. This has been changed due to the current set up of the trial
- Sections 8 and 12: Reporting of a MESI in case of *one* positive inhibitor test has been clarified
- Section 12: Some text has been amended to make the text more clear
- Other editorial corrections have been made to the protocol
- Attachment I to the protocol has been updated due to changes in key personnel

The following changes have been made to the Subject Information/Informed Consent Form and are therefore reflected in this global substantial amendment:

- Section 1.3: guidance on treatment of a bleeding episode between visit 2a and 2b
- Section 3.2: update to the identification of lab samples

In this substantial protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~
- Minor typographical changes not affecting the content of the text, e.g. grammatical and spelling errors will not be disclosed in the following sections

The protocol version 4 incorporates all the above changes.

2 Changes to Protocol

2.1 List of Abbreviations

pd-aPCC plasma derived activated plasma ~~prothrombin complex coagulation factor concentrates~~

pd-PCC plasma derived ~~prothrombin complex plasma coagulation factor concentrates~~

2.2 Section 1 Summary

Trial Population:

Foot note added: *An “exposure day” is defined as any day the patient has been exposed to N8-GP including on demand, prophylaxis, during surgery and in PK sessions. If N8-GP is administered more than once during the same day, this will still count as one exposure day*

Key Inclusion criteria:

Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia, ~~and~~ The Netherlands *and France* where the lower age limit will be 18 years)

2.3 Section 2

Table 2–1 Flow Chart for Patients on Prophylaxis and On-Demand Treatment

‘X’ has been added to the follow-up visit in the flowchart to indicate that N8-GP binding antibodies must be measured.

2.4 Section 5 Trial design

5.1 Type of Trial:

...

Furthermore, if the patients need to undergo surgery during the present trial they can switch into the surgery trial pathfinderTM 3 and upon completion of the surgery they can return to the pathfinderTM 2^d trial. Recruitment into the surgery trial pathfinderTM 3 will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pivotal trial pathfinderTM 2. ~~For US:~~ The surgery trial will not be initiated until at least 20 bleeding episodes in at least 10 patients are treated with N8-GP *in the present trial*.

5.3 Treatment of Patients

...

The following medications are not allowed during the course of the trial until after the EOT visit:

- Bypassing products: rFVIIa, pd-PCC and pd-aPCC
- Coagulation factors containing products ~~FVIII~~, FIX, FVII and FVIII other than N8-GP
(exception: current FVIII is allowed until 72 hours before visit 2a and in case of home treatment of a bleeding episode that requires immediate treatment between visit 2a and 2b)

5.3.2 Treatment of Bleeding Episodes

...

Any dose used for treatment of a known active bleed must be recorded as treatment of bleed and not as prophylaxis treatment. When the bleed has resolved (*e.g. pain reduction and no increase in swelling*), the patient can resume the prophylaxis treatment.

If a dose for treatment of a bleed is taken, the next prophylaxis dose should follow the original dosing scheme and not be altered by the additional treatment of bleed administration. If a bleed occurs on the same day as the planned prophylaxis, the dose must be registered for the bleed and not as prophylaxis.

If a bleeding episode occurs between visit 2a and 2b, the patient must contact the site and preferably come to the site for treatment with N8-GP. In case of a bleeding episode between visit 2a and 2b that requires immediate treatment or the Investigator judges it as necessary, the patient can treat the bleed at home with his previous FVIII product..

If a haemostatic response cannot be achieved after 48 hours using adequate doses of N8-GP treatment when treating bleeding episodes, another FVIII product may be selected at the discretion of the Investigator. The use of other FVIII products will result in withdrawal of the patient (*exception: current FVIII product is allowed until 72 hours before visit 2a and in case of home treatment of a bleeding episode that requires immediate treatment between visit 2a and 2b*).

An electronic diary (eDiary) will be kept to register all bleeding episodes and their treatment (*except treatment with the patients' current FVIII product between visit 2a and 2b in case of a bleeding episode that requires immediate treatment at home. In this case the information will be entered into the eCRF*). The Investigator must review the eDiary data and rate the bleeding episodes at every visit. *The review of the eDiary must be documented.*

2.5 Section 6 Trial Population

6.2 Inclusion criteria:

Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia, ~~and~~ The Netherlands *and France* where the lower age limit will be 18 years)

6.4 Criteria for rescheduling planned visits:

Criteria 3: In a bleeding state (all visits including PK). *If a patient experiences a bleeding episode during a PK session between visit 2a and 2b, PK sampling will be stopped and the patient will receive treatment with N8-GP, (or the patients' previous FVIII product if the bleeding episode occurs at home and requires immediate treatment)^g. In case of mild or moderate bleeding episodes, rescheduling of PK sessions can be done at the discretion of the Investigator taking the patient's safety into account. In case of a severe bleeding episode the PK session must be discontinued.*

Footnote g: A 7 days wash-out is needed before the rescheduled PK session if the bleeding episode was treated with N8-GP and a 4 days wash-out is needed if the bleeding episode was treated with previous FVIII product.

6.5 Withdrawal Criteria:

- Criteria 4: Use of Coagulation Factors FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma or cryoprecipitate (**Exception:** current FVIII is allowed until 72 hours before visit 2a *and in case of home treatment of a bleeding episode that requires immediate treatment between visit 2a and 2b*)

2.6 Section 8 Methods and Assessments

8.1.2 Visit Schedule for Patients on Prophylaxis not Undergoing PK Evaluation and for Patients on On-Demand Treatment

At visit 2a, the patients will have their first dose of N8-GP (50 U/kg ~~BW~~) administered at the site. The second dose (50 U/kg BW) is given at visit 2b 4 days after visit 2a. If a bleeding occurs during this period the patient must *contact the site and preferably* come to the site for treatment with N8-GP. *If the patient has a bleeding episode that requires immediate treatment or the Investigator judges it as necessary, the patient can treat himself at home with his previous FVIII product.*

After each of the 2 initial doses of N8-GP, patients must be observed for adverse reactions for at least 1hr after dosing.

The samples taken post-dose must not be taken from the same vein as previously used for administration of N8-GP.

Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instructions in reporting details of bleeding episodes and prophylactic treatment including doses administered at *all visits after visit 2b*.

8.1.3.1 Visit 2a for Patients on Prophylaxis Undergoing PK Evaluation

.....

At visit 2a the patients will receive their first dose of N8-GP (50 U/kg BW) at the site and 9 PK samples will be taken during the following 4 days. *If a bleeding occurs between visit 2a and 2b the patient must contact the site and preferably come to the site for treatment with N8-GP. If the patient has a bleeding episode that requires immediate treatment or the Investigator judges it as necessary, the patient can treat himself at home with his previous FVIII product.*

.....

Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic treatment including doses administered at all visits after visit 2b.

8.1.4 Follow-up visit (only for patients withdrawn due to development of FVIII inhibitors)

.....

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see section 8.3.2.2
- *N8-GP binding antibodies, see section 8.3.2.1*

8.1.5 Unscheduled Visits

...

The following can be performed/reported at an unscheduled visit:

...

- *Check date and time of last coagulation factor administration (see section 8.4.3)*

8.2.1 Bleeding episodes

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

.....

- *Date and time for Sstop of bleed (e.g. pain reduction with no increase in swelling) (~~date and time~~)*

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: current FVIII is allowed until 72 hours before visit 2a and in case of home treatment of a bleeding episode that requires immediate treatment between visit 2a and 2b*).

8.3.2.2 FVIII inhibitors

...

If the Investigator decides to send a sample for inhibitor testing to a local laboratory, the Investigator must also send a duplicate sample for inhibitor testing to the Central Laboratory. The data from the Central Laboratory will then be used in the official analysis. *Any single A-positive inhibitor test must be reported as a MESI (please refer to section 12.1.2).*

...

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

8.3.6.2 Urinalysis

...

Urinalysis will be performed locally with sticks provided by the central laboratory and should be recorded *on the laboratory requisition form ~~directly in the e-CRF~~*. Results from the urinalysis other than pH, proteins, glucose, bilirubin and blood should not be reported to Novo Nordisk.

8.3.7 Central Laboratory Assessments

.....

All blood samples including genotyping blood sample will be destroyed after finalisation of the trial report. Blood samples of patients who are suspected of inhibitors or who have developed inhibitors will be stored at least until evaluation of the clinical trial data by the authorities in the patient's country.

8.3.7.4 Viral Assessments (HIV, Hepatitis B and C):

Viral assessments ~~should~~ *must* be performed if status is unknown *or if known* or the investigator consider there is an indication to test

8.3.7.5 FVIII genotype testing:

At visit 1, all patients/LARs will be asked about documentation of previous FVIII genotype tests. If not available or if it needs to be re-tested FVIII genotype testing will be offered at visit 3~~4~~. Investigator and patients/LARs have the right to refuse to provide patient's FVIII genotype documentation or to refuse genotyping.

8.4.3 eDiaries:

...

- Bleeding episodes

...

- *Date and time* for Sstop of bleed (*e.g. pain reduction with no increase in swelling*)(~~date and time~~)

Trial product administration performed at the site should also be entered in the eDiary by the patient, *except the first two doses of N8-GP administrated at visit 2a and 2b. These will be entered into the eCRF by the site. If the patient have used their previous FVIII product to treat a bleeding episode between visit 2a and 2b, this information will be entered in the eCRF.*

8.4.4.1 Documentation of Inhibitor Status

A positive 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 must include the following:

- two inhibitor test result should be documented within the period since diagnosis, *not necessary within the last 8 years*
- FVIII recovery test + *evaluation of the bleeding history AND/OR negative inhibitor testing* performed at least every third year during the last 8 years ~~+ evaluation of the bleeding history AND/OR negative inhibitor testing at least every third year during the last 8 years.~~

2.7 Section 11 Concomitant Illness and Concomitant Medication

Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma or cryoprecipitate (exception: current FVIII is allowed until 72 hours before visit 2a *and in case of home treatment of a bleeding episode that requires immediate treatment between visit 2a and 2b*)

2.8 Section 12 Adverse Events and Pregnancies

12 Adverse Events, *Technical Complaints* and Pregnancies

12.1.2 Medical event of Special interest

...

A MESI should *be* reported following the same reporting requirements and timelines for SAEs (see section 12.2) irrespective of if the MESI fulfils an SAE criterion.

The following events are defined as MESIs in this trial;

1. Medication error

- Administration of wrong drug or *use of wrong device*
- wrong route of administration such as intramuscular instead of intravenous
- Administration of an accidental overdose, ie dose which may lead to significant health consequence as judged by the investigator irrespective of whether a SAE criterion is met.
- Administration of a high dose with the intention to cause harm *e.g. suicide attempt*

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 ($BU \geq 0.6/mL$) should be reported as a MESI. *A patient is only considered to be inhibitor positive ($BU \geq 0.6/mL$) if the inhibitor test is positive at two consecutive tests - sampled preferably within 2 weeks.*

...

MESIs are reported by completing an AE form and safety information form. Complete the AE form in the eCRF. If for any reason the EDC application is unavailable, then fax, telephone or email Novo Nordisk. Complete the safety information forms on paper CRFs.

12.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported ~~for all medicinal products.~~

12.2.1 Follow up of Adverse Events:

...

Non-serious AEs must be followed until 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. Cases of chronic conditions or cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with an outcome of “recovering” or “not recovered” ~~All non-serious AEs classified as severe or possibly/probably related to the trial product must be followed until the subject has “recovered” or “recovered with sequelae”, and all queries have been resolved. Cases of chronic conditions or cancer or AEs ongoing at time of death (i.e. subject dies from another AE) can be closed with an outcome of “recovering” or “not recovered”. Cases can be closed with an outcome of “recovering” when the subject has completed the post-trial follow-up period and is expected by the Investigator to recover.~~

~~All other 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 post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. AEs ongoing at time of death (i.e. subject dies from another AE) can be closed with an outcome of “recovering” or “not recovered”.~~

12.3.2 Collection, Storage and Shipment of Technical Complaint Samples

...

The **technical complaint sample** and a **paper copy of the technical complaint form** must be sent to Novo Nordisk within **5 calendar days** of receiving the technical complaint sample at trial site by using the following address:

- Novo Nordisk A/S,
Att.: Customer Complaint Center,
Krogshøjvej 55,
DK-2880 Bagsværd,
Denmark

2.9 Section 18 Statistical Considerations

18.1 Sample Size Calculations

Co-Primary Endpoint: Incidence Rate of *FVIII*-inhibitors ~~Inhibitory Antibodies against *FVIII*~~ Defined as ~~Titre~~ ≥ 0.6 BU/mL

Given the rarity of the disease, a sample size of 105 patients treated for a minimum of 50 exposure days will allow for a reasonable evaluation of inhibitor formation in this pivotal trial.

The aim is to demonstrate that the upper confidence limit for the inhibitor rate is below 6.8%. In practical terms this will happen if 2 or less inhibitors are observed in the planned 105 patients with 50 exposure days (3 or less if the trial should end with 127 patients with 50 EDs). If the true inhibitor rate of N8-GP is 0,5 ±% then the chance/power to achieve a maximum of 2 inhibitors out of 132 patients entered into the trial will be ~~85%~~ 97%.

Co-Primary Endpoint: Annualised bleeding rate in the prophylaxis arm

The clinical efficacy of N8-GP in long term bleeding prophylaxis will be evaluated based on all the prophylaxis period data. This will give different period lengths for the different patients but on average it is expected to give about 12 month prophylaxis treatment per patient (~7 months for the last recruited patients and ~17-19 months for the first recruited patients). Prophylactic effect will be concluded if the upper 97.5% confidence limit for the annualised bleeding frequency is < 8.5.

Annualised bleeding rate for withdrawals will be imputed for the missing period based on their observed bleeding rate except for patients withdrawn within one month where imputation will be performed based on an annualised bleeding rate of 24. The true bleeding rate will be assumed to be 6.8 as for historical prophylaxis data but for the sample size calculation it will be assumed that 1 patient will withdraw within 1 month and that will lift the effective annualised bleeding rate for the power calculation by $24/120 = 0.2$, i.e. from 6.8 to 7.0.

The model will be a Poisson regression allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom (i.e. Scale=Pearson in SAS)) and using log observation time as offset to account for the differing treatment lengths. Based on an approximation to the normal distribution and assuming that the patients bleed 7.0 ~~6.8~~ times per year and an over-dispersion of 5 (so variance ~~34~~ 35) 120 patients entered on prophylaxis will give a power of ~~89%~~ 79%.

The power calculation is sensitive to the assumed over-dispersion (OD) of 5. For this reason, an interim analysis will be performed to evaluate the OD when approximately 90 patients have been recruited to prophylaxis: If the estimated OD for the full study is larger than 6, then the sample size will be adjusted up to 160 on prophylaxis to ensure that the power holds. The sample size will not be increased without issuing a protocol amendment.

The following table shows the power for the various assumptions of bleeding rates and over-dispersions (OD).

True <i>ABR</i>	OD	Power for the Prophylaxis test power
7.0 6.8	5	79% 89%
6.8 6.5	5	89% 97%
6.5 6	5	97% 99,9%
7.0 6,8	4	87% 83%
7.0 6,8	6	72% 95%

Combined *p*Power

With 97% power for the first co-primary endpoint and 79% power for the second co-primary endpoint, the combined power for the study with the given sample size is expected to be about $97\% * 79\% = 76\%$

~~With 85% power for the first co-primary endpoint and 89% power for the second co-primary endpoint the combined power for the study with the given sample size is expected to be about $85\% * 89\% = 76\%$.~~

18.2.2 Primary Endpoint(s)

Incidence Rate of *FVIII* inhibitors \geq Inhibitory Antibodies against *FVIII* defined as Titre \geq 0.6 BU/ml.

The rate of *inhibitors neutralising antibodies* will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution.

...

Annualised bleeding rate (total number of bleeding episodes per patient assessed as annualised bleeding rate) in the prophylaxis arm

~~Number of bleeding episodes (total bleeding episodes assessed as Annualised Bleeding Rate) per patient in the prophylaxis arm~~

...

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 this method is considered to give too uncertain LOCF values, hence imputation will not be attempted for such patients and such patients will only contribute with the observed bleeding episodes and observation time imputation, will be conducted by assuming an annualised bleeding rate of 24 for the missing period.~~

Sensitivity analyses:

Analysis without imputation to planned trial duration

The primary prophylaxis analysis will be repeated but without imputing number of bleeding episodes ~~from early~~ for any withdrawals. Instead only the observed bleeding episodes will be counted and the offset will be actual observation duration rather than planned.

Analysis imputing by LOCF without imputation for withdrawals occurring within the first month

The primary analysis will be repeated but without using imputation of 24 bleeding episodes for withdrawals within the first month. Instead only the observed bleeds and the observed duration will be used for such subjects.

Analysis imputing a minimum of 24 bleeds per year to planned trial duration

A conservative sensitivity analysis will be performed imputing for all withdrawals the observed bleeding rate into the missing period if it is greater than 24 per year and otherwise 24 per year. As an example a patient with 3 bleeds in 2 months (observed ABR 18) that should have been in the study for 12 months will have 20 bleeds imputed for the missing 10 months. Patients with 6 bleeds in 2 months (observed ABR 36) will have 30 bleeds imputed into the missing 10 months.

18.2.3 Confirmatory Secondary Endpoints

Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.

Sensitivity analyses

Analysis on observed responses only (i.e. excluding missing observations)

A sensitivity analysis will be performed similar to the primary analysis but only analysing bleeding episodes with recorded responses (i.e. not counting any bleeding episodes with missing response as failures).

Analysis imputing missing haemostatic response based on number of infusions used

A sensitivity analysis will be performed using the number of infusions given to impute the haemostatic response for missing data. Specifically missing responses where only 1 dose was used will be counted as success while missing responses where 2 doses were used will be counted as failures.

Analysis imputing missing haemostatic response based on patients recorded responses on other bleeding episodes

A sensitivity analysis will be performed where missing treatment responses will be imputed based on recorded treatment responses from that particular patients recorded treatment responses. The imputation will be done randomly based on the recorded success rate. As an example if a patient has 2 missing responses and 4 treatment successes in 5 treated bleeds with recorded response then the missing responses will be imputed randomly based on an 80% success chance. Patients with missing responses for all treated bleeding episodes will be imputed as failures for all bleeding episodes.

18.2.4 Supportive Secondary Endpoints

Consumption of N8-GP (number of infusions and U/Kg) per bleed

The Number of Infusions per bleed will be summarised and listed.

The number of U/Kg per bleed will be summarised and listed.

Consumption of N8-GP (number of infusions and U/Kg per month and per year) during prophylaxis and on-demand treatment

The number of infusions per month and per year will be summarised and listed by treatment regimen (prophylaxis and on-demand)

The number of U/Kg per month and per year will be summarised and listed by treatment regimen (prophylaxis and on-demand)

Haemostatic effect as measured by recovery and trough levels FVIII:C (in all patients in the prophylaxis treatment arm)

Recovery and trough levels measured at scheduled visits will be summarised and listed.

A sensitivity analysis will be performed excluding troughs > 30% and excluding recoveries < 30%. This will aim to eliminate any troughs recorded as recoveries and vice versa that has not been possible to clarify during data cleaning.

~~18. 2.4.1 The Number of Injections of N8-GP required per Bleed~~

~~This endpoint will be summarised and listed.~~

~~— Amount of N8-GP required per Bleed~~

~~Amount of N8-GP required per bleed (U/kg BW/bleeding episode) will be summarised and listed~~

18.3 Safety Endpoints

Adverse Events (AEs) and Serious Adverse Events (SAEs) reported during the trial

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

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

~~HCP antibodies will be listed.~~

Changes in vital signs (BP, pulse, temperature, respiratory rate)

These endpoints will be summarised and listed.

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

18.4 Exploratory endpoints

Incidence of binding, non-inhibitory antibodies to N8-GP/turoctocog alfa

Binding non-inhibitory antibodies will be listed.

18.5 Interim analysis

In order to obtain regulatory permission to start the surgery treatment ~~in the US~~, prophylaxis treatment in the US and paediatric trial in the EU lists of acute treatment responses will be prepared at certain time-points. They will include patient details as well as dose given and response to treatment.

Interim analysis to decide if the sample size should be adjusted

The power calculation for the annualised bleeding rate analyses assumes an over-dispersion (OD) of 5. This is based on experience from similar studies with turoctocog alfa but is nevertheless a somewhat uncertain assumption that can have major impact on the power of the study. For that reason, the OD will be estimated when approximately 90 patients have entered prophylaxis.

This interim analysis will only be based on number of bleeding episodes and exposure time on prophylaxis regimen. These data will be cleaned for the interim and archived but not locked in the sense that any errors in these data discovered later may still be corrected for the final analysis.

*The most likely explanation for the over-dispersion is a patient level effect on the annualised bleeding rates. Some patients bleed more often than others. Since such an effect will induce a higher over-dispersion in studies of longer duration, it is essential to adjust the OD estimate from an interim up to what it can be expected to be for the whole trial where the trial duration will be longer. With Exp_int denoting average exposure time at the interim and Exp_full denoting the expected average exposure time at end of trial the expected OD at end of trial (OD_full) for the so far recruited (100) patients can be estimated from the OD at the interim (OD_int) as $OD_full = 1 + (OD_int - 1) * (Exp_full / Exp_int)$. As an example if the estimated OD is 3 and the exposure is expected to double before end of trial, OD_full will be estimated as 5.*

To ensure proper detachment from the data in the trial while it is still ongoing this analysis will be performed by a project independent statistician and only the exposure and the OD will be communicated to the project - not the annualised bleeding rate.

If the OD estimate for the full study is greater than 6, then a decision will be taken to amend the protocol to increase the sample size to 160 patients recruited to prophylaxis treatment.

3 Changes to Sample Subject Information Informed Consent Form

Changes to Sample Subject Information Informed Consent form and Sample Subject Information Informed Consent without PK:

Section 1.3 Procedures during the trial conduct

...

Note that if a bleeding episode occurs during the period between your first and second dose you must *contact your trial doctor and preferably go to the clinic to be treated with trial medication. In case of a bleeding episode between visit 2a and 2b that requires immediate treatment or the trial doctor judges it as necessary, you can treat the bleed at home with your previous FVIII product.*

Section 3.2 Will your participation in the trial be kept confidential?

...

None of your trial data will be identified by your name. Your trial data will be identified only by a trial assigned subject number, *and by your date of birth (if allowed by local law)*. Any laboratory samples taken including the test for genotyping, will be identified in the same way.

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

12 April 2012
1.0
Final
1 of 4

Novo Nordisk

Substantial Protocol Amendment

No. 7

to Protocol, Final version 1.0, dated 30-Sep-2011

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable for Brazil

Amendment originator:



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Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:	12 April 2012	Novo Nordisk
Version:	1.0	
Status:	Final	
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1 Introduction including rationale for the substantial protocol amendment

In this substantial protocol amendment:

- Any new text is written *in italic*.
- Any text deleted from the protocol is written with a ~~strike through~~.

This substantial amendment is being issued as a response to a query from the Brazilian National Ethics Committee (CONEP) where it states that the protocol does not specify what are the acceptable contraception procedures for the Brazilian population.

This substantial amendment is applicable for Brazil only.

2 Changes to Protocol

6.3 Exclusion Criteria

The following text has been added to the end of section 6.3 in the protocol. However, it is not to be considered an exclusion criteria.

For Brazil only: *Patients who are sexually active and have partners who could become pregnant must be willing and are required to use a barrier method of contraception (e.g. condom). Furthermore, the patient's partner must also use a contraceptive method. The contraceptive methods should be used for the duration of the trial and for 3 months following the last dose of trial medication.*

Patients who declare sexual abstinence due to personal decision will have their decision documented and respected and the use of a contraceptive method will not be applicable in this case.

Substantial Protocol Amendment

no 8_RU

to Protocol, final version 2.0, dated 09 December 2011

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to Russia

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

This local substantial amendment is being issued as a response to conclusion by Ministry of Health and Social Development of the Russian Federation in connection with submission of the NN7088-3859 protocol: due to absence of data from clinical trials in population from 12 to 17 years old, patients below 18 years of age cannot be included in this trial.

The following change has been made to the protocol:

- Inclusion criterion number 4 has been modified to exclude patients of age < 18 years in Russia.

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

1 Summary

Key Inclusion Criteria

- Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia ~~and~~, The Netherlands *and Russia* where the lower age limit will be 18 years)

6 Trial Population

6.2 Inclusion Criteria

...

4. Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia ~~and~~, The Netherlands *and Russia* where the lower age limit will be 18 years)

Substantial Protocol Amendment
Trial ID: NN7088-3859
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Date: 19 October 2012
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Novo Nordisk

Substantial Protocol Amendment

no 9-FR

to Protocol, final version 4.0

dated 30 March 2012

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to France

Amendment originator:



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Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN:U1111-1119-7416
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~~CONFIDENTIAL~~

Date:	19 October 2012	Novo Nordisk
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1 Introduction including rationale for the substantial protocol amendment

The rationale for issuing this substantial amendment is the addition of a new site in France in order to help reaching international recruitment target.

Attachment II is updated accordingly.

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

The following changes to Attachment II to NN7088-3859:

Site added:

Investigator: Name:

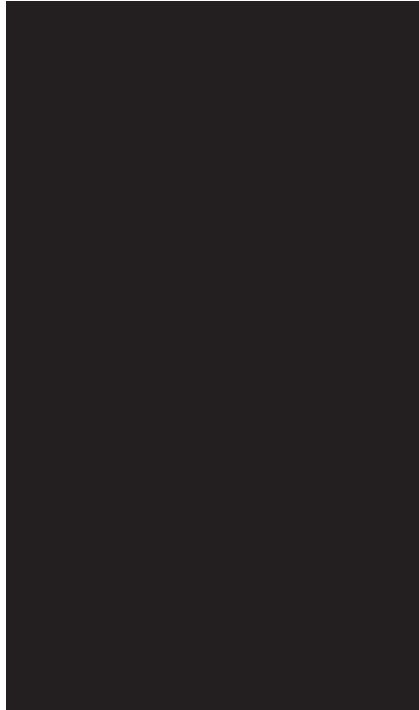
Title:

Address:

Tel:

Fax:

E-mail:



Substantial Protocol Amendment

no 10

to Final Protocol, version 4

dated 30 March 2012

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

The power calculation is sensitive to an assumed over-dispersion (OD) of 5. For this reason it is stated in the protocol that an interim analysis will be performed to evaluate the OD when approximately 90 patients have been recruited to prophylaxis: If the estimated OD for the full study is larger than 6, then the sample size will be adjusted up to 160 patients on prophylaxis and in that way ensure that the power holds.

It is stated in the protocol that the sample size will not be increased without issuing an amendment to the protocol. Therefore, this global substantial protocol amendment is being issued in order to allow for an increase in sample size following the described interim analysis, should it be determined to be necessary.

The estimated number of enrolled, dosed and completed patients have therefore changed to reflect the maximum number that would be included, should the interim analysis result in an increase in sample size. Sections of the protocol reflecting this change include Summary section 1, Trial Design sections 5.1, 5.2 and 5.3, Trial Population section 6.1, Patient Replacement section 6.6, section 7 and Statistical sections 18.1, and 18.5.

A few spelling 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

Section 1 Summary

Trial design:

.....

~~A minimum of~~ *Approximately 115 (155)¹* patients must complete the trial in 2 treatment arms including at least 10 patients in on-demand treatment and *105 (145)¹* patients in prophylaxis treatment with N8-GP every 4 days. Whether a patient will receive prophylaxis treatment or on-demand treatment is the choice of the patient and Investigator and will be decided at the screening visit.

Trial Population:

Approximately *150 (190)¹* previously treated patients (PTPs) with severe (FVIII <1%) haemophilia A in a non-bleeding state will be screened to allow for ~~a minimum of~~ *approximately 115 (155)¹* patients to complete the trial.

Section 5.1 Type of Trial

.....

~~A minimum of~~ *Approximately 115 (155)¹* (see section 18.5) patients must complete the trial including at least 10 patients in on-demand treatment and *105 (145)¹* (see section 18.5) patients in prophylaxis treatment with N8-GP every 4 days.

.....

The distribution of patients will be as follows:

It is expected that approximately *120 (160)¹* (see section 18.5) patients will be dosed in the prophylaxis arm in order to obtain *105 (145)¹* (see section 18.5) completed patients on prophylaxis treatment. These patients will receive treatment with 50 U/kg of N8-GP every 4

¹ An interim analysis is planned when approximately 90 patients have been dosed in order to decide if the sample size should be adjusted. If the over-dispersion of the annual bleeding rate is greater than 6 then the sample size will increase to the patient number stated in brackets (see section 18.5)

days during a period of approximately 7-19 months. In case of a bleed the patients will be treated with doses between 20-75 U/kg BW.

Section 5.2 Rationale for Trial Design

The purpose of the prophylaxis arm is to provide sufficient exposure to N8-GP to evaluate immunogenicity and to provide efficacy data from 50-100 EDs of prophylaxis treatment with N8-GP in ~~at least~~ *approximately 105 (145)¹ (see section 18.5)* patients with severe haemophilia A ≥ 12 years. The reason for not having a prophylaxis control is that no FVIII product is globally approved for prophylaxis treatment.

Section 5.3 Treatment of Patients

Approximately 150 (190)¹ (see section 18.5) patients are planned to be screened in order to dose approximately 132 (172)¹ (see section 18.5) patients in the trial out of which 105 (145)¹ (see section 18.5) patients are expected to complete the prophylaxis part of the trial and a minimum of 10 patients are expected to complete approximately 6 months in the on-demand part of the trial.

Section 6.1 Number of Patients to be Studied

Countries planned to participate: Australia, Brazil, Croatia, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

Planned number of patients to be screened (i.e. documented informed consent) approximately: 150 (190)¹ (see section 18.5)

Planned number of patients to be started on trial product(s) approximately: 132 (172)¹ (see section 18.5)

Planned number of patients to complete the trial *approximately*: ≥ 115 (155) (see section 18.5)

- Minimum 15 patients must be 12-17 years old at screening
- Minimum 10 patients must be in the on-demand arm
- ~~Minimum~~ *Approximately 105 (145)¹ (see section 18.5)* patients must be in the prophylaxis arm

Planned number of trial sites (approximately): 75

Section 6.6 Patient Replacement

Patients withdrawn from the trial can be replaced until *approximately* 105 (145)¹ (see section 18.5) patients in the prophylaxis arm have had at least 50 EDs, and 10 patients have had 20 bleeding episodes in the on-demand and/or the prophylaxis arm.

Section 7 Trial Schedule

Planned duration of recruitment period: 12 (14)¹ months

.....

Planned date for LPLV: 01-Oct (Dec) (See section 18.5)--2013

Section 18.1 Sample Size Calculation

Co-Primary Endpoint: Annualised bleeding rate in the prophylaxis arm

.....

The power calculation is sensitive to the assumed over-dispersion (OD) of 5. For this reason an interim analysis will be performed to evaluate the OD when approximately 90 patients have been recruited to prophylaxis: If the estimated OD for the full study is larger than 6, then the sample size will be adjusted up to 160 on prophylaxis and in that way ensure that the power holds. ~~The sample size will not be increased without issuing a protocol amendment.~~

Section 18.5 Interim Analysis

.....

If the OD estimate for the full study is greater than 6, then a decision will be taken to ~~amend the protocol~~ increase the sample size *up to approximately* 160 patients recruited to prophylaxis treatment.

NNC 0129-0000-1003
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Substantial Protocol Amendment no. 11 to Final Protocol version 4.0 dated 30 Mar 2012

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial Phase: 3

Applicable for Israel only

Amendment originator:



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Appendix A Approval of Final Substantial Protocol Amendment no. 11	
Appendix B Agreement on Final Substantial Protocol Amendment no. 11	

1 Introduction including Rationale for the Substantial Protocol Amendment

As genetic approval in Israel is a long process, it was decided for Israel that the genetic testing (or if performed previously, to have genotype information made available for this trial) will be indicated in the protocol as “Not applicable for Israel”

Furthermore, in Israel, adolescents will not be included in the trial which has implications on inclusion criteria 4 section 6.2.

In this substantial protocol amendment:

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

2 Changes

Section Table of Contents

8.3.7.5 FVIII genotype testing (Not applicable to Brazil *and Israel*).....17

Section 1 Summary

....

Key Inclusion Criteria

Male patients with severe congenital haemophilia A (FVIII activity <1%, according to medical records)

Documented history of at least 150 EDs to other FVIII products

Age >12 years and body weight \geq 35 kg (except for Croatia, The Netherlands ~~and~~ France *and Israel* where the lower age limit will be 18 years)

Section 6.2 Inclusion Criteria

Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject.)

Male patients with severe congenital haemophilia A (FVIII activity <1%, according to medical records)

Documented history of at least 150 exposure days to other FVIII products

Age >12 years and body weight \geq 35 kg (except for Croatia, The Netherlands ~~and~~ France *and Israel* where the lower age limit will be 18 years)

Body Mass Index (BMI) \leq 35

The patient and/or caregiver is capable of assessing a bleed, capable of home treatment of bleeding episodes and otherwise following the trial procedures

NNC 0129-0000-1003
Trial ID: NN7088-3859
Protocol/UTN: U1111-1119-7416
EudraCT No.:2011-001142-15

~~CONFIDENTIAL~~

Date:	05 December 2012	Novo Nordisk
Version:	1.0	
Status:	Final	
Page:	5 of 5	

Section 8.3.7.5 **FVIII genotype testing (Not applicable to Brazil *and* Israel)**

Section 19.1 **Informed Consent Form for Trial Patients**

...

FVIII Genotype Testing / Collection of Previous Genotype Documentation (Not applicable to Brazil *and* Israel)

Substantial Protocol Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

~~CONFIDENTIAL~~

Date:
Version:
Status:
Page:

05 March 2013
1.0
Final
1 of 6

Novo Nordisk

Substantial Protocol Amendment

no 12

to Protocol, final version 5

dated 03 December 2012

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

This global substantial amendment is being issued in order to extend the maximum treatment period with 3 months, from 24 to 27 months, due to an extension of the recruitment period. Therefore additional visits Visit 12a to Visit 12j have been added.

Patients for the surgery trial, NN7088-3860 (pathfinder™ 3), are recruited via this trial where they must have had at least 5 exposure days (EDs) before entering the surgery trial. This amendment will allow the continued recruitment of major surgery patients after the recruitment of this trial has been completed. This is in order to ensure recruitment into the surgery trial and fulfilment of regulatory requirements regarding collection of major surgery data. The extension trial will not await these patients to complete 50 EDs before it's initiation.

The following changes has been made to the protocol: Sections 2, 5.1, 7.0, 8.1, 8.1.6 and 18.2.2

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

2.1 Section 2 Flow Chart

Table 2-1

Visit number		1	2a ¹	2b	3	4	5	6	7 ^{1,2}	8	9	10	11	12 ^{1,4}	13 ¹³	14	Un-schedule d visit
--------------	--	---	-----------------	----	---	---	---	---	------------------	---	---	----	----	-------------------	------------------	----	------------------------

Footer to table 2-1

14	<i>Additional visits can be added between Visit 12 and 13 if needed. These will be called Visit 12a, Visit 12b etc. and contain the same assessments as Visit 12</i>
----	--

2.2 Section 5.1 Type of trial

...

Treatment duration is approximately 6 months in the on-demand arm and from approximately 7 (200 days plus screening period of 2-3 weeks) to approximately 19 months in the prophylaxis arm. The maximum treatment period in this trial is 24 27 months. In the prophylaxis arm, all patients will continue in the trial until the last patient has received at least 50 EDs of N8-GP, thus all patients in the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be more than 1 year. *Patients enrolled in pathfinder^{TM2} with the intention of entering the pathfinder^{TM3} for major surgery can be enrolled in pathfinder^{TM2} after the end of normal recruitment period. For the purpose of defining LPLV, the definition of LPLV excludes these patients and the opening of the extension trial will not await these patients to complete 50 EDs in the trial.* When this trial is completed, all patients will be offered to continue treatment in the extension trial pathfinder^{TM4}, if approved by country. As all patients will complete the present trial at the same time (or within a short timeframe) the transition of patients from pathfinder^{TM2} to pathfinder^{TM4} will be gradual and within a window of approximately 1 month.

2.3 Section 7 Trial Schedule

...

Planned date for FPFV: 01-Feb-2 012

Planned date for LPLV: 01-Oct (Dec) (see section 18.5) 2013

Patients enrolled in pathfinder™ 2 with the intention of entering the pathfinder™ 3 for major surgery can be enrolled in pathfinder™ 2 after the end of normal recruitment period. The definition of LPLV excludes these patients and the opening of the extension trial will not await these patients to complete 50 EDs in the trial.

The end of the clinical trial is defined as LPLV.

2.4 Section 8.1 Visit Procedures

...

All patients will complete at least 8 visits depending on when they are enrolled in the trial as the trial will be completed when the last prophylaxis patient has had 50 EDs. The last patient will have EOT visit at visit 7 after having received at least 50 EDs whereas the first patient enrolled in the trial will have the EOT visit at Visit 13. Therefore, the EOT visit can be all visits from visit 7 to visit 13. More visits may be added *between Visit 12 and 13* depending on when the last patient has had at least 50 EDs (*or approval of Extension trial in country*). *These visits will be called Visit 12a, 12b, etc.*

2.5 Section 8.1.6 Transfer of Patients to pathfinder™ 3 due to Major Surgeries

...

Upon completion of pathfinder™ 3, patients ~~will~~ *may* return to pathfinder™ 2, re-entering the prophylactic or on-demand treatment arm as per their prior participation in the trial. The patient will return to the next visit in line in Pathfinder™ 2 and the visit assessments performed at the EOT visit in pathfinder™3, will be used. *The patient enrolled in pathfinder™2 with the intention of entering the pathfinder™3 for major surgery at the end of normal recruitment period in pathfinder™2 will not have to complete Visit 7 and reach 50 EDs before continuing into the Extension trial, if the Extension trial is open. Though, a Visit 13 must take place before continuing into the Extension trial. Furthermore, the opening of the Extension trial will not await these patients to complete 50 EDs in the trial.*

2.6 Section 18.2.2 Primary Endpoint(s)

...

Analysis of 12 months data from patients that could have had 12 months prophylaxis

Since patients will stay in the trial until the same end date some patients will get only about 7 months prophylactic treatment while others may get ~~as much as~~ *more than* 19 months (*except for patients entering the trial with the intention of major surgery after the end of normal recruitment period*). To investigate if the varying durations have any impact on the results a sensitivity analysis will be performed looking only at 12 months data from patients with planned trial duration of 12 or more months. Otherwise this analysis will be performed similarly to the primary analysis.

To investigate the effect over time the bleeding rates per month will be calculated and summarised numerically and graphically. For months after month 7 not all patients will be available since the last patients recruited will only receive about 7 months treatment (*except for patients entering the trial with the intention of major surgery after the end of normal recruitment period*). This may create an apparent time effect really caused by fewer and fewer patients being available. This will be investigated by also summarising by month only for the first 12 months data from patients that could have received 12 months treatment (i.e. patients recruited earlier than 12 months before LPLV).

Substantial Protocol Amendment

no 13, Global

to Protocol, final version 6

dated 07 March 2013

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the substantial protocol amendment

In the current version of the NN7088-3859 (pathfinder™ 2) protocol version 6.0 patients can be transferred to the extension trial NN7088-3861 (pathfinder™4) where they can continue treatment with N8-GP until it is commercially available.

Instead of setting up a separate trial, the extension trial will be included in the current pathfinder™ 2 trial as an extension phase which have the following implications:

- The trial will consist of a Main Phase (the current pathfinder™ 2 protocol) and an Extension Phase where patients will be offered to continue treatment with N8-GP until it is commercially available
- The Extension Phase of will consist of two parts: part 1 and 2:
 - Part 1 will investigate the efficacy and safety of a once weekly (every 7 days) prophylaxis dosing regimen in a sub-population. The remainder of the patients will continue with the 4 days or on-demand treatment regimen as described in the current pathfinder™ 2 protocol
 - Part 2 will investigate the long-term safety and efficacy of N8-GP for prophylaxis and on-demand treatment with the possibility of individualised prophylaxis treatment (every 4, 5, 6 or 7 days treatment) based on the patient's individual bleeding pattern
- The dose in the Extension Phase will be 50 U/kg in the every 4 days treatment, as in the Main Phase, 60 U/kg for the every 5 and 6 days treatment and 75 U/kg for the every 7 day treatment
- The statistical section has been updated explaining the analyses of the data collected during the Extension Phase
- Furthermore, minor incorrectness, misspellings and typographical 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 to Protocol

2.1 List of Abbreviations

...
EOM *End of Main Phase*
...
OD *over- dispersion*
...

2.2 Section 1 Summary

...

Co-Primary Endpoints

The Incidence rate of FVIII-inhibitors ≥ 0.6 BU
Annualised bleeding rate *for patients receiving prophylaxis treatment in the prophylaxis arm*

Key Secondary Endpoint

Haemostatic effect of N8-GP when used for treatment of bleeds, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure

All efficacy endpoints will be analysed and reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase part 2 of the trial. All safety endpoints will be reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase part 2 as well as based on accumulated data (Main Phase + Extension Phase part 1 and Main Phase + both Extension Phases). The endpoint will be analysed based on all available information until the end of trial (EOT) visit and up to approximately 19 months.

Trial design:

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety, pharmacokinetics and clinical efficacy of N8-GP when used for treatment of bleeding episodes and for long-term prophylaxis. *The trial consists of a Main Phase followed by an Extension Phase.*

Approximately 115 (155)¹ patients must complete the trial in 2 treatment arms including at least 10 patients in on-demand treatment and 105 (145)¹ patients in prophylaxis treatment with N8-GP every 4 days *in the Main Phase of the trial*. Whether a patient will receive prophylaxis treatment or on-demand treatment is the choice of the patient and Investigator and will be decided at the screening visit.

A minimum of 15 of the patients in the prophylaxis arm must undergo two PK sessions to obtain 13 patients with two PK profiles. In order to ensure recruitment of patients for PK it is planned that the first patients (approximately 10) entering the prophylaxis arm must undergo PK sessions.

Main Phase: Treatment duration is approximately 7-19 months. In the prophylaxis arm, all patients ~~in the prophylaxis arm~~ will continue in the *Main Phase* ~~trial~~ until the last patient initiated in the *prophylaxis arm* has received at least 50 exposure days (EDs)² of N8-GP, thus all patients in the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be above 1 year. The purpose of the on-demand arm is to ensure that sufficient bleed treatment data are collected in the trial. The on-demand patients can switch to prophylaxis treatment after approximately 6 months on-demand treatment if, the prophylaxis arm is still open for enrolment, or continue on-demand treatment until end of trial (EOT).

When ~~this~~ *the Main Phase* of this trial is completed, all patients will be offered to continue treatment in the *Extension Phase of the trial* NN7088-3861 (pathfinderTM4) provided approval in the respective countries.

Extension Phase: The *Extension Phase* will investigate the long-term safety and efficacy of N8-GP for prophylaxis patients on a 4-7 day dosing regimen and on-demand treatment.

If the patients need to undergo surgery during the present trial they can switch into the surgery trial NN7088-3860 (pathfinderTM3). Upon completion of the surgery the patients can return to the NN7088-3859³ (pathfinderTM2) trial.

.....

Key Inclusion Criteria

- Male patients with severe congenital haemophilia A (FVIII activity <1%, according to medical records)
- Documented history of at least 150 EDs to other FVIII products

- Age ≥ 12 years and body weight ≥ 35 kg (except for Croatia, The Netherlands, France, Russia and Israel where the lower age limit will be 18 years)

....

Trial Product(s):

...

In the prophylaxis arm(s), each patient will receive prophylaxis treatment with a N8-GP dose of 50 U/kg body weight (BW) every 4 days *in the Main Phase*. *During part 1 of the Extension Phase a sub-group of patients will receive prophylaxis treatment every 4 day or every 7 day. In part 2 of the Extension Phase patients can be treated on every 4 day to once weekly (every 7 day)*. In most cases this will be home treatment with intravenous (i.v.) self-injection by the patient. Patients participating in the on-demand arm and patients in the prophylaxis arm will be treated with 20-75 U/kg BW in case of bleeding episodes.

2.3 Section 2 Flow Chart

Table 2-1 Flow Chart for Patients on Prophylaxis and On-Demand Treatment in Main Phase

Visit number	1	2a ¹	2b	3	4	5	6	7 ^{1,2}	8	9	10	11	12 ¹⁴	13 ¹³	±4	Un- sched uled visit
Time of visit	2w prior to visit 2a	0	4 days after Visit 2	4w	8w	12w	20w	28w	36w	44w	52w	60w	68w	76w EO M	Follow -up	
Visit window	Weeks +1			Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1	Weeks ±1		
SUBJECT RELATED INFO/ASSESSMENTS																
Informed consent		X												X ¹⁵		

...

Footer	Description
1	Please refer to Table 2-2 for the patients that need to undergo PK
2	Patients in the on-demand arm can switch into prophylaxis treatment after 6 months treatment
3	Confirmation of screening visit 1 in- and exclusion criteria
4	If applicable, i.e. following patient consent and in accordance with local law
5	To be measured before dosing and 30 min (±10min) after dosing.
6	Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment since last visit
7	A wash-out period of minimum 96 hrs is needed before the sample (except visit 1 and visit 2a where wash out is minimum 72 hours)
8	Only in case of an unexpected allergic/anaphylactic reaction
9	Trough to be sampled before dosing and recovery to be sampled 30 min (± 5min) after dosing <i>only for prophylaxis patients</i>
10	Only to be taken if HIV status is positive
11	From visit 2a -13 only BW will be measured
12	From visit 3-12, only for patients in the prophylaxis arm
13	Assessments to be performed at the EOEOM visit. The EOEOM visit (Visit 13) can take place at any time after be any visit from visit 7 to visit 13 depending on when the patient entered the trial. The Main Phase will be terminated when the last patient has received 50 exposure days.
14	Additional visits can be added between Visit 12 and 13 if needed. These will be called Visit 12a, Visit 12b etc and contain the same assessments as Visit 12
15	Addendum Informed Consent on comparison of data from pathfinder TM 1 or guardian TM trials

Visit number	Part 1					Part 2		Follow-up	Un-scheduled Visit ^{1,4}
	14 ¹⁵	15	16	17 ¹⁵	18-n ^{1,15}	EOT	12w ³		
Time of visit		8w ²	16w ²	24w ²					
Visit window	Weeks	±2	±2	±2	±2				
Affirmation statement	Weeks								
End of trial									
eDiary training		x	x	x	x				x
eDiary data review			x	x	x				x
Home treatment training		x	x	x	x				x

Footer	Description
1	n = visit number from 19 and onwards
2	weeks after Visit 14
3	weeks apart
4	weeks since last visit
5	Only in case of expected unexpected allergic/anaphylactic reaction
6	Only every second visit (V19, V21, V23....)
7	Antibody sample will only be drawn from patients in the on-demand arm if they received treatment since last visit
8	A wash-out period of minimum 96 hrs is needed before the sample
9	Trough to be sampled before dosing and recovery to be sampled 30 min (±5 min) after dosing, only for prophylaxis patients
10	Only for patients in prophylaxis treatment
11	Only height every year for patients below 18 years, otherwise only BW
12	Only yearly (at V21, V25...)
13	Only to be taken if HIV status is positive
14	Assessment during unscheduled visit are not mandatory but can be performed
15	It is recommended to contact patients approximately 4 weeks after change of regimen (see section 8.14)

2.4 Section 3 Introduction

3.1 Basic Information

....

3.1.4 Risk and Benefits.

....

To minimise the switching between FVIII products, the patients, will upon completion of the ~~present~~ *Main Phase of the trial*, be offered to continue treatment with N8-GP in the *Extension Phase of the trial (pathfinderTM 4)*, where patients have the opportunity to continue with N8-GP treatment until commercially availability².

3.2 Rationale for the Trial

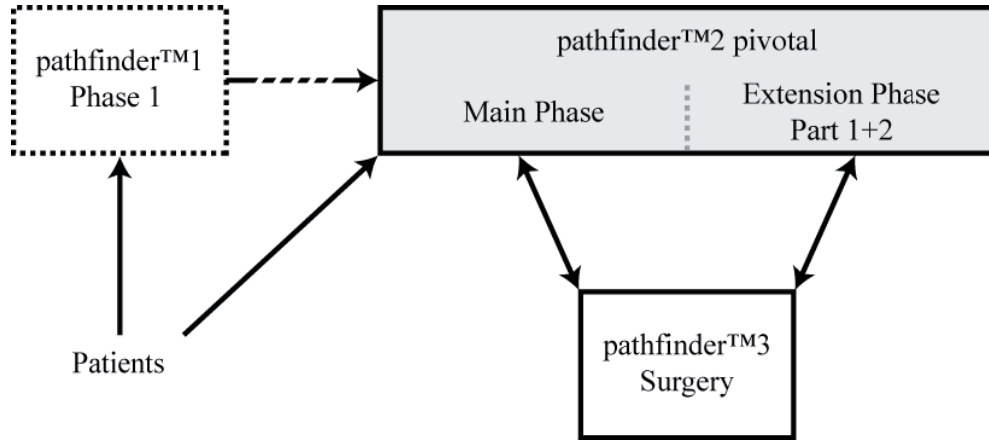
This trial is part of a clinical development programme that at present includes a completed phase 1 trial (pathfinderTM 1), the present pivotal (*including Main and Extension Phase*) phase 3a trial (pathfinderTM 2), ~~an extension phase 3b trial (pathfinderTM 4)~~ and a surgery phase 3a trial (pathfinderTM 3). The phase 3 trials are offered as one package to each investigational site to ensure that patients are offered to continue N8-GP until commercially available and patients in need of surgery can undergo surgery without having to switch product. The clinical programme is illustrated in Figure 3-1.

In the preceding phase 1 trial (pathfinderTM 1), 26 patients with haemophilia A had one PK session with their current FVIII product followed by one PK session with N8-GP. The trial was completed on 18 April 2011 and the results formed the basis for the doses selected in the present trial.

The rationale for this trial is to investigate the safety and efficacy, including PK and long-term safety of N8-GP in Haemophilia A patients from 12 years of age. *In the Main Phase of the trial the safety and efficacy of an every 4 day prophylaxis dosing regimen will be investigated. The main objective of the Extension Phase part 1 is to investigate the safety and efficacy of once weekly prophylaxis dosing of N8-GP in a subset of patients. This option will only be available to patients on prophylaxis treatment having a low bleeding rate on an every 4 days dosing regimen in the Main Phase of the trial. The main objective of part 2 of the Extension Phase is to collect long term safety and efficacy data*

² For UK only: The end of the *Extension Phase trial* will be defined by exact date and not when commercially available

New figure:



To be deleted:

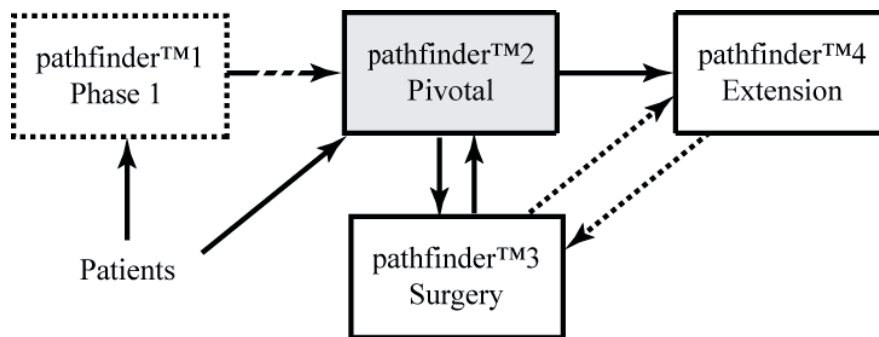


Figure 3-1 Overview of the pathfinder™ clinical trial programme.

Arrows indicate possible transfer of patients between trials. Patients completing the phase 1 trial may also be enrolled in the coming trials if found eligible.

2.5 Section 4 Objective(s) and Endpoint(s)

....

4.2 Endpoint(s)

4.2.1 Co-Primary Endpoints

The incidence rate of FVIII-inhibitors ≥ 0.6 BU

Annualised bleeding rate for patients receiving prophylaxis treatment in the prophylaxis arm

.....
4.2.2.2 Additional Supportive Efficacy Endpoints

- Consumption of N8-GP (number of infusions and U/kg) per bleed
- Consumption of N8-GP (number of infusions and U/kg per month and per year) during prophylaxis and on-demand treatment
- Haemostatic effect as measured by recovery and trough levels FVIII:C (in all *patients receiving prophylaxis treatment in the prophylaxis treatment arm*)
- Patient Reported Outcomes and Health Economic Endpoints
 - PRO scores and ~~their~~ changes in *PRO scores in from baseline to the end of the trial phases*
 - Bleed related health economic resource use and patient/caregiver burden

.....
4.2.3 Exploratory Endpoints

Incidence of binding, non-inhibitory antibodies to N8-GP/ turoctocog alfa

4.2.4 Timeframe for evaluation of the endpoints

The pharmacokinetic endpoints will be based on assessments performed from 1 hour prior to and up to 96 hours after administration for visit 2a and Visit 7.

All efficacy endpoints will be analysed and reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase part 2 of the trial. All safety endpoints will be reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase part 2 as well as based on accumulated data (Main Phase + Extension Phase part 1 and Main Phase + both Extension Phases).

2.6 Section 5 Trial Design

5.1 Type of Trial

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety, pharmacokinetics and clinical efficacy of N8-GP when used for treatment of bleeding episodes and for long-term prophylaxis. The trial consists of a Main Phase followed by an Extension Phase.

A minimum of 115 (155) (see section 18.5) patients must complete the trial including at least 10 patients in on-demand treatment and 105 (145) (see section 18.5) patients in prophylaxis treatment

with N8-GP every 4 days *in the Main Phase of the trial*. In order to ensure recruitment of patients for PK it is planned that the first patients (approximately 10) entering the prophylaxis arm must undergo PK sessions. Whether a patient will receive prophylaxis treatment or on-demand treatment is non-randomised and will be the choice of the patient and Investigator. This will be based on medical needs and decided at the Screening visit. For the US, recruitment will open for the on-demand arm before enrolling patients in the prophylaxis arm, whereas both arms will open concurrently at non-US sites.

The distribution of patients *in the Main Phase of the trial* will be as follows:

...

Treatment duration is approximately 6 months in the on-demand arm and from approximately 7 (200 days plus screening period of 2-3 weeks) to approximately 19 months in the prophylaxis arm. The maximum treatment period *in the Main Phase of this trial* is ~~24~~ 27 months. In the prophylaxis arm, all patients will continue in the *Main Phase* ~~trial~~ until the last patient *initiated in the prophylaxis arm* has received at least 50 EDs of N8-GP, thus all patients in the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be more than 1 year. Patients enrolled in pathfinder™ 2 with the intention of entering the pathfinder™ 3 for major surgery can be enrolled in pathfinder™2 after the end of normal recruitment period. For the purpose of defining LPLV, the definition of LPLV *in the Main Phase* excludes these patients and the opening of the Extension Phase will not await these patients to complete 50 EDs in the trial. When *the Main Phase* is completed, all patients will be offered to continue treatment in the Extension ~~trial~~ Phase, if approved by country. As all patients will complete the *Main Phase* at the same time (or within a short timeframe) the transition of patients from *the Main Phase to the Extension Phase*, will be gradual and within a window of approximately 2 months *following the patient's visit schedule*. When the Extension Phase has opened and has been approved in the country the patient must at the next visit end the *Main Phase (Visit 13)* and continue into the *Extension Phase (Visit 14)*.

The distribution of patients *in the Extension Phase of the trial* will be as follows:

The Extension Phase of the trial includes two parts: part 1 and part 2. In part 1, patients who were on prophylaxis treatment every 4 days dosing with N8-GP during the Main Phase of the trial and with a 0-2 bleeding episodes during the last 6 months (180 days) before entering the Extension Phase, will be offered to be randomised to every 7 days or every 4 days treatment (2:1 randomisation). Patients with 3 or more bleeding episodes within the last 6 months of the Main Phase before entering the Extension Phase as well as patients with low bleeding rates who are unwilling to be randomised will continue with the same treatment regimen as in the Main Phase of the trial. Recruitment into the randomisation sub-group in the Extension Phase part 1 will stop

approximately at mid-May 2014, hereafter also patients with a low bleeding rate will continue the same treatment as in Main Phase.

In the part 2 patients can continue being on prophylaxis but can change between dosing regimens according to their bleeding episode pattern. When patients randomised to either every 4 or 7 day regimen complete the part 1, the part 2 will open also for patients not having completed the 6 months treatment in part 1.

Patients treated on-demand in the Main Phase will continue with the on-demand regimen.

Furthermore, if the patients need to undergo surgery during the present trial they can switch into the surgery trial pathfinder™³ and upon completion of the surgery they can return to the pathfinder™²³ trial. Recruitment into the surgery trial pathfinder™³ will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pivotal trial pathfinder™². The surgery trial will not be initiated until at least 20 bleeding episodes in at least 10 patients are treated with N8-GP in the present trial.

5.2 Rationale for Trial Design

The purpose of the prophylaxis arm *in the Main Phase* is to provide sufficient exposure to N8-GP to evaluate immunogenicity and to provide efficacy data from 50-100 EDs of prophylaxis treatment with N8-GP in approximately 105(145) (see section 18.5) patients with severe haemophilia A ≥ 12 years. The reason for not having a prophylaxis control is that no FVIII product is globally approved for prophylaxis treatment.

...

The purpose of continuing all patients in the prophylaxis arm in the *Main Phase of the* trial until the last patient has completed at least 50 EDs of N8-GP is to ensure that the average exposure to N8-GP will be above 1 year for a considerable portion of the patients.

...

For clinical efficacy of N8-GP in the prevention of bleeding episodes, historical data on annualised bleeding frequency during on-demand treatment and prophylaxis will be used for comparison. The historical data derive from a recent review by an independent board of haemophilia treaters within the Swedish Council on Health Technology Assessment, including all published clinical studies on treatment of severe haemophilia A during the last 25 years which were comprised of at least 20 patients¹⁰. The review selected in total 37 separate studies of haemophilia A replacement therapy, seven of which contained data on bleeding frequency in an adult and/or adolescent population¹¹.

The part 1 of the Extension Phase will include 4 treatment arms: prophylaxis treatment every 4 day, a randomised sub-group of treatment every 4 or every 7 day, or on-demand treatment. The primary aim of part 1 of the Extension Phase is to investigate the safety and efficacy of every 7 day dosing of N8-GP. In the interest of patient safety this treatment will be offered only to a sub-set of patients who have low bleeding rates (see section 5.1) from prophylaxis treatment in the Main Phase. In order to control for season effects, subjects will continue with every 4 day dosing as control group in the randomised group. Allocation to the treatment arms will be done by randomisation. Subjects who do not wish to be randomised can continue in the Extension Phase part 1 with the treatment regimen from the Main Phase. This ensures that patients with low bleeding rate, who are not willing to be on every 7 day treatment, can stay in the trial in the non-randomised arm.

Part 2 of the Extension Phase will consist of a single prophylaxis treatment arm where it will be possible to individualise treatment according to recommended guidelines (see section 5.3) taken the patients bleeding pattern into account. The single treatment arm design has been chosen as the primary objective is to obtain long term safety and efficacy data in more daily life setting.

On demand patient will throughout the Extension Phase continue as previously and will contribute with long term safety and efficacy data.

Patients can leave the trial at the End-of-Main Phase Visit without being considered as withdrawals. If leaving the trial at any other visits than End-of- Main Phase or End-of-Trial the patients will be considered as withdrawals.

....

5.3.1 Prophylaxis

Main Phase: In the prophylaxis arm, one single bolus dose of 50 U/kg BW of N8-GP is administered intravenously every 4 days (96 hours interval). The dose chosen is based on phase 1 data from the pathfinder™ 1 trial and is chosen to ensure a trough level of >1% FVIII:C activity in the majority of patients in the prophylaxis arm. During treatment a shortening of the dosing interval for prophylaxis to twice weekly may be undertaken at the Investigator's discretion, if deemed necessary for the individual patient (see section 5.3.2). If the dosing regimen is changed to twice weekly, doses should be separated with at least 3 calendar days and no more than 4 calendar days. Other changes of the dose or dosing interval for prophylaxis are not allowed within the trial. However, extra doses of N8-GP will be administered if a patient experiences a treatment requiring bleeding episode or in case of minor surgery.

Extension Phase part 1: *The prophylaxis dose of N8-GP is administered in the non-randomised group every 4 days or in the randomised group every 4 day or every 7 day depending on which treatment arm the patient is allocated to. Based on the bleeding pattern, the Investigator may*

change the every 7 day prophylaxis treatment to an every 4 day treatment regimen (the non-randomised arm), but changing vice versa is not permitted. The recommended doses to treat a bleeding episode will be the same as in the Main Phase. Patients moving from the randomised prophylaxis treatment every 7 day to the non-randomised prophylaxis treatment every 4 day will not be replaced in the randomisation distribution. The twice weekly regimen will only be allowed in the Extension Phase for patients who already in the Main Phase changed to twice weekly.

Extension Phase part 2: *During this period it is possible to adjust the prophylaxis treatment of patients to an individualised regimen. Treatment regimens ranging from once weekly to every 4 day will be allowed: every 4 day, every 5 day, every 6 day or every 7 day. For deciding to change a regimen it is strongly recommended to follow below guidelines for change of regimen:*

- *0-2 bleeding episodes within last 6 months on same regimen would allow a less frequent dosing interval to a lowest frequency of every 7 day*
- *3 or more bleeding episodes within last 6 months on same regimen allows to stay on regimen or change to a more frequent regimen to a highest frequency of every 4 day*
- *Change of regimen can only take place after being on the same regimen for at least 6 months*

Clinical judgement has to be applied in order to avoid increased risk to the subject's safety and must always overrule guidelines when deemed necessary by the Investigator.

The dose for the Extension Phase part 1 and 2 will be:

- *50 U/kg BW of N8-GP for prophylaxis treatment every 4 day*
- *60 U/Kg BW of N8-GP for prophylaxis treatment every 5 and 6 day*
- *75 U/Kg of N8-GP for prophylaxis treatment every 7 day*

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5.3.5 Patients Continuing Into ~~Other N8-GP Trials~~ the Extension Phase

All patients in the prophylaxis arm will continue in the *Main Phase of the trial* until the last patient initiated in the prophylaxis arm has received at least 50 EDs. After completion of the *Main Phase trial*, all patients will be offered to continue prophylaxis or on-demand treatment in the *Extension Phase of the trial* ~~pathfinder™ 4~~ for up to approximately two years or until N8-GP becomes commercially available⁴ in the patient's country. (*For UK only: the end of extension trial will be defined by exact date and not when commercially available.*) As all patients will complete the *Main Phase present trial* at the same time the *continuation transition* of patients from the *Main Phase to the Extension Phase* ~~pathfinder™ 2 th pathfinder™ 4~~ will be gradual and within a window of approximately ±2 months *depending on approval of the Extension Phase in the country and of*

⁴ For UK only: The end of the Extension Phase will be defined by exact date and not when commercially available.

patients' next scheduled visit. Please refer to Figure 3.1 for an overview of the flow of patients between trials in the clinical development programme.

If the N8-GP programme is terminated or if the health 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~~ trial will be stopped and treatment with N8-GP will be ended. ~~All data collected up to the point where the patient is transferred to the extension trial~~ will be used in the data analysis in the trial.

2.7 Section 6 Trial Population

6.1 Number of Patients to be Studied

Countries planned to participate: Australia, Brazil, *Bulgaria*, Croatia, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

2.8 Section 7 Trial Schedule

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Planned date for FPFV: 01-Feb-2012

Planned date for LPLV: ~~03-Dec-2018~~ 01-Oct(Dec)(see section 18.5) 2013

Patients enrolled in pathfinder™ 2 with the intention of entering the pathfinder™ 3 for major surgery can be enrolled in pathfinder™ 2 after the end of normal recruitment period *until pathfinder™ 3 has 15 completed surgeries.* The definition of LPLV *of the Main Phase* excludes these patients and the opening of the extension trial will not await these patients to complete 50 EDs in the trial.

The end of the clinical trial is defined as LPLV.

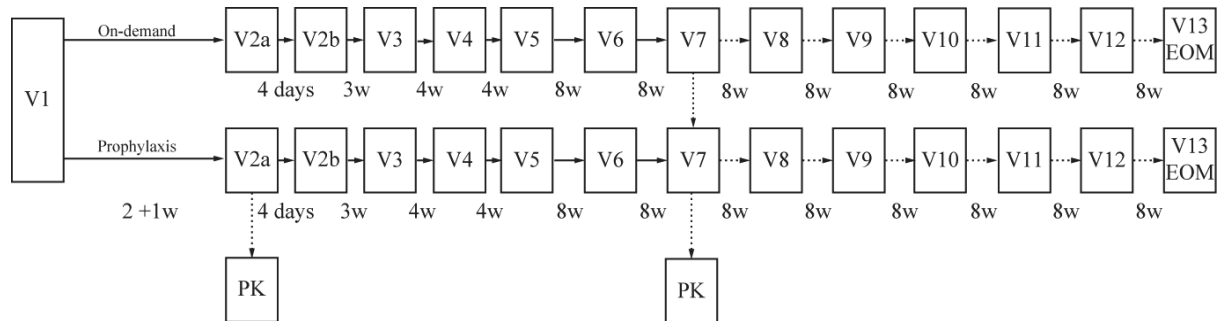
Planned completion of clinical trial report: within 6 months after LPLV. *Primary completion date will be at the end of the part 1 of the Extension Phase in the last quarter of 2014.*

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2.9 Section 8 Methods and Assessments

8.1 Visit Procedures

New figure:



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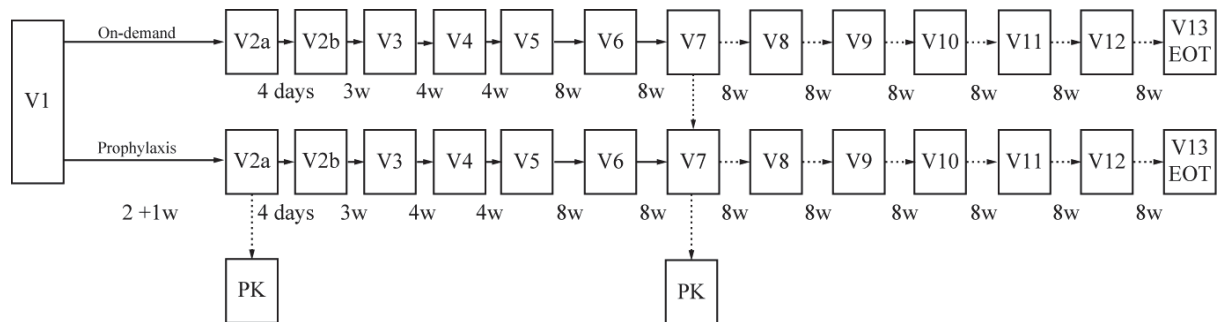


Figure 8-1 Overview of visits and home treatment periods in the Main Phase of the trial

All patients will complete at least 8 visits depending on when they are enrolled in the trial as the *Main Phase of the trial* will be completed when the last prophylaxis patient has had 50 EDs. *Thereafter the Extension Phase will be initiated when approved in the country. All patients need to complete at least 8 visits up to EOT visit at Visit 7 after having received at least 50 EDs whereas the first patient enrolled in the trial will have the visits up to EOT visit at Visit 13.* Therefore, the *Visit 13 -End-of-Main Phase* ~~EOT~~ visit can take place at any time after ~~be all visits from~~ Visit 7 during the *Main Phase* provided that the last patient has received 50 EDs ~~to visit 13~~. More visits may be added between Visit 12 and 13 (*EOM*) depending on when the last patient has had at least 50 EDs (or approval of *Extension Phase* ~~trial~~ in country). These visits will be called Visit 12a, 12b etc. *To complete the Main Phase all patients need to have a Visit 13- End-of-Main Phase visit.*

New figure:

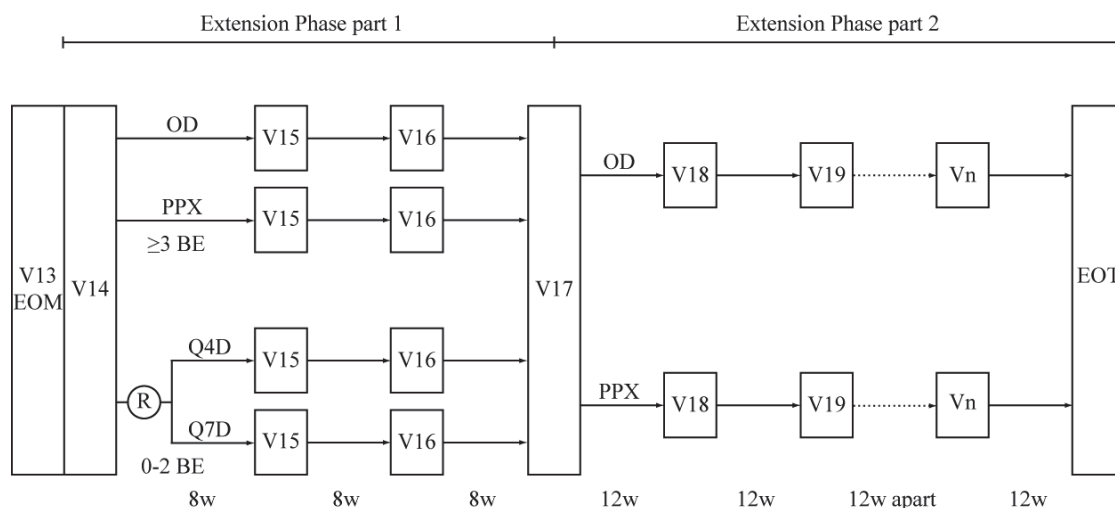


Figure 8.2 Overview of visits and home treatment periods in the Extension Phase part 1 and part 2

OD = on-demand, PPX = prophylaxis, BE = bleeding episodes, ® = randomisation, Q4D = prophylaxis every 4 day, Q7D = prophylaxis every 7 day, w = weeks.

The Extension Phase part 1 will for a patient last for 24 weeks, and the Extension Phase part 2 will last until the product become available on market in each country or a defined exact date depending on country.

The Main Phase of the trial includes the following visits:

- **Visit 1:** Screening visit
- **Visit 2a and 2b:** Visits at the site.
 - All patients will have their first and second dose administered at the site.
 - Patients in the prophylaxis arm undergoing PK evaluation will undergo first PK evaluation at Visit 2a.
- **Visit 3-1213:** Visits at the site.
 - Patients in the prophylaxis arm will be dosed during the visits
 - Patients in the prophylaxis arm undergoing PK evaluation will undergo second PK evaluation at Visit 7
 - Patients in the on-demand arm will not be dosed during the visits
- **Visit 13: End-of-Main Phase visit.** Visit at the site
 - End of Main Phase assessments (No patients will be dosed as part of the visit)

The Extension Phase will include the following visits:

- ***Visit 14 (same date as Visit 13 (EOM)):*** patients are enrolled in Extension Phase
- ***Visit 15+16: Visits at the site***
 - ***Patients in the randomised treatment arms*** will be dosed during the visits
 - ***Patients on prophylaxis NOT in the randomised treatment arm*** will be dosed during the visits
 - ***Patients on the on-demand treatment arm*** will not be dosed during the visits
- ***Visit 17-n : Visit at site***
 - ***Dosing regimen*** will be considered
 - ***Patients on prophylaxis regimen*** will be dosed at visits
 - ***Patients on the on-demand arm*** will not be dosed during the visits
- ***Visit EOT: Visit at site***
 - ***End of trial assessments, no treatment***

Follow-up visit (FU) (not shown in 8.1 and 8-2): only for patients withdrawn due to development of FVIII inhibitors

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Informed Consent Procedure: The patient and/or the patient's legally acceptable representative (LAR) will receive verbal and written information about the trial prior to conduct of any trial related procedures/activities. The information will include e.g. descriptions of N8-GP, the procedures involved, the practical consequences of participating, responsibilities and rights while participating in the trial including the possible advantages and disadvantages. Qualified site staff will ensure that patients and caregivers are fully informed both verbally and in writing. Patients and LAR(s) will have the opportunity to ask questions and have ample time to consider participation. If the patient wishes to participate in the trial, the patient and/or the patients LAR(s) will be requested to sign and date the Informed Consent Form. If the patient is a minor, he can in addition sign a child assent form, as per local regulations. When signing consent for *the Main Phase of* this trial the patient and /or the patients LAR(s) should be informed about the *surgery trial* and the *Extension Phase of the trials* as well.

It must be emphasised that any change in a patient's normal treatment routine is a trial-related activity, which is not allowed before the patient has consented to participate in the trial. For example: If a patient is taken off prophylaxis to allow for 72 hours without FVIII treatment before screening and the interval between the patient's normal prophylaxis doses is less than 72 hours, it is a trial related activity. In such case, it is essential that the informed consent procedure is completed prior to the trial related activities undertaken at the screening visit.

Before entering the Extension Phase of the trial a new Informed Consent covering the Extension Phase part 1 and 2 must be obtained following the above described procedure. If the patient is part

of the group of patients that can be randomised to either prophylaxis treatment every 4th day or every 7th day in the part 1 of the Extension Phase, the randomisation procedure must be discussed with the patient and an addendum to the informed consent must be signed if the patient agrees to be randomised.

Patients having previously participated in Novo Nordisk trials; in guardian™ trials (NN7008-3543 + 3545 + 3568) and/or pathfinder™ 1 (NN7088-3776), must be asked if they give their acceptance to compare data from the guardian™/pathfinder™ 1 trial(s) with data from this trial. If patients agree they must sign a separate addendum to the informed consent. This must be asked also to patients not continuing in the Extension Phase as part of Visit 13.

For screening failures: Screening failures are defined as patients who have signed the Informed Consent Form *for the Main Phase of the trial*, but fail to comply with the inclusion and exclusion criteria or if patients withdraw consent prior to dosing. Data in respect to the screening visit (Visit 1) will be entered in the screening failure form in the electronic case report form (eCRF) preferably 3 days after data are available. A screening failure call must be made in the interactive voice/web response system (IV/WRS). Serious and non-serious AEs from screening failures will be entered by the Investigator in the eCRF, and consequently transferred to the clinical database. When the trial related procedures have been finalised for screening failures, no more AEs should be entered in the eCRF. Follow-up of AEs should be made according to section 12.

Screening failures may be re-evaluated for participation in the trial and is allowed once. This will require a renewed informed consent to be obtained from the patient, a new eCRF should be started and the patient should be allocated a new patient number.

For withdrawn patients: Withdrawn patients are defined as patients who meet the withdrawal criteria after dosing, see section 6.5. In case a patient is prematurely withdrawn from the trial the Investigator must aim at undertaking procedures for the last visit (*EOM or EOT* visit) as soon as possible, if possible. The primary reason (AE, non-compliance with protocol or other) for discontinuation must be specified in the eCRF. The end-of-trial form must be completed, and final drug accountability must be performed even if the patient is not able to attend. 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 8.1.4.

Patients can leave the trial at Visit 13 (EOM) at the end of the Main Phase, without being considered as withdrawals. If leaving the trial at any other visits than EOM and EOT during the Main Phase and during the Extension Phase the patients will be considered as withdrawals.

End-of-Main Phase of the trial visit (Visit 13): The ~~EOT~~ End-of-Main (EOM) Phase of the trial visit can *take place after* ~~be~~ all visits from Visit 7 until Visit 12-13 depending on when the patient is

enrolled in the trial. For patients continuing in the Extension *Phase of the trial* (~~pathfinder™4~~) the *EOM of the trial* ~~EOT~~ visit will take place the same day as the ~~also be~~ Visit 14 in the Extension Phase part ~~this trial~~. If patients end their participation in the trial at the EOM Phase of the trial visit, this is not considered as a withdrawal, and the EOT form should be filled in. If a patient is withdrawn prior to completion of the Main Phase of the trial a EOM visit should be scheduled if possible and EOT form should be filled in.

End of Trial visit: *When a patient ends trial participation of the Extension Phase the assessments in the End-of-Trial visit should take place and EOT form must be filled in. If a patient is withdrawn prior to completion of the trial* ~~If a patient is withdrawn during the Extension Phase~~, all attempts must be made to schedule an EOT visit for the patient. The EOT form should be signed at the EOT visit. If a patient continues in FU the EOT form will be signed at the FU Visit.

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8.1.2 Visit Schedule for Patients on Prophylaxis not Undergoing PK Evaluation and for Patients on On-Demand treatment

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The samples taken post-dose must not be taken from the same vein as previously used for administration of N8-GP.

~~Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic including doses administered at all visits after visit 2b.~~

At Visit 2a the following assessments will be performed and/or recorded in the eCRF

- Confirmation of inclusion and exclusion criteria, see section 6.2 and 6.3
- Withdrawal criteria, see section 6.5
- Concomitant medication, see section 11
- Check date and time of last coagulation factor administration
- AEs: before and after dosing, see section 12.1
- Body measurements (weight only), see section 8.4.2
- Physical examination, see section 8.3.3
- Vital signs (before dosing and 30 min (\pm 10 min) after dosing), see section 8.3.4
- ~~eDiary training, see section 5.3 and 8.4.3~~
- ~~eDiary dispensing~~
- Dispensing of N8-GP in IV/WRS, see section 10

....

Blood sampling for central laboratory assessments

- Biochemistry, see section 8.3.7.1
- Coagulation related parameters, aPTT and INR before dosing and 30 min (± 10 min) after dosing, see section 8.3.7.2
- FVIII activity, trough and recovery, i.e. before dosing and 30 min (± 5 min) after dosing, see section 8.3.7.3
- FVIII inhibitors, see section 8.3.2.2
- N8-GP binding antibodies, see section 8.3.2.1

Visit 2b: Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic treatment including doses administered at all visits after Visit 2b.

At Visit 2b (4 days after first dose) the following assessments will be performed and/or recorded in the eCRF

- Withdrawal criteria, see section 6.5
- Concomitant medication, see section 11
- AEs: before and after dosing, see section 12.1
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section 10.
- Dispensing of N8-GP in IV/WRS, see section 10
- *e-Diary training, see section 5.3 and 8.4.3*
- *e-Diary dispensing*
- ~~Home treatment /eDiary training, see section 5.3 and 8.4.3~~
- Administration of second dose of N8-GP (patients to be observed for at least 1 hr after administration for adverse reactions)
- ~~eDiary data review and rating severity of bleeding episodes, see section 8.2.1~~

Reminders:

- An appointment for Visit 3 (4 weeks \pm 1 week after Visit 2a) should be made.
- Withhold N8-GP minimum 96 hours prior to next visit

8.1.2.1 Visit 3-13 for Patients on Prophylaxis not Undergoing PK Evaluation and Patients on On-Demand Treatment

The home treatment period for patients on prophylaxis and on-demand is approximately 4 weeks \pm 1 week between Visit 3, 4 and 5 and approximately 8 weeks \pm 1 weeks between Visit 6, 7, 8, 9, 10, 11, 12 and 13, see Table 2-1. At ~~the EOT visit~~ *Visit 13 EOM Phase* the patients will not be dosed at the site *as part of the visit*.

Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment during the home treatment period since last visit

The samples taken post dose, must not be taken from the same vein as previously used for administration of N8-GP.

The following will be performed and/or recorded in the eCRF:

- Withdrawal criteria, see section 6.5
- PRO questionnaires, ~~EOT~~ Visit 13 (EOM) only, see section 8.4.5
- Concomitant medication, see section 11
- Check date and time of last coagulation factor administration, see section 8.4.3
- AEs: Since previous visit, see section 12.1
- Body measurements (weight only), see section 8.4.2
- Physical examination (only at Visit 5, 9 and ~~EOT visit~~ Visit 13 (EOM)), see section 8.3.3
- Vital signs, (before dosing), see section 8.3.4
- ECG (only at ~~EOT visit~~ Visit 13 (EOM)), see section 8.3.5
- e-Diary data review and rate severity of bleeding episodes, see section 8.2.1
- Home treatment/e-Diary training (not at Visit 13 EOM~~†~~)
- N8-GP administration, not at ~~EOT visit~~ Visit 13 (EOM) and not for on-demand patients (Stop time of injection must be recorded in the eCRF, this corresponds to time “0”)
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section 10
- Dispensing of N8-GP for clinic dosing/home treatment must be performed via IV/WRS (except at ~~EOT visit~~ Visit 13 (EOM)), see section 10
- EOT form (at last visit, *only if not continuing into Extension Phase*)
- Affirmation statement (at EO only, *only if not continuing into Extension Phase*)
- Completion of *Main Phase* session in IV/WRS (at EOM~~†~~ only)
- Return eDiary (at EOT only, *only if not continuing into Extension Phase*)
- *Informed Consent for addendum on data comparison (at EOM only)*

Blood sampling for local laboratory assessments:

- Haematology (to be taken within 1 hour prior to dosing), see section 8.3.6.1

Blood sampling for central laboratory assessments:

- Biochemistry, see section 8.3.7.1
- FVIII activity (trough level and recovery), i.e. before dosing and 30 min (± 5 min) after dosing ~~8.3.7.3~~. Recovery not to be done in the on-demand arm and not at ~~EOT visit~~ Visit 13 (EOM), see section 8.3.7.3

- FVIII inhibitors, see section 8.3.2.2
- N8-GP binding antibodies, see section 8.3.2.1
- FVIII genotype (only Visit 3). If documentation is not available in the patient chart and as allowed per local law. In addition, the Investigator, patient or LAR has the right to refuse, see section 8.3.7.5

Reminders for each visit:

- An appointment for the next visit should be made.
- Withhold N8-GP minimum 96 hours prior to next visit
- For patients continuing in the *Extension Phase of the trial pathfinder™ 4*, the ~~EOT~~ EOM Visit (Visit 13) will take place at the same day as the first visit in the *Extension Phase of the trial (Visit 14)*, therefore informed consent must be obtained prior to ~~EOT~~ EOM Visit.

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8.1.3.1 Visit 2a for Patients on Prophylaxis Undergoing PK Evaluation

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The samples taken 30 min post dose must not be taken from the same vein as previously used for administration of N8-GP. The lines/tubes must be flushed immediately after administration of the trial product.

~~Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic including doses administered at all visits after visit 2b.~~

The following will be performed and/or recorded in the eCRF:

Assessments to be made before the PK session at the day of dosing

- Confirmation of inclusion and exclusion criteria, see section 6.2 and 6.3
- Withdrawal criteria, see section 6.5
- Concomitant medication at all time points during PK, see section 11
- Check date and time of last coagulation factor administration (see section 8.4.3)
- AEs, see section 12.1
- Body measurements (weight only), see section 8.4.2
- Physical examination, see section 8.3.3
- Vital signs, see section 8.3.4
- ~~eDiary dispensing~~

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Laboratory assessments are to be analysed at central Laboratory

~~Training~~

- ~~• eDiary training, see 5.3 and 8.4.3~~

8.1.3.2 Visit 2b for Patients on Prophylaxis Undergoing PK Evaluation

The second dose of N8-GP will be administered at the site after the last PK sample is taken.

Patients will be provided with an eDiary and will be carefully trained in the use of this eDiary including instruction in reporting details of bleeding episodes and prophylactic treatment including doses administered at all visits after Visit 2b.

Four days after first dose the following assessments will be performed and/or recorded in the eCRF

- Withdrawal criteria, see section 6.5
- AEs: before and after dosing, see section 12.1
- *e-Diary training, see section 5.3 and 8.4.3*
- *e-Diary dispensing*
- ~~• eDiary data review and rate severity of bleeding episodes 8.2.1~~
- Home treatment/e-Diary training, see section 5.3 and 8.4.3
- Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS, see section 10.

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8.1.4 Visit 14-n and EOT Visit- visit in the Extension Phase of the trial

Before any trial related procedures/activities related to the Extension Phase of the trial, the patient and/or the LAR must have signed the informed consent form after having received written and verbal information about the Extension Phase part of the trial.

It should be decided if the patient is eligible to be part of the randomised group in part 1 of the Extension Phase before the patient comes for Visit 13 (EOM) and 14. If the patient for the last 6 months (180 days) prior to Visit 13/14 only has had 0 - 2 bleeding episode the patient is eligible for randomisation. If the patient is eligible to be in the randomised part of the Extension Phase part 1 and the patient has agreed to be part of the randomisation group, the patient should give written consent through the informed consent addendum so agreement to randomisation is documented. Recruitment into the sub-group of the Extension Phase part 1 will stop approximately at mid-May

2014, hereafter also patients with a low bleeding rate will continue the same treatment as in the Main Phase.

When patients randomised in part 1 have completed the part 1, all patients can start part 2 at their next visit beginning at visit 17. Skipping visit 15 and/or 16 should be entered with a comment in EDC.

While performing the EOM visit, IV/WRS will collect the response whether or not the subject will be randomised. For the subjects who are willing to be randomised, IV/WRS will then randomise the subject to either once weekly prophylaxis or every 4 day prophylaxis arm. For subjects who are not eligible or unwilling to be randomised, IV/WRS will dispense the trial product according to their chosen treatment regimen. The patient should be instructed to follow the treatment regimen in the assigned treatment arm. The numbers of bleeding episodes should be counted before all visits from visit 13 in preparation for a potential change in dosing regimen.

The home treatment period for patients on prophylaxis and on-demand is approximately 8 weeks (\pm 2 week) between visits during the first 4 visits in the Extension phase part 1 (Visit 14-17) and 12 weeks apart in part 2 (from the Visit 17), see Table 2-3.

Visit 14 will take place at the same day as Visit 13 in the Main Phase of the trial.

Antibody samples will only be drawn from patients in the on-demand arm at visits if they have received treatment during the home treatment period since last visit.

The samples taken post dose must not be taken from the same vein as previously used for administration of N8-GP.

The following will be performed and/or recorded in the eCRF at all visits during the Extension Phase:

- *Withdrawal criteria, see section 6.5 (not at Visit 14)*
- *PRO questionnaires, Visit 17, and every 4th visit approximately every year (Visit 21, 25...) and EOT, see section 8.4.5*
- *Concomitant medication, see section 11 (not at Visit 14)*
- *Check date and time of last coagulation factor administration, see section 8.4.3 (not at Visit 14)*
- *AEs: Since previous visit, see section 12.1 (not at Visit 14)*
- *Body measurements, see section 8.4.2 (not at Visit 14)*
- *Physical examination at Visit 17 and every 2nd visit (Visit 19, 21...) and at EOT, see section 8.3.3*
- *Vital signs, (before dosing if dosing take place at visit, not at Visit 14), see section 8.3.4*
- *ECG at Visit 17 and every 4th visit (Visit 21, 25...) and at EOT, see section 8.3.5*
- *e-Diary data review and rate severity of bleeding episodes, see section 8.2.1 (not at Visit 14)*

- *Home treatment/e-Diary training (not at EOT) if applicable*
- *N8-GP administration, not for on-demand patients (stop time of injection must be recorded in the eCRF, this corresponds to time “0”) (not at EOT)*
- *Dosing regimen choice or change and reason if change (not at visit EOT)*
- *Affirmation statement (at EOT Visit)*
- *End-of-trial form (at EOT Visit)*

On EOT form the first date on trial product refers to trial drug in this trial, and not trial drug taken as part of pathfinder™ 1, if the patient has participated in pathfinder™ 1.

Blood sampling for local laboratory assessments:

- *Haematology (to be taken within 1 hour prior to dosing), see section 8.3.6.1 (not at Visit 14)*

Blood sampling for central laboratory assessments:

- *Biochemistry, see section 8.3.7.1 (not at Visit 14)*
- *FVIII activity (trough level and recovery), i.e. before dosing (not at Visit 14) and 30 min (± 5 min) after dosing. Recovery not to be done in the on-demand arm and at EOT Visit, see section 8.3.7.3*
- *FVIII inhibitors, see section 8.3.2.2 (not at Visit 14)*
- *N8-GP binding antibodies, see section 8.3.2.1 (not at Visit 14)*

IV/WRS:

- *Drug accountability for the trial medication dispensed or returned from the previous visits must be recorded in IV/WRS (not at Visit 14), see section 10*
- *Dispensing of N8-GP for clinic dosing/home treatment must be performed via IV/WRS (for Visit 14 done together with Visit 13 (EOM) call, not at EOT) , see section 10*
- *Completion session in IV/WRS (at EOT Visit)*

Reminders for each visit:

- *An appointment for the next visit should be made (not at EOT Visit).*
- *Withhold N8-GP minimum 96 hours prior to next visit (not at EOT Visit)*
-

Telephone Contact:

It is recommended that a phone call is made to patients who have changed prophylaxis treatment regimen approximately 4 weeks or at time which seem appropriate after the change.

No same assessments should be done both at Visit 13 (EOM) and Visit 14. Data may be transferred from Visit 13 and to Visit 14 and vice versa.

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8.1.7 Transfer of Patients to pathfinder™ 3 due to Major Surgeries

In case major surgery is needed the patients should be transferred to the pathfinder™ 3 trial. To enable patients to be transferred the following assessments have to be performed:

- To ensure that N8-GP is available for the surgery, notify the IV/WRS system at least 14 days prior to a planned surgery by using the IVRS "Dispensing session". This ~~can~~ *should* be done ~~both at a planned and unscheduled~~ visits.
- At the day of transferring to the pathfinder™ 3 trial the IV/WRS "Major surgery transfer" session should be used in order to transfer the patient into pathfinder™ 3
- Drug accountability – the patient must return and account for all drug dispensed in the current trial before entering pathfinder™ 3
- After completion of pathfinder™ 3 trial an IV/WRS "surgery transfer session" should be performed in order to transfer the patient into pathfinder™ 2
- ~~Fill in the Surgery transfer form in the eCRF~~

Upon completion of pathfinder™ 3, patients may return to pathfinder™ 2, re-entering the prophylactic or on-demand treatment arm as per their prior participation in the trial. The patient will return to the next visit in line in pathfinder™ 2 and the visit assessments performed at the EOT visit in pathfinder™ 3, will be used. The patient enrolled in pathfinder™ 2 with the intention of entering the pathfinder™ 3 for major surgery at the end of normal recruitment period in pathfinder™ 2 will not have to complete Visit 7 and reach 50 EDs before continuing into the Extension ~~trial~~ Phase of the trial if the Extension ~~trial~~ Phase is open. Though, a Visit 13 (EOM) must take place before continuing into the Extension ~~trial~~ Phase. Furthermore, the opening of the Extension ~~trial~~ Phase will not await these patients to complete 50 EDs in the Main Phase of the trial.

In case patients who had surgery in pathfinder™ 3 cannot follow the normal visits in the flowcharts (see figure 8-1 and 8-2) the patient can start at Visit 3, if the trial is in the period of the Main Phase, or Visit 14 if the trial is in the Extension Phase. The surgery patients do not have to complete all visits in the Main Phase before continuing into the Extension Phase, but need to follow the visit frequencies and need to have the Visit 13 (EOM) before continuing into the Extension Phase. If patients cannot return to the treatment regimen as before surgery, the investigator must choose the most appropriate regimen within the possibilities of the current phase of the trial.

8.2 Efficacy Assessments

8.2.1 Bleeding Episodes

During the entire trial period all treatment requiring bleeding episodes (*after Visit 2b*) will be entered by the patient or caregiver in the patient's eDiary. In case a patient is unable to enter a bleeding episode in the eDiary or hospitalised the Investigator will have to report it in the eCRF as an unscheduled visit, please refer to section 8.1.6.

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8.3.2 Antibody Assessments

Blood samples for assessment of antibody formation against N8-GP will be drawn at the screening visit, pre-dose of N8-GP administration at all visits (except Visit 2b, *Visit 14*). *Antibody formation is also assessed in case of* at the follow-up visit approximately one month after the End of Trial visit. Antibody samples will only be drawn from patients in the on-demand arm at Visit 3-13 if they have received treatment during the home treatment period since last visit. The samples will be analysed both using the Bethesda assay identifying inhibitory antibodies towards FVIII and using an assay capable of identifying the occurrence of any antibodies towards ~~both FVIII and~~ N8-GP.

8.3.2.1 N8-GP antibody assay

...

Levels of N8-GP binding antibodies will be compared by *Novo Nordisk* to pre-dose samples throughout the trial. If a patient develops N8-GP binding antibodies and the incremental recovery value at that visit is less than 60% of screening value *and FVIII level at time of inhibitor sampling (pre-dose) is more than 0.015U/mL*, *Novo Nordisk will ask the Investigator to call the patient for an unscheduled visit for collection of a new inhibitor sample which should* will be taken after a 7 days wash out period.

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

This algorithm will not apply for those who enter the trial with positive *test for* N8-GP binding antibodies and will not be triggered more than twice for an individual patient, *unless increases in antibody levels are observed*. Furthermore, a 7 days wash out period will only be applied if the 96 hours wash out is not sufficient to avoid drug interference in the inhibitor assay.

N8-GP antibodies results will be reported to site at EOM and EOT.

....

8.3.2.3 Antibody Assessments in case of Allergic/Anaphylactic Reaction

Any patient who experiences an ~~unexpected~~ *acute severe* allergic/anaphylactic reaction will be assessed for inhibitors and antibodies against drug product content, such as IgG/IgE against N8-GP and Host Cell Proteins (HCP). Additional blood samples may be requested for this purpose. If it is deemed necessary, the same analyses will be performed for all patients enrolled in the trial using available blood samples.

....

8.3.5 ECG

ECG must be performed at Screening (Visit 1), *End of Main Phase, at Visit 17(end of part 1), every year during Extension Phase part 2 (Visit 21, 25...)* and EOT visit. ECGs will be performed using a 12-lead Electro Cardiogram. For the ECG recording the patients must be resting and in a horizontal position. Any irregularities observed during the ECG e.g. cough, should either induce a re-run of the ECG and/or be annotated in the eCRF page with description of the occurrence. Print-outs must include date, time, patient's identification, and initials of the Investigator, and at least 2 complexes for each lead and a single rhythm strip of 6 beats. Electronic capture of these measurements may also be performed.

....

8.3.7.3 FVIII Activity (central laboratory)

...

Exploratory assays for measuring N8-GP activity

A non validated exploratory Thrombin generation assay (TGA) and/or other assays can be applied for measuring activity of N8-GP and analysed by the end of *main phase and by end of* the trial. The results from these assays will be reported separately.

...

8.4.2 Body Measurements

All body measurements (weight, height and BMI) will be performed at Visit 1. *During the Extension Phase patients under 18 years will have their height measured yearly.* On all other visits only weight will be measured. The weight measured at the respective visits should be used for calculating the amount of N8-GP to be dispensed and the dose of N8-GP to be administered.

- Weight (registered with one decimal), wearing light clothing only (kg/pounds) and without shoes
- Height, without shoes (cm/inches), Visit 1 only
- BMI calculation (kg/m^2), Visit 1 only

...

8.4.4 Medical History/Concomitant Illness

....

Haemophilia Details (including history)

- Diagnosis of haemophilia A (date)
- Other coagulation related diseases
- Classification of haemophilia A (severe form requested in this trial – *only collected as confirmation of inclusion criterion 2*) and FVIII:C activity level (%) from medical history
- Underlying gene defect (if known)
- Clinical suspicion of inhibitors data from medical history
- Number of inhibitor tests and/or FVIII:C recovery tests within the last 8 years
- History of switching FVIII products (type of products (from/ to) and age at switching) if available
- Relatives with haemophilia A (yes/no)
If yes – specify any relatives with haemophilia A and inhibitors (as recalled by patient)

...

8.4.5 PRO Questionnaires and Health Economics

PROs will be collected at screening visit (Visit 1), *at Visit 17 (end of part 1) and every year during Extension Phase part 2 (Visit 21, 25...)* ~~and at EOT~~ *End of Trial* visit for all patients. The questionnaires should preferably be completed prior to any other trial related activities during the two visits. Health economic data will be collected after treatment starts in connection with bleeding episodes.

Several questionnaires will be used to assess disease and age-group specific quality of life and treatment satisfaction from the screening and *until* EOT Visits.

The following questionnaires should be completed by the patients and, where relevant, also by the parent/LAR:

For trial patients aged 12-16:

HAEMO-QOL: Questionnaire for children/adolescents (8-12 years, 13-16 years)

EQ-5D: Questionnaire (13 years and above)

HAEMO-QOL: Parents proxy; Questionnaire for parents/LARs of Children/adolescents (8-12 years, 13-16 years)

HEMO-SAT(P): Parents proxy; Questionnaire for parents/LARs of adolescents (13-16 years)

For trial patients aged 17 and above:

HAEM-A-QOL: Questionnaire for adults aged 17 and above

HEMO-SAT(A): Questionnaire for adults aged 17 and above

EQ-5D: Questionnaire (13 years and above)

The patient (and parents or LAR(s) if applicable) should throughout the trial complete the questionnaires corresponding to his age group at screening visit despite the patient changes age group during the trial.

....

8.5.1 Definition of Treatment Compliance

Good compliance: If the prophylaxis infusions of N8-GP is 50 U/kg BW \pm 5 U/kg BW for at least 80% of the prophylaxis infusions and the time interval between two prophylaxis infusions is *as prescribed* ~~4 days~~ for at least 80% of the time.

Less compliance: If the prophylaxis infusions of N8-GP is outside 50 U/kg BW \pm 5 U/kg BW for more than 20% of the prophylaxis infusions or the time interval ~~if there is more or less than 4 days~~ between two ~~dosis~~ *prophylaxis infusions is not as prescribed* for more than 20% of the time.

2.10 Section 9 Trial Supply

....

9.3 Packaging and Labelling of Trial Product(s)

Novo Nordisk A/S will label and pack the trial product.

N8-GP drug product and sodium chloride will be provided in separate boxes. All trial products will be packed open labelled.

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

Labelling will be in accordance with ~~GCP~~ Annex 13¹⁶, local law and trial requirements.

The details of the packaging and labelling of N8-GP drug product will be provided in the TMM supplied by Clinical Supplies Coordination, Novo Nordisk A/S.

....

9.4 Storage, Handling, Accountability and Destruction of Trial Product(s)

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Dispensing and Drug Accountability

The IV/WRS will allocate the 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.

- No trial product should be dispensed to any person not enrolled in the trial
- Unused trial product must be stored separately from used trial product
- All vials (used, partially used, unused, returned, and lost/damaged)(except NaCl *containers vials*) must be recorded in the IV/WRS drug accountability module

....

The TMM detailing the handling of the trial materials will be provided by Novo Nordisk.

Dispensing in Extension Phase

For patients entering the randomisation of the Extension Phase part 1 the IV/WRS system will randomise the patient to either treatment every 4 day or every 7 day. Hereafter the IV/WRS system will dispense the needed number of DUNs for the patient. For non-randomised patients IV/WRS will dispense needed number of DUNs according to treatment regimen.

In the Extension Phase part 2 the investigator will be able to change the treatment regimen for the patient in the IV/WRS system and dispense DUNs accordingly.

2.11 Section 10 Interactive Voice/Web Response System (IV/WRS)

A trial specific IV/WRS will be set-up, and can be accessed at any time via the internet. Some sessions may be available through a toll-free telephone number. Accessibility 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,
- *randomising of patients*
- dispensing of trial product,
- controlling of expiry date of trial product,
- ordering of trial product,
- drug accountability
- screening failure data
- Completion of the trial and
- withdrawal information
- surgery transfer session

....

2.12 Section 12 Adverse Events, Technical Complaints and Pregnancies

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12.2 Collection, Recording and Reporting of Adverse Events

...

The Investigator should record the diagnosis, if available. If no diagnosis is available then the Investigator should record each sign and symptom as individual AEs.

All AEs must be recorded by the Investigator on the ~~standard~~ AE form. If more than one sign or symptom is to be reported, use a separate AE form for each sign and symptom. For serious AEs, the safety information form must also be completed. If several signs or symptoms occur as part of the same clinical picture only one set of safety information pages need be used to describe these SAEs.

.....

2.13 Section 13 Case Report Forms

....

13.3 eCRF Flow

The Investigator must ensure that data is recorded in the CRFs as soon as possible after the visit (preferably within 3 days). When data is entered it will be available to Novo Nordisk for data verification activities. *Queries to data in the eCRF must be answered in the system preferably within 3 days and during interim or DBL preferably daily.*

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 EDC has been removed. This data will be retained by the site.

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

13.4 eDiary

Novo Nordisk will provide patients with an eDiary for electronic recording of details of their bleeding episodes *and treatment*, see section 8.4.3. The eDiary and related support services will be supplied by a vendor that will be working under the direction and supervision of Novo Nordisk.

At Visit *2ba*, the patients will be provided with the eDiary and trained in the use hereof. The eDiary will be returned by the patient at the ~~EOT Visit~~ *end of the trial*.

Data will be entered by the patient or caregiver in the eDiary device. All data entered will be automatically transferred from the device to the 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.

....

2.14 Section 14 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. The intervals between visits must not exceed 12 weeks *during the Main Phase and the Extension Phase part 1. During the*

Extension Phase part 2 the interval must not exceed 16 weeks, as long as the site has active patients.

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. In addition the Monitor should be available for discussions e.g. by telephone.

...

2.15 Section 16 Computerised Systems

...

The eDiary software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection). 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~~ 50 years or as required by local data retention laws for trial data.

...

2.16 Section 17 Evaluability of Patients for Analysis

17.1 Safety Analysis Set

The Safety Analysis Set consists of all patients exposed to N8-GP *in this trial*. The analyses of the safety endpoints will be based on the Safety Analysis Set and all available information until the last visit.

17.2 Full Analysis Set

The Full Analysis Set (FAS) consists of all patients exposed to N8-GP in this trial. The efficacy analysis and the PK analysis will be based on the FAS and all available information until EOT visit.

.....

2.17 Section 18 Statistical Considerations

All efficacy endpoints will be analysed and reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase part 2 of the trial. All safety endpoints will be reported separately for the Main Phase, for the Extension Phase part 1 and for the Extension Phase

part 2 as well as based on accumulated data (Main Phase + Extension Phase part 1 and Main Phase + both Extension Phases).

Section 18.1 to 18.9 describes the statistical methods relating to the Main Phase of the trial while the statistical methods relating to part 1 and part 2 of the Extension Phase are described in section 18.10.

18.1 Sample Size Calculation

The study has two co-primary endpoints *for the Main Phase* that both need to succeed for the study to succeed. The two endpoints can reasonably be considered approximately independent and combined power then becomes the product of the individual power for each co-primary endpoint.

.....

Co-Primary Endpoint: Annualised bleeding rate in the prophylaxis arm

The clinical efficacy of N8-GP in long term bleeding prophylaxis will be evaluated based on all the prophylaxis period data. This will give different period lengths for the different patients but on average it is expected to give about 12 month prophylaxis treatment per patient (~7 months for the last recruited patients and *approximately 17–19 months* for the first recruited patients).

Prophylactic effect will be concluded if the upper 97.5% confidence limit for the annualised bleeding frequency is < 8.5. Annualised bleeding rate for withdrawals will be imputed for the missing period based on their observed bleeding rate except for patients withdrawn within one month where imputation will be performed based on an annualised bleeding rate of 24. The true bleeding rate will be assumed to be 6.8 as for historical prophylaxis data but for the sample size calculation it will further be assumed that 1 patient will withdraw within 1 month and that will lift the effective annualised bleeding rate for the power calculation by $24/120 = 0.2$, i.e. from 6.8 to 7.0.

.....

Operationally the null-hypothesis will be rejected and a success rate acceptably close to 80% is considered confirmed if the lower bound of the 1-sided 97.5% confidence interval for the rate is above 65%. By assuming that the observations are independent, the power may be calculated exact using the binomial distribution. The power will depend on the number of bleeding episodes actually observed. It is expected that more than 200 bleeding episodes will occur in the *Main Phase of the trial* in the on-demand arm and the prophylaxis arms combined. Assuming a true response rate of 80% the power for this endpoint is greater than 95%. Correlation between observations corresponding to the same patient may reduce this power but is not expected to affect it too much.

18.2 Statistical Methods

18.2.1 General Considerations

Novo Nordisk A/S will be responsible for the statistical analysis. All tests will be performed as 1-sided tests on 2.5% significance level.

All bleeding endpoints will be evaluated based on bleeding episodes requiring treatment with N8-GP. Non-treatment requiring bleeding episodes that coincide with regular prophylaxis doses are not included.

18.2.2 Primary Endpoint(s)

.....

Let AR be the ~~observed~~-true yearly bleeding rate. The null-hypothesis will be tested against the alternative hypothesis as given by:

....

Analysis of 12 months data from patients that could have had 12 months prophylaxis

Since patients will stay in the *Main Phase of the* trial until the same end of *Main Phase* date some patients will get only about 7 months prophylactic treatment while others may get more than 19 months (except for patients entering the trial with the intention of major surgery after the end of normal recruitment period). To investigate if the varying durations have any impact on the results a sensitivity analysis will be performed looking only at 12 months data from patients with planned trial duration of 12 or more months. Otherwise this analysis will be performed similarly to the primary analysis.

.....

18.2.3 Confirmatory Secondary Endpoints

....

Let R be the ~~observed~~ true success rate. The null-hypothesis will be tested against the alternative hypothesis as given by:

.....

18.2.4.1 PK Endpoints

.....

Table 18-2 Definition and Calculation of PK Parameters

Parameter	Description	Calculation
Incremental Recovery	Dose-normalised activity recorded 30 min after end of infusion and reported as [U/mL]/[U/kg]. Expected to be the highest dose-normalised activity observed.	The incremental recovery is calculated by subtracting dividing the FVIII activity (U/mL) measured in plasma <i>at time 0 from that measured at time 30 min after dosing and dividing this difference</i> by the dose injected at time 0 expressed as U/kg BW

.....

18.4 Exploratory endpoints

Incidence of binding, non-inhibitory antibodies to N8-GP/~~uroctocog alfa~~

Binding non-inhibitory antibodies will be listed.

18.5 Interim Analysis

In order to obtain regulatory permission to start the surgery treatment prophylaxis treatment in the US and paediatric trial in the EU lists of acute treatment responses will be prepared at certain time-points. They will include patient details as well as dose given and response to treatment.

All data from the Main Phase of the trial will be analysed and reported when all patients have reached 50 EDs (except for patients having had surgery as part of pathfinder™ 3). All main conclusions from the trial will be based on this reporting. Furthermore, an interim analysis will be performed when the patients enrolled in the randomised part of the Extension have completed part 1.

.....

18.9 Health Economics and/or Patient Reported Outcome

PROs will *in the Main Phase* be assessed through PRO questionnaires at screening visit (Visit 1) and EOT visit for patients in the on-demand arm for patients in the prophylaxis arm.

The main PRO endpoint will be subgroup total scores. Changes in scores over time of the main PRO endpoints at Visit 1 to ~~EOT~~ EOM visit will be explored and presented graphically. Evaluations of PRO data will alone be based on descriptive statistics, i.e. summary tables, listings and figures.

HE calculations will be performed separately by the Novo Nordisk HE department. Novo Nordisk A/S will be responsible for the statistical analysis.

18.10 Analyses of Extension Phase Data

Data from part 1 of the Extension Phase

*The main objective of part 1 of the Extension Phase is to investigate the safety and efficacy of every 7 day dosing by evaluating ABR for this dosing regimen and comparing it to the same historical bleeding episode rates as used in the primary analysis for the co-primary efficacy endpoint in the Main Phase. Prophylactic effect of every 7 day dosing will be concluded if the bleeding rate is significantly below 50% of the historical on-demand bleeding rate (i.e. significantly lower than 12) as well as within 25% of the historical prophylaxis bleeding rates (i.e. significantly lower than $6.8 * 1.25 = 8.5$). Since both must be met in practice it must be shown that the bleeding rate is significantly lower than 8.5.*

An analysis similar to that for the co-primary endpoint in the Main Phase will be carried out for the bleeding episodes in the two randomised treatment regimens during the Extension Phase part 1, adding treatment regimen as a factor to the model. Subjects switching from the every 7 day dosing arm to the non-randomised every 4 day dosing arm will be handled as withdrawals in this analysis. The imputation for withdrawals will be similar to that for the Main Phase, except that planned maximum duration is now 6 months.

Estimates of the annualised bleeding rates for each randomised regimen will be provided with 95% confidence intervals. Prophylactic effect of every 7 day dosing will be concluded if the upper limit of the 95% CI is below 8.5. In addition, the two randomised treatment regimens will be compared by reporting the estimated ratio between the two randomised treatment regimens with corresponding 95% confidence interval.

As for the co-primary endpoint in the Main Phase, a sensitivity analysis will be carried out where bleeding episodes for withdrawals are not imputed.

ABR based on accumulated number of bleeding episodes (Main Phase + Extension Phase part 1) will be evaluated for the every 4 day dosing regimens combined, i.e., combining the randomised and non-randomised arm. The model used will be the same as for the primary analysis of the Main Phase data.

Only treatment requiring bleeding episodes will be considered in the above evaluations of ABR

Incidence rate of FVIII-inhibitor and haemostatic effect of N8-GP when used for treatment of bleeding episodes will be evaluated based on accumulated data (Main Phase + Extension Phase part 1).

Adverse events, consumption of N8-GP, recovery and trough levels will be summarised based on accumulated data (Main + Extension Phase part 1) by treatment regimen combining the every 4 day dosing regimens. In addition, separate summaries including data from part 1 only will be presented by treatment regimen for the randomised subset of patients to support the main objective of part 1 of the Extension Phase.

Other safety endpoints will be summarised based on accumulated data (Main Phase + Extension Phase part 1). Binding non-inhibitory antibodies will be listed.

PRO endpoints at end the Extension Phase part 1 will be evaluated and presented as described in section 18.9.

Data from part 2 of the Extension Phase

All evaluations/summaries based on accumulated data in part 1 will be repeated in part 2, accumulating data from the entire trial (Main Phase + Extension Phase part 1 + part 2).

In addition, ABR during part 2 will be summarised for the prophylaxis regimens combined. Furthermore, ABR during each 6 month interval in this period will be summarised by prophylaxis regimen used during that period.

Frequency and time used of treatment regimens will be summarised for the different treatment prophylaxis regimens used during the Extension Phase part 2.

PRO endpoints at end of each year in Extension Phase part 2 and at end of Extension Phase will be evaluated and presented as described in section 18.9.

18.11 Additional Evaluations

Exploratory analysis comparing results from study NN7008-3543, NN7008-3545, NN7008-3568 and NN7088-3776 with results from this study will be performed and reported separately. This analysis will include overall comparisons as well as individual comparisons for patients participating in one of the above listed trials and this NN7088-3859 trial, if the patient through the informed consent has given approval of such comparison of data.

2.18 Section 19 Ethics

...

When a patient's participation in the *Main Phase of the trial* ends due to completion of the trial, the patient will be offered to continue in the *Extension Phase of the trial* (~~NN7088-3861~~) upon consent. No patient will consent to a trial in the N8-GP clinical programme before all required IRB/IEC and regulatory approvals have been obtained for the trial. If the patient does not wish to continue in the *Extension Phase of the trial* (~~NN7088-3861~~), the patient will consult with the Investigator to decide on the best available treatment.

...

19.1 Informed Consent Form for Trial Patients

....

FVIII Genotype Testing / Collection of Previous Genotype Documentation (Not applicable to Brazil and Israel)

Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient should give their consent before the data is collected for trial purpose. Prior to any trial-related activity, the Investigator must provide the patient the possibility to abstain from the genetic testing/collection of previous documentation but still be able to participate in the trial.

Comparison of data in this trial to data in guardian™ trials and/or pathfinder™ 1 (only relevant for countries having participated in guardian™ trials and/or the pathfinder™ 1 trial)

Patients having previously participated in Novo Nordisk trials; in the guardian™ programme (Trial NN7008-3543 + 3545 + 3568) with FVIII turoctocog alfa and/or in pathfinder™ 1 (NN7088-3776), will be asked in the informed consent for the Extension Phase of the trial if data from their participation in a guardian™/pathfinder trial(s) can be compared to the data in this trial. Patients will be asked to sign an addendum to the informed consent specifically addressing this matter. It is not a requirement for these patients to give consent to the comparison of data to participate in the Extension Phase of the trial.

Protocol Amendment no 14
to Protocol, final version 7.0
dated 03 May 2013

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the protocol amendment

This global substantial amendment no 14 is being issued primarily as a response to a Voluntary Harmonised Procedure (VHP) assessment, which involve a central EU CTA submission of the NN7088-3859 (pathfinder™ 2) protocol version 7.0 in 8 European countries.

The following changes have been made to the protocol version 7.0:

- VHP raised concerns of the risk of break-through bleeding on every 7 day treatment regimen in the extension phase. Therefore section 5.3.1 has been updated to describe rules for when a patient should be switched from every 7 day to every 4 day treatment regimen. This will be monitored by the Investigator and Novo Nordisk. Furthermore section 5.3.1 has been updated with a rule to define when the every 7 day treatment arm should be closed. The text regarding telephone contacts has been updated in section 2 Table 2-3 and section 8.1.4 and the risk/benefit section 3.1.4 has been updated to describe the risk of break-through bleeding in the once weekly treatment arm.
- The VHP recommended to follow the dosing regimen of the main part in the extension phase. In addition, the VHP raised concerns regarding the efficacy of every 5 and 6 day dosing regimen of 60 U/kg, since this dose regimen has not been tested in clinical trial setting. These dosing regimens have therefore been deleted from the protocol. Patients will continue on every 4 day or every 7 day dosing throughout the extension. Section 5.3.1 has been updated to reflect this.
- A few updates have been made in section 5.1 and 18.5, to clarify when data will be reported for end of main phase.
- Section 12.1.3 has been updated to ensure alignment across Novo Nordisk haemophilia trials
- Some inconsistencies and minor corrections have been updated in the protocol

In this protocol amendment:

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

2 Changes

1 Summary

Trial design:

...

Extension Phase: The Extension Phase will investigate the long-term safety and efficacy of N8-GP for prophylaxis patients on a 4 *or*- 7 day dosing regimen and on-demand treatment.

Trial Product(s):

...

In the prophylaxis arm(s), each patient will receive prophylaxis treatment with a N8-GP dose of 50 U/kg body weight (BW) every 4 days in the Main Phase. During part 1 of the Extension Phase a sub-group of patients will receive prophylaxis treatment every 4 day or every 7 day. In part 2 of the Extension Phase patients can be treated on every 4 day ~~to~~ or once weekly (every 7 day).

2 Flow Chart

Table 2-3 Flow Chart for Patients on Prophylaxis and On-Demand Treatment in Extension Phase

Footer	Description
15	It is recommended to contact patients <i>by phone at the 4 and 6-week interval between the site visits</i> approximately 4 weeks after change of regimen (see section 8.1.4)

3 Introduction

3.1.4 Risk and Benefits

...

The burden of disease with current FVIII prophylaxis treatment is high – long-term, intra-venous injections, several times a week. Identifying patients that could have adequate bleeding protection with a once weekly injection would be an important break-through for FVIII treatment and could potentially improve the uptake of prophylaxis.

In the extension part 1, patients with a low bleeding rate on every 4 day prophylaxis in the main phase have the possibility of being randomised to once weekly dosing. It cannot be excluded that patients changing from every 4 day prophylaxis to every 7 day will have a risk of more frequent break-through bleeding episodes. Therefore specific rules for switching patients back to every 4 day dosing and for closing the every 7 day treatment arm are included (see section 5.3.1).

5 Trial Design

5.1 Type of Trial

...

Treatment duration is approximately 6 months in the on-demand arm and from approximately 7 (200 days plus screening period of 2-3 weeks) to approximately 19 months in the prophylaxis arm. The maximum treatment period in the Main Phase of this trial is *approximately 27 months*. In the prophylaxis arm, all patients will continue in the Main Phase until the last patient initiated in the prophylaxis arm has received at least 50 EDs of N8-GP (*except for patients having had surgery as part of pathfinderTM 3*), thus all patients in the prophylaxis arm will receive at least 50 EDs of N8-GP and the average exposure to N8-GP will be more than 1 year.

...

In the part 2 patients can continue being on prophylaxis but can change between *every 4 or 7 day dosing regimens in accordance with the rules described in section 5.3.1* ~~according to their bleeding episode pattern.~~

5.2 Rationale for Trial Design

...

Part 2 of the Extension Phase will consist of a single prophylaxis treatment arm where it will be possible to ~~individualise~~ *change between every 4 day or 7 day treatment in accordance with the rules described in section 5.3.1* ~~according to recommended guidelines (see section 5.3) taken the patients bleeding pattern into account.~~

5.3.1 Prophylaxis

...

Other changes of the dose or dosing interval for prophylaxis are not allowed within *the main phase of the trial*. However, extra doses of N8-GP will be administered if a patient experiences a treatment requiring bleeding episode or in case of minor surgery.

Extension Phase part 1: The prophylaxis dose of N8-GP is administered in the non-randomised group every 4 days or in the randomised group every 4 day or every 7 day depending on which treatment arm the patient is allocated to. Based on the bleeding pattern, the Investigator may change the every 7 day prophylaxis treatment to an every 4 day treatment regimen (the non-randomised arm) *at any time*. ~~but~~ Changing vice versa is not permitted. *In addition the Investigator must monitor the patient on an on going basis and change patients from every 7 day prophylaxis treatment to an every 4 day treatment regimen in accordance with the following rule. A patient on every 7 day prophylaxis must be switched back to every 4 day prophylaxis if either of the following criteria are met over a 8 week period:*

- *Two or more spontaneous bleeding episodes*
- *One severe bleeding episode requiring hospitalisation.*

Novo Nordisk will monitor that patients are switched from the every 7 day prophylaxis treatment to an every 4 day treatment regimen adhering to the rule mentioned above. Novo Nordisk will furthermore monitor the number of patients switching from every 7 day to every 4 day treatment regimen and will terminate the 7 day treatment arm if the below rule is met:

- *If at least 15 out of 30 patients (or 50% of 30 or more) whom have been randomised to the every 7 day treatment arm are switched back to the every 4 day treatment arm, then the every 7 day treatment arm will be closed and all remaining patients will be switched to every 4 day treatment.*

...

Extension Phase part 2: During this period it is possible to ~~adjust~~*change* the prophylaxis treatment of patients to *every 4 day or 7 day treatment*~~an individualised regimen. Treatment regimens ranging from once weekly to every 4 day will be allowed: every 4 day, every 5 day, every 6 day or every 7 day.~~ For deciding to change a regimen it is strongly recommended to follow *the Investigator must monitor the patient on an on going basis and follow the below* ~~guidelines~~*rules for change of regimen:*

- *0-2 bleeding episodes within last 6 months on same regimen would allow a less frequent dosing interval to a lowest frequency of every 7 day. Change to a less frequent treatment regimen should be done while the patient is at a site visit*
- *If a patient on every 7 day treatment regimen over a 8 week period experiences two or more spontaneous bleeding episodes or one severe bleeding episode requiring hospitalisation, then the patient must be switched back to every 4 day treatment regimen* ~~3 or more bleeding episodes within last 6 months on same regimen allows to stay on regimen or change to a more frequent regimen to a highest frequency of every 4 day~~
- ~~Change of regimen can only take place after being on the same regimen for at least 6 months~~

Clinical judgement has to be applied in order to avoid increased risk to the subject's safety and must always overrule ~~guidelines~~ *the above described rules* when deemed necessary by the Investigator.

The dose for the Extension Phase part 1 and 2 will be:

50 U/kg BW of N8-GP for prophylaxis treatment every 4 day

~~60 U/Kg BW of N8-GP for prophylaxis treatment every 5 and 6 day~~

75 U/Kg of N8-GP for prophylaxis treatment every 7 day

5.3.2 Treatment of Bleeding episodes

...

Due to individual patient's bleeding pattern during the *main phase of the trial*, an adaptation in dosing regimen to 50 U/kg twice weekly will be permitted at the investigator's discretion.

8 Methods and Assessments

8.1.4 Visit 14-n and EOT Visit- visit in the Extension Phase of the trial

...

When patients randomised in part 1 have completed the part 1, ~~all~~ *remaining* patients can start part 2 at their next visit beginning at visit 17. Skipping visit 15 and/or 16 should be entered with a comment in EDC.

...

Telephone Contact:

It is recommended that a phone call is made to patients *at the 4 or 6-week interval between the site visits*. ~~who have changed prophylaxis treatment regimen approximately 4 weeks or at time which seem appropriate after the change.~~

8.1.6 Unscheduled Visits

...

The following can be performed/reported at an Unscheduled visit:

...

- *Dosing regimen choice or change and reason if change*

10 Interactive Voice/Web Response System (IV/WRS)

...

As a minimum, the system will be used for:

...

- *changing of dosing frequency*

12 Adverse Events, Technical Complaints and Pregnancies

12.1.3 Disease-related Bleeding

...

In case of *a life-threatening event or a fatal outcome*, the bleeding episode must be reported as an SAE.

18 Statistical Considerations

18.5 Interim Analysis

...

All data from the Main Phase of the trial will be analysed and reported when all patients have reached *at least 50 EDs* (except for patients having had surgery as part of pathfinder™ 3), *and all patients have had their first visit after 50 EDs where all planned assessments including inhibitors have been performed. The analysis of the main phase of the trial will be based on all data up to the patient's last visit at this point.* All main conclusions from the trial will be based on this reporting. Furthermore, an interim analysis will be performed when the patients enrolled in the randomised part of the Extension have completed part 1.

Protocol Amendment
No 15
to Protocol, final version 8.0
dated 12 July 2013

pathfinder™ 2

Trial ID: NN7088-3859

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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2 Changes	4

1 Introduction including rationale for the protocol amendment

The VHP requested that patients in the every 7 days treatment arm (Q7D) receive the same visit schedule as patients in the every 4 days treatment arm (Q4D) of the Main Study Phase i.e. monthly visits at the start of treatment, followed by visits every second month.

In addition, it was agreed with the VHP to also implement this visit schedule for patients randomised to Q4D in the extension phase part 1. This is to avoid any bias in the randomised arms. Part 1 of the extension is 6 months in duration, therefore monthly visits for the first 4 months have been introduced, followed by a visit 2 months later.

The VHP stipulated that this visit schedule should apply for every switch to Q7D independent of the part of the extension phase. Therefore, this requirement has also been implemented for Q7D patients in Part 2 of the extension. In Part 2, those switching to Q7D, will have visits every month for the first 4 months and subsequently every two months while on Q7D.

- Therefore the flowchart table 2-3 in section 2 describing the extension phase has been updated to describe this
- Section 5.3.1 has been updated accordingly
- The text regarding telephone contacts has been deleted in Table 2-3 and section 8.1.4 since more often visits has been added instead
- The trial figure 8-2, section 8 and section 8.1.4 describing the visits in extension phase has been revised.

In this protocol amendment:

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

2 Changes

Table 2-3 Flow Chart for Patients on Prophylaxis and On-Demand Treatment in Extension Phase

	Part 1						Part 2		
		14 ^{1,5}	15	16	17 ^{1,5}	18 ^{1,1,5}	12w ²	EOI	
Visit number	-		8w ²	16w ²	24w ²	12w ²	12w ²	Follow-up	-
Time of visit	Weeks							Un-scheduled Visit ^{1,4}	-
Visit window	Weeks								-
Informed Consent		*	-	-	-	-	-		-
Randomisation considerations		*							-
Withdrawal criteria		-	*	*	*	*	*		*
Concomitant medication		-	*	*	*	*	*		*
Date and time of last coagulation factor administration		-	*	*	*	*	*		*
EFFICACY		-	-	-	-	-	-		-
Bleeding episodes (rating severity)		-	*	*	*	*	*		*
SAFETY		-	-	-	-	-	-		-
Adverse events		-	*	*	*	*	*		*
EKG		-	-	-	*	*	*		*
Physical examination		-	-	-	*	*	*		*
Vital signs		-	*	*	*	*	*		*
Antibodies		-	-	-	-	-	-		-
FVIII inhibitors^{7,8}		-	*	*	*	*	*		*
N8-GP-binding antibodies^{7,8}		-	*	*	*	*	*		*

Visit number	Weeks	Part 1					Part 2			Follow-up	Un-scheduled Visit ¹⁴
		14 ¹⁵	15	16	17 ¹⁵	18 ^{14,15}	12w ²	EQI	12w ⁴		
Time of visit	Weeks	same date as V13	8w ²	16w ²	24w ²	12w ²	12w ⁴	12w ⁴			
Visit window	Weeks	-	±2	±2	±2	±2	±2	±2	-	-	
Administration of trial product ¹⁰	-	*	*	*	*	*	*	*	-	*	
Drug accountability	-	-	*	*	*	*	*	*	-	*	
IV/IVRS call	-	*	*	*	*	*	*	*	-	*	
Dispensing trial product	-	*	*	*	*	*	*	*	-	*	
Dosing regimen change	-	*	*	*	*	*	*	*	-	*	
Dispensing trial card	-	*	-	-	-	-	-	-	-	-	
REMINDERS	-	-	-	-	-	-	-	-	-	-	
Affirmation statement	-	-	-	-	-	-	-	-	*	-	
End of trial	-	-	-	-	-	-	-	-	*	-	
eDiary training	-	*	*	*	*	*	*	*	-	*	
eDiary data review	-	-	*	*	*	*	*	*	-	*	
Home treatment training	-	*	*	*	*	*	*	*	-	*	

Footer	Description
1	n = visit number from 19 and onwards
2	weeks after Visit 14
3	weeks apart
4	weeks since last visit
5	Only in case of expected unexpected allergic/anaphylactic reaction
6	Only every second visit (V19, V21, V23, ...)

7	Antibody sample will only be drawn from patients in the on-demand arm if they received treatment since last visit
8	A wash-out period of minimum 96 hrs is needed before the sample
9	Trough to be sampled before dosing and recovery to be sampled 30 min (\pm 5 min) after dosing, only for prophylaxis patients
10	Only for patients in prophylaxis treatment
11	Only height every year for patients below 18 years, otherwise only BW
12	Only yearly (at V21, V25...)
13	Only to be taken if HIV status is positive
14	Assessment during unscheduled visit are not mandatory but can be performed
15	It is recommended to contact patients by phone at the 4 and 6-week interval between the site visits (see section 8.1.4)

	Extension Part 1							Extension Part 2						
	14	14a	15	15a	16	17	Visit number	17 ^a	18	18 ^a	19 ^a -n ² / 19 ^b -n ²	EOT	Follow-up	Un-scheduled Visit ⁴
Visit number	14	14a	15	15a	16	17		17 ^a	18	18 ^a	19 ^a -n ² / 19 ^b -n ²	EOT	Follow-up	Un-scheduled Visit ⁴
Non-randomised PPX/ On-Demand patients Time of visit (weeks)	same date as V13	-	8w ¹	-	16w ¹	24w ¹	Q4D, Twice weekly PPX/ On-demand	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients Time of visit (weeks)	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	Q7D PPX	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
Informed Consent	x													
Randomisation considerations	x													
Withdrawal criteria		x	x	x	x	x		x	x	x	x	x		x
Concomitant medication		x	x	x	x	x		x	x	x	x	x		x
Date and time of last coagulation factor administration		x	x	x	x	x		x	x	x	x	x		x
EFFICACY														
Bleeding episodes (rating severity)		x	x	x	x	x		x	x	x	x	x	x	x
SAFETY														
Adverse events		x	x	x	x	x		x	x	x	x	x	x	x
ECG											x ²	x		x
Physical examination											x ⁶	x		x

Visit number	Extension Part 1							Extension Part 2					
	14	14a	15	15a	16	17	17a ⁴	18	18a ⁴	19a-n ² / 19a-n ²	EOT	Follow-up	Un-scheduled Visit ⁴
Non-randomised PPX/ On-Demand patients Time of visit (weeks)	same date as V13	-	8w ¹	-	16w ¹	24w ¹	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients Time of visit (weeks)	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
Dispensing trial card	x												
REMINDEES													
Affirmation statement											x	x	
End of trial											x	x	
eDiary training	x	x	x	x	x	x	x	x	x	x			x
eDiary data review		x	x	x	x	x	x	x	x	x	x		x
Home treatment training	x	x	x	x	x	x	x	x	x	x			x

Footer	Description
1	weeks after Visit 14
2	n = additional visit number until end of trial
3	weeks since last visit
4	It is mandatory to attend 2 consecutive a-visits upon switching to every 7 day treatment regimen in order to achieve visits every 4 weeks (± 1 week) during the first 4 months. After this time period the patient must attend visits every 8 weeks (± 1 week) while on every 7 day treatment regimen.
5	Only in case of expected unexpected allergic/anaphylactic reaction
6	Only every second non a-visits, e.g. visit (V19, V21, V23...)
7	Antibody sample will only be drawn from patients in the on-demand arm if they received treatment since last visit
8	A wash-out period of minimum 96 hrs is needed before the sample
9	Trough to be sampled before dosing and recovery to be sampled 30 min (± 5 min) after dosing, only for prophylaxis patients
10	Only for patients in prophylaxis treatment
11	Only height every year for patients below 18 years, otherwise only BW
12	Only yearly (at V21, V25...)
13	Only to be taken if HIV status is positive
14	Assessment during unscheduled visit are not mandatory but can be performed

5 Trial Design

...

5.3.1 Prophylaxis

...

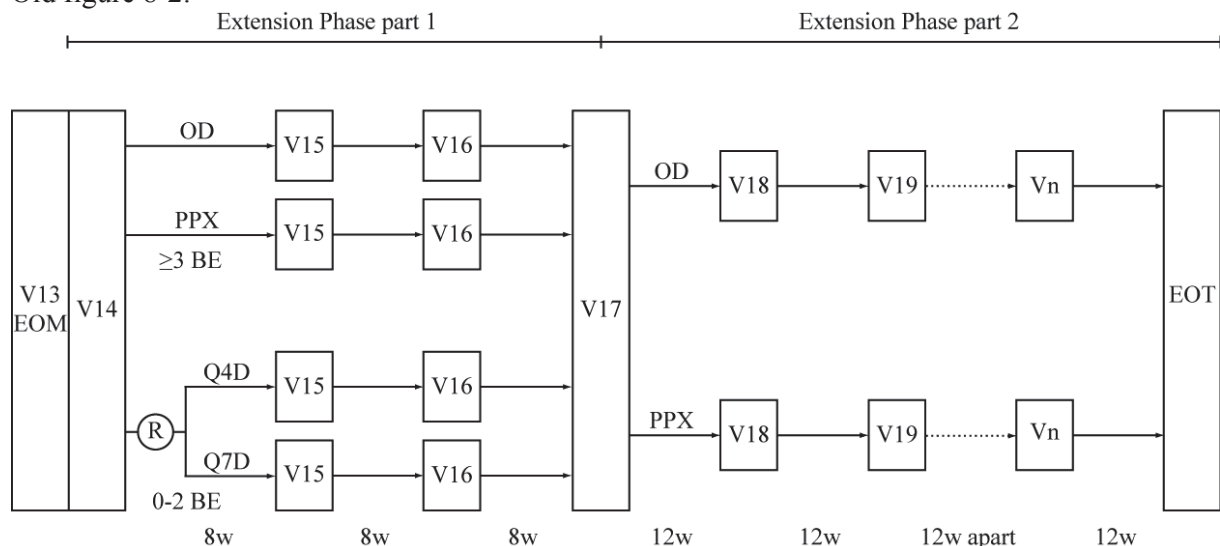
Extension Phase part 2: During this period it is possible to change the prophylaxis treatment of patients to every 4 day or 7 day treatment. For deciding to change a regimen the Investigator must monitor the patient on an on going basis and follow the below rules:

- 0-2 bleeding episodes within last 6 months on same regimen allow a less frequent dosing interval of every 7 day. Change to a less frequent treatment regimen should be done while the patient is at a site visit. *After switching, the patient must attend the next sequential a-visit in line. The a-visits are applicable to attend 2 times following a switch to every 7 day treatment regimen to allow for monthly visits the first 4 months and thereafter visits every second month while on every 7 day treatment regimen, see Table 2-3 and Figure 8-2*
- If a patient on every 7 day treatment regimen over a 8 week period experiences two or more spontaneous bleeding episodes or one severe bleeding episode requiring hospitalisation, then the patient must be switched back to every 4 day treatment regimen. *The patient must attend the next sequential visit in line and attend visits every third month while on every 4 day treatment regimen, see Table 2-3 and Figure 8-2.*

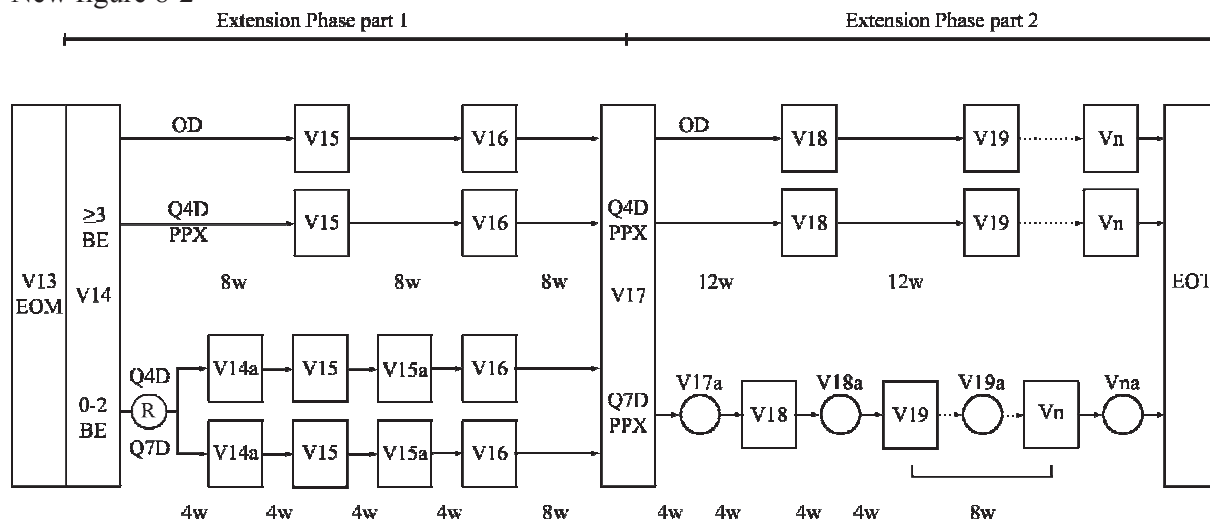
8 Methods and Assessments

...

Old figure 8-2:



New figure 8-2



OD = on-demand, PPX = prophylaxis, BE = bleeding episodes, ® = randomisation, Q4D = prophylaxis every 4 day, Q7D = prophylaxis every 7 day, w = weeks, ○ 2 consecutive a-visits are mandatory to attend upon switching to Q7D in order to achieve visits every 4 weeks (± 1 week) during the first 4 months

...

The Extension Phase part 1 will include the following visits:

- *Non-randomised prophylaxis and on-Demand patients*
Visit 14 (same date as Visit 13 (EOM)): patients are enrolled in Extension Phase
Visit 15+16: Visits at the site
 - ~~Patients in the randomised treatment arms~~ will be dosed during the visits
 - Patients on prophylaxis NOT in the randomised treatment arm will be dosed during the visits
 - Patients on the on-demand treatment arm will not be dosed during the visits
- *Randomised PPX patients*
Visit 14 (same date as Visit 13 (EOM)): patients are enrolled in Extension Phase
Visit 14a, 15, 15a +16: Visits at the site
 - Patients in the randomised treatment arms will be dosed during the visits

The Extension Phase part 2 will include the following visits:

- Visit 17-n** : Visit at site
Visit 17a-visits-n: 2 consecutive a-visits are mandatory to attend upon switching to every 7 day treatment regimen in order to achieve visits every 4 weeks (± 1 week) during the first 4 months
- Dosing regimen will be considered
 - Patients on prophylaxis regimen will be dosed at visits
- Patients on the on-demand arm will not be dosed during the visits

...

8.1.4 Visit 14-n and EOT Visit- visit in the Extension Phase of the trial

...

The numbers of bleeding episodes should be counted before all visits from visit 13 in preparation for a potential change in dosing regimen, *see section 5.3.1.*

The home treatment period for patients on *non-randomised every 4 day* prophylaxis and on-demand is approximately 8 weeks (± 2 week) between visits during the first 4 visits in the Extension phase part 1 (Visit 14-17). *The home treatment period for patients randomised to every 4 or 7 day prophylaxis in Extension phase part 1 is 4 weeks (± 1 week) for the first 4 months and thereafter 8 weeks (± 1 week) (Visit 14-17), see Table 2-3.*

The home treatment period for patients on every 4 day and twice weekly prophylaxis, and on-demand is ~~and~~ 12 weeks (± 2 weeks) ~~apart~~ in the Extension phase part 2 (from the Visit 17). Patients continuing on every 7 day prophylaxis from Extension phase part 1 into Extension phase part 2, will continue a home treatment period of 8 weeks (± 1 weeks). Whenever a patient in Extension phase part 2 switches to every 7 day prophylaxis, the home treatment period will be 4 weeks (± 1 weeks) for the first 4 months and thereafter 8 weeks (± 1 week) for the remaining of the period on every 7 day prophylaxis, see Table 2-3.

...

The following will be performed and/or recorded in the eCRF at all visits during the Extension Phase:

...

~~Telephone Contact:~~

~~It is recommended that a phone call is made to patients at the 4 or 6-week interval between the site visits.~~

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Trial ID: NN7088-3859
UTN: U1111-1119-7416
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27 September 2013
1.0
Final
1 of 6

Novo Nordisk

Protocol Amendment
No 16
to Protocol, final version 9.0
dated 28 August 2013

NN7088-3859

**A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC
0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients
with Haemophilia A**

Trial phase: 3

Applicable to US site 924

Amendment originator:



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2.3 Protocol Section 8.3.2.2: FVIII inhibitors	4

1 Introduction including rationale for the protocol amendment

In the current version of the NN7088-3859 (pathfinderTM2) protocol (section 6.5) it is stated that a patient must be withdrawn if the following applies:

- FVIII inhibitor (≥ 0.6 BU/mL) 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 2013, Haemophilia).

Therefore the withdrawal criteria section 6.5 of the protocol will be amended to allow patients with a low titre inhibitor (≤ 5 BU/mL), that does not result in clinically ineffective treatment with N8-GP, to continue in the trial.

Furthermore section 8.1.5 and 8.3.2.2 are updated to reflect this change of process.

In this protocol amendment:

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

2 Changes

2.1 Protocol Section 6.5: Withdrawal Criteria

The patient may withdraw at will 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.

A patient must be withdrawn if the following applies:

2. FVIII inhibitor ($\geq 0.6 > 5$ BU/mL) as confirmed by re-testing by Central Laboratory

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

2.2 Protocol Section 8.1.5: Follow-up visit (only for patients withdrawn due to development of FVIII inhibitors)

In case of withdrawal due to FVIII inhibitor development (*that makes treatment, prophylaxis or treatment of bleeding episodes, with N8-GP clinically ineffective or inhibitor titre > 5 BU/mL*), 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 \pm 2 weeks) after the EOT Visit the patient must attend a FU Visit, please see Section 8.3.2.2. 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 \pm 2 week as long as clinically warranted up until 3 months after confirmation of the FVIII inhibitor.

2.3 Protocol Section 8.3.2.2: 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 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 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 second samples should preferably be taken prior to any change of treatment, and after a 96 hours wash-out period. A 7 days wash out period may be applied if the 96 hours wash out is not sufficient to avoid drug interference in the inhibitor assay.*

~~At this Unscheduled Visit, a recovery test must also be performed.~~ If the second (*confirmatory*) inhibitor test is also positive, the patient must be withdrawn *if FVIII inhibitor >5 BU/mL or FVIII inhibitor ≥ 0.6 and ≤ 5 BU/mL that makes treatment (prophylaxis or treatment of bleeding episodes) with N8-GP clinically ineffective*, 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/mL and the Investigator judges that the inhibitor does not clinically interfere with treatment (prophylaxis or treatment of bleeding episodes) the patients may stay in pathfinderTM 2 on current treatment.

A patient has inhibitors (≥ 0.6 BU/mL) if the patient has been tested positive for inhibitors at two consecutive test samples performed at the central laboratory preferably with no more than 2 weeks between the tests.

For withdrawn patients: A follow-Up Visit must be scheduled 1 month after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted up to 3 months after the EOT Visit.

For patients continuing in pathfinderTM 2 with inhibitor (≥ 0.6 and ≤ 5 BU/mL): the patient must follow previous dosing schedule and the scheduled visits as described in Flowchart Table 2-1. Additional visits can be scheduled if closer monitoring is needed. In the event of a concern about reduced treatment efficacy a PK session may be performed. The PK can be evaluated after a wash out period of at least 96 hours.

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 12.1.2)

Blood samples for measurement of inhibitors towards FVIII will be analysed according to the Nijmegen modification of the Bethesda assay¹⁵. Any sampling for the inhibitor test must be performed at least 96 hours after last administration of N8-GP to allow for maximum wash-out of the drug.

An inhibitor test with a result ≥ 0.6 BU/ml will be considered as a positive inhibitor test. A patient is verified inhibitor positive if two independent samples from same patient are inhibitor positive (≥ 0.6 BU) – and the patient ~~should~~ *may* discontinue the trial including an EOT Visit and FU Visits *or remain in pathfinderTM 2 as described above.*

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

If more than two patients are verified inhibitor positive an unscheduled Safety Committee Meeting will be called by Global Safety – and a decision whether to continue, modify or stop the trial will be made, see Section 12.5.3.

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Novo Nordisk

Substantial Amendment no 17-FR

Trial ID: NN7088-3859

pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to FRANCE

Amendment originator:



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1 Introduction including rationale for the protocol amendment

The rationale for issuing this substantial amendment is the address' change for Pr Negrier's site.

Attachment II is updated accordingly.

In this protocol amendment:

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

2 Changes

The following changes to Attachment II to NN7088-3859 :

Address change:

From:

National
coordinating
Investigator

Name:

Title
/qualification:

Address:

Tel:

Fax:

E-mail:

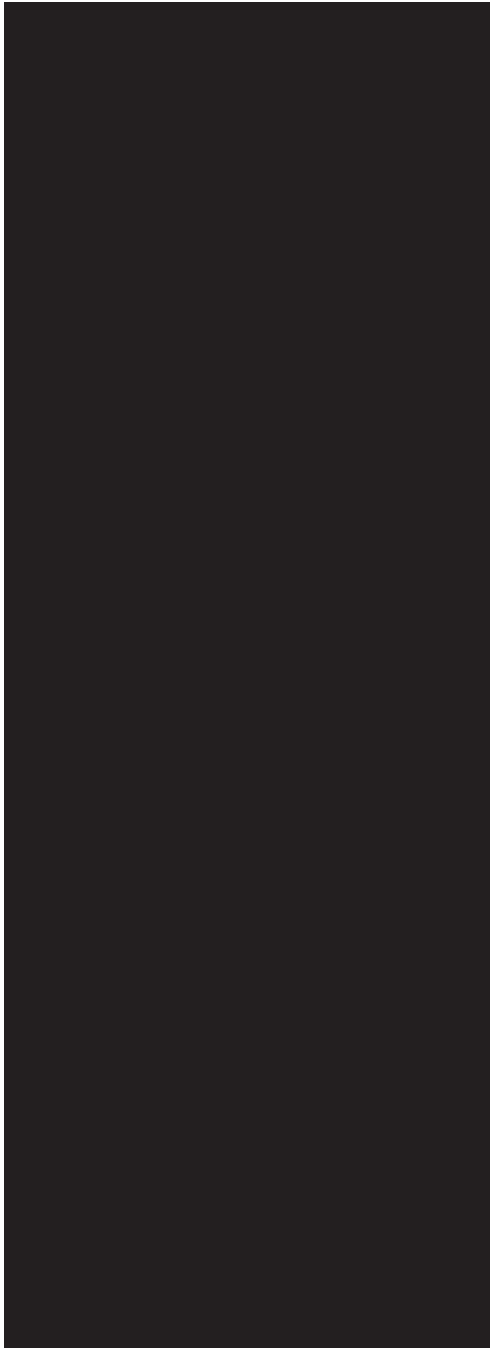
to

National
coordinating
Investigator

Name:

Title
/qualification:

Address:



Substantial Amendment
Trial ID: NN7088-3859
UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

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Tel:

Fax:

E-mail:



Protocol Amendment
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pathfinder™ 2

Trial ID: NN7088-3859

**A Multi-national Trial Evaluating Safety and Efficacy,
including Pharmacokinetics, of NNC 0129-0000-1003 when
Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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2 Changes	4

1 Introduction including rationale for the protocol amendment

In the current version of the NN7088-3859 (pathfinderTM2) protocol (section 6.5) it is stated that a patient must be withdrawn if the following applies:

- FVIII inhibitor (≥ 0.6 BU/mL) 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 6.5 of the protocol will be amended to allow patients with a low titre inhibitor (≤ 5 BU/mL), that does not result in clinically ineffective treatment with N8-GP, to continue in the trial. Furthermore section 8.1.5 and 8.3.2.2 are updated to reflect this change of process.

Furthermore a few other updates have been performed concurrently:

- A new PK endpoint has been added in section 4.2.2.4 and 18.2.4.1
- Minor update to flowchart in section 2, update to when recruitment into the randomised arm in extension phase part 1 will end in section 5.1 and 8.1.4, Bulgaria has been deleted from the country list in section 6.1 and update to section 9.3 regarding labelling and packaging of trial product.
- Minor addition to section 8.1.7 regarding major surgery patients.
- Section 8.3.2.1 has been updated to include an assay to analyse for antibodies towards PEG.
- Section 8.3.7 has been updated to reflect what the patient has consented to regarding storage of samples in pathfinderTM2 main and extension phase.
- Text regarding adverse events has been updated in section 12.1 and 18.10.

In this protocol amendment:

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

2 Changes

2 Flow chart

Table 2-3 Flow Chart for Patients on Prophylaxis and On-Demand Treatment in Extension Phase

	Extension Part 1							Extension Part 2						
	14	14a	15	15a	16	17	Visit number	17a ⁴	18	18a ⁴	19-n ² / 19a-n ²	EOT	Follow-up	Un-scheduled Visit ^{1,4}
Non-randomised PPX/On-Demand patients	same date as V13	-	8w±2 ¹	-	16w±2 ¹	24w±2 ¹	Q4D, Twice weekly PPX/ On-demand	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	Q7D PPX	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
Informed Consent	x													
Randomisation considerations	x													
Withdrawal criteria		x	x	x	x	x		x	x	x	x	x		x
Concomitant medication		x	x	x	x	x		x	x	x	x	x		x
Date and time of last coagulation factor administration		x	x	x	x	x		x	x	x	x	x		x
EFFICACY														
Bleeding episodes (rating severity)		x	x	x	x	x		x	x	x	x	x	x	x
SAFETY														
Adverse events		x	x	x	x	x		x	x	x	x	x	x	x

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Visit number	Extension Part 1							Extension Part 2						
	14	14a	15	15a	16	17	Visit number	17a ⁴	18	18a ⁴	19-n ² / 19a-n ²	EOT	Follow-up	Un-scheduled Visit ¹⁴
Non-randomised PPX/On-Demand patients	same date as V13	-	8w±2 ¹	-	16w±2 ¹	24w±2 ¹	Q4D, Twice weekly PPX/ On-demand	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	Q7D PPX	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
ECG						x					x ¹²	x		x
Physical examination						x					x ⁶	x		x
Vital signs		x	x	x	x	x		x	x	x	x	x	x	x
Antibodies														
FVIII inhibitors^{7,8}		x	x	x	x	x		x	x	x	x	x	x	x
N8-GP binding antibodies^{7,8}		x	x	x	x	x		x	x	x	x	x	x	x
IgE, IgG, HCP⁵														x
Biochemistry		x	x	x	x	x		x	x	x	x	x		x
Coagulation parameters														
Lupus anticoagulant														x
APTT														x
von Willebrand factor														x
FVIII activity⁹														
FVIII trough level		x	x	x	x	x		x	x	x	x	x		x
FVIII recovery¹⁰	x	x	x	x	x	x		x	x	x	x	x		x
Haematology		x	x	x	x	x		x	x	x	x	x		x

Visit number	Extension Part 1							Extension Part 2					Un-scheduled Visit ¹⁴	
	14	14a	15	15a	16	17	Visit number	17a ⁴	18	18a ⁴	19-n ² / 19a-n ²	EOT		Follow-up
Non-randomised PPX/On-Demand patients Time of visit (weeks)	same date as V13	-	8w±2 ¹	-	16w±2 ¹	24w±2 ¹	Q4D, Twice weekly PPX/ On-demand	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients Time of visit (weeks)	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	Q7D PPX	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
Hepatitis														X
HIV ¹³														X
Viral Load														X
CD4+ T cells														X
Urinalysis														X
OTHER ASSESSMENTS														
Body measurements ¹¹		X	X	X	X	X		X	X	X	X	X	X	X
PRO questionnaires						X					X ¹²	X		X
TRIAL MATERIAL														
Administration of trial product ⁶	X	X	X	X	X	X		X	X	X	X	X	X	X
Drug accountability		X	X	X	X	X		X	X	X	X	X	X	X
IV/IWRS call	X	X	X	X	X	X		X	X	X	X	X	X	X
Dispensing trial product	X	X	X	X	X	X		X	X	X	X	X	X	X
Dosing regimen /change ⁶	X	X	X	X	X	X		X	X	X	X	X	X	X

Visit number	Extension Part 1							Extension Part 2					Un-scheduled Visit ¹⁴	
	14	14a	15	15a	16	17	Visit number	17a ⁴	18	18a ⁴	19-n ² / 19a-n ²	EOT		Follow-up
Non-randomised PPX/On-Demand patients Time of visit (weeks)	same date as V13	-	8w±2 ¹	-	16w±2 ¹	24w±2 ¹	Q4D, Twice weekly PPX/ On-demand	-	12w±2 ³	-	12w±2 ³	12w±2 ³		
Randomised PPX patients Time of visit (weeks)	same date as V13	4w±1 ¹	8w±1 ¹	12w±1 ¹	16w±1 ¹	24w±1 ¹	Q7D PPX	4w±1 ³	8w±1 ³	4w±1 ³	8w±1 ³ / 4±1	8w±1 ³ / 4±1		
Dispensing trial card	x													
REMINDERS														
Affirmation statement												x	x	
End of trial												x	x	
eDiary training	x	x	x	x	x	x		x	x	x	x			x
eDiary data review		x	x	x	x	x		x	x	x	x			x
Home treatment training	x	x	x	x	x	x		x	x	x	x			x

Footer	Description
1	weeks after Visit 14
2	n = additional visit number until end of trial
3	weeks since last visit
4	It is mandatory to attend 2 consecutive a-visits upon switching to every 7 day treatment regimen in order to achieve visits every 4 weeks (\pm 1 week) during the first 4 months. After this time period the patient must attend visits every 8 weeks (\pm 1 week) while on every 7 day treatment regimen.
5	Only in case of expected unexpected allergic/anaphylactic reaction
6	Only every second non a-visits, e.g. visit (V19, V21, V23...) Change of dosing regimen from every 4 day to every 7 day treatment regimen can only take place at non a-visits in extension phase part 2. Change of dosing regimen from every 7 day to every 4 day treatment regimen can take place at all visits in extension phase part 1 and 2
7	Antibody sample will only be drawn from patients in the on-demand arm if they received treatment since last visit
8	A wash-out period of minimum 96 hrs is needed before the sample
9	Trough to be sampled before dosing and recovery to be sampled 30 min (\pm 5 min) after dosing, only for prophylaxis patients
10	Only for patients in prophylaxis treatment
11	Only height every year for patients below 18 years, otherwise only BW
12	Only yearly (at V21, V25...)
13	Only to be taken if HIV status is positive
14	Assessment during unscheduled visit are not mandatory but can be performed

4 Objective(s) and Endpoint(s)

4.2.2.4 Pharmacokinetic Endpoints

- *FVIII activity 30 min post-injection (C_{30min})*

5 Trial Design

5.1. Type of Trial

...

Recruitment into the randomisation sub-group in the Extension Phase part 1 will stop approximately ~~at mid-May~~ *April* 2014, hereafter also patients with a low bleeding rate will continue the same treatment as in Main Phase.

6 Trial Population

6.1 Number of Patients to be Studied

Countries planned to participate: Australia, Brazil, ~~Bulgaria~~, Croatia, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom and United States

6.5 Withdrawal criteria

...

2 - FVIII inhibitor (~~≥ 0.6~~ > 5 BU/mL) as confirmed by re-testing by Central Laboratory

...

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

8 Methods and Assessments

8.1.4 Visit 14-n and EOT Visit- visit in the Extension Phase of the trial

...

Recruitment into the sub-group of the Extension Phase part 1 will stop approximately ~~at mid-May~~ *April* 2014, hereafter also patients with a low bleeding rate will continue the same treatment as in the Main Phase.

8.1.5 Follow-up visit (only for patients withdrawn due to development of FVIII inhibitors)

In case of withdrawal due to FVIII inhibitor development *that makes treatment (prophylaxis and/or treatment of bleeding episodes) with N8-GP clinically ineffective or inhibitor titre >5 BU/mL*, 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.

8.1.7 Transfer of Patients to pathfinder™3 due to Major Surgeries

...

Upon completion of pathfinder™3, patients may return to pathfinder™2, re-entering the prophylactic or on-demand treatment arm as per their prior participation in the trial. *Randomised patients in extension part 1 on every 4 or 7 day prophylaxis treatment regimen must return to the non-randomised every 4 days prophylaxis treatment regimen*

8.3.2.1 N8-GP antibody assay

...

Levels of N8-GP binding antibodies will be compared by Novo Nordisk to pre-dose samples throughout the trial. If a patient develops N8-GP binding antibodies and the recovery value at that visit is less than 60% of screening value and FVIII level at time of inhibitor sampling (pre-dose) is more than 0.0452 U/mL, Novo Nordisk will ask the Investigator to call the patient for an unscheduled visit for collection of a new inhibitor sample which should will be taken after a 7 days wash out period.

...

A selection of the samples collected for N8-GP binding analysis will only be analysed for PEG binding antibodies twice before treatment with N8-GP, approximately every 4 months in main phase and extension phase part 1 and every year in extension phase part 2 if sufficient sample material is available. The PEG antibodies will be based on a validated assay.

8.3.2.2. FVIII inhibitors

...

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 samples should preferably be taken prior to any change of treatment, and after at least 96 hours wash-out period. *A 7 days wash out period may be applied if the 96*

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/mL or if FVIII inhibitor ≥ 0.6 and ≤ 5 BU/mL that makes treatment (prophylaxis or treatment of bleeding episodes) with N8-GP clinically ineffective, 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/mL 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 pathfinderTM2 on per-protocol treatment.

A patient has inhibitor (≥ 0.6 BU/mL) if the patient has been tested positive for inhibitors at two consecutive test samples performed at the central laboratory preferably with no more than 2 weeks between the tests.

For withdrawn patients: A follow-Up Visit must be scheduled 1 month after the EOT Visit and additional monthly follow-up visits may be arranged at intervals as long as clinically warranted up to 3 months after the EOT Visit.

For patients continuing in pathfinderTM2 with inhibitor (≥ 0.6 and ≤ 5 BU/mL): the patient must follow per-protocol treatment schedule and the scheduled visits as described in Flowchart Table 2-1 and Table 2-3. 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 may be performed. The PK can be evaluated after a wash out period of at least 96 hours. Blood sampling during the PK profile session can be performed at the following time points: pre-dose, 30 minutes (± 10 min), 24h (± 8 hours), 48h (± 8 hours), 72h (± 8 hours) and 96h (± 8 hours).

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 $\geq 66\%$ 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/mL), low responders (peak inhibitor titre ≤ 5 BU/mL), and whether the inhibitor is transient (disappearing (inhibitor titer < 0.6 BU/mL on ≥ 2 consecutive measurements) spontaneously within 6 months without a change in treatment regimen), or not.

...

An inhibitor test with a result ≥ 0.6 BU/ml will be considered as a positive inhibitor test. A patient is verified inhibitor positive if two independent samples from *the* same patient are inhibitor positive

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UTN: U1111-1119-7416
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(≥ 0.6 BU/mL) – and the patient *may* discontinue the trial including an EOT Visit and FU Visits *or* remain in *pathfinderTM2* as described above.

8.3.7 Central Laboratory Assessments

...

For pathfinderTM2 main phase: All blood samples including genotyping blood sample will be destroyed after finalisation of the trial report. Blood samples of patients who are suspected of inhibitors or who have developed inhibitors will be stored at least until evaluation of the clinical trial data by the authorities in the patient's country.

For pathfinderTM2 extension phase: Laboratory samples will be destroyed after trial completion

If allowed by local law and consented to, in pathfinderTM2 extension phase addendum 'Storage of blood samples from pathfinderTM2', samples drawn for analysis of antibodies in pathfinderTM2 main and extension phase will be stored until market authorisation in case further characterisation of the samples should be required by authorities.

9 Trial Supplies

9.3 Packaging and Labelling of Trial Product(s)

Novo Nordisk A/S will ~~label and pack the~~ be responsible for labelling and packaging of the trial product. *Third party vendors may be employed.*

12 Adverse Events, Technical Complaints and Pregnancies

12.1 Definitions

...

Serious Adverse Event (SAE):

- Important medical events ^{d)} that may not result in death, be life-threatening ^{a)} or require hospitalisation may be considered a SAE when, based upon 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. *Suspicion of transmission of infectious agents via the trial product and formation of inhibitory antibodies must always be considered a SAE.*

18 Statistical Considerations

18.2.4.1 PK Endpoints

- *FVIII activity 30 min post-injection (C_{30min})*

...

All pharmacokinetic endpoints will be modelled and analysed by an ANOVA on the log transformed parameter by visit. Estimates of each endpoint with 95% confidence intervals will be provided back-transformed to the natural scale. *In addition, the 90% confidence intervals will be provided back-transformed to the natural scale for AUC and C_{30min}.*

18.10 Analyses of Extension Phase Data

...

Data from part 2 of the Extension Phase

All safety parameters except Adverse Events and Serious Adverse Events, will in Extension Phase Part 2 be presented by listings and individual graphical representation only.

All *other* evaluations/summaries based on accumulated data in part 1 will be repeated in part 2, accumulating data from the entire trial (Main Phase + Extension Phase part 1 + part 2).

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2.0
Final
1 of 10

Protocol Amendment
no 19
to Protocol, final version 11
dated 29 November 2013

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of
NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in
Patients with Haemophilia A**

Trial phase: 3

Applicable to all countries

Amendment originator:



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1 Introduction including rationale for the protocol amendment

This protocol amendment has been prepared to include the following changes to the protocol:

- Allow some parthfinderTM2 patients to participate in a separate PK trial NN7088-4033 (pathfinderTM7). The rationale for conducting the pathfinderTM7 is to compare the PK profile for N8-GP produced at two different manufacturing sites
- Monitor antibody development against Host Cell Protein (HCP). No new blood samples will be required since the samples collected for the N8-GP binding antibody analysis will be used. The rationale for implementing the HCP antibody analysis is based on a recommendation from the U.S. Food and Drug Administration (FDA)
- Interim analysis including data from the extension phase part 2 are planned prior to submission of Biologics License Application and Marketing Authorisation Application
- Prolonged storage of leftover blood samples to enable further characterisation as new biomarkers related to the disease and/or safety, efficacy, or mechanism of action may evolve. This might improve the understanding and treatment of haemophilia in the future.

Furthermore minor mistakes and inconsistencies have been corrected.

In this protocol amendment:

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

2 Changes

2.1 Section 1 Summary

...

If the patients need to undergo surgery during the present trial they can switch into the surgery trial NN7088-3860 (pathfinderTM3). Upon completion of the surgery the patients can return to the NN7088-3859 (pathfinderTM2) trial.

In some countries patients will have the possibility to participate in a separate PK trial NN7088-4033(pathfinderTM7). If a patient decides to participate in the pathfinderTM7, the patient will return to the pathfinderTM2 trial after completion of the pathfinderTM7.

...

- N8-GP drug product

N8-GP 2000 U/vial 211µg/vial drug product is a lyophilised powder in single use vials with a nominal content of 2000 U/vial produced by Novo Nordisk A/S, ~~Denmark~~.

2.2 Section 2 Flow Chart

...

Footer 12: *Approximately every year* ~~Only yearly~~ (at V21, V25...)

For 'N8-GP binding antibodies' the following footnote is added:

Footer 15: *HCP antibodies will be analysed using samples taken for the N8-GP binding antibodies at the time points described in section 8.3.2.3*

2.3 Section 3.2 Rational for trial design

...

The phase 3 trials are offered as one package to each investigational site to ensure that patients are offered to continue N8-GP until commercially available and patients in need of surgery can undergo surgery without having to switch product. *In addition patients in some countries will be offered to participate in a PK trial NN7088-4033 (pathfinder™7). Patients will return to pathfinder™2 after completion or withdrawal from pathfinder™7.*

...

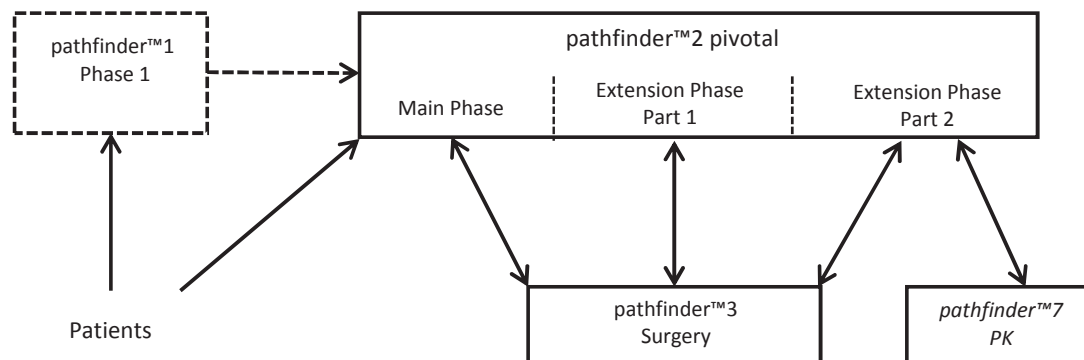


Figure 1 Figure 3-1 Overview of the pathfinder™ clinical trial programme.

2.4 Section 5.1 Type of Trial

...

Recruitment into the surgery trial pathfinderTM3 will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pivotal trial pathfinderTM2. The surgery trial will not be initiated until at least 20 bleeding episodes in at least 10 patients are treated with N8-GP in the present trial.

In addition patients in some countries will be offered the opportunity to participate in a PK trial (pathfinderTM7). Patients will be allowed to return to pathfinderTM2 after completion or withdrawal from pathfinderTM7.

2.5 Section 5.3.5 Patients Continuing Into the Extension Phase

...

As all patients will complete the Main Phase at the same time the continuation of patients from the Main Phase to the Extension Phase will be gradual and within a window of approximately 2 months depending on approval of the Extension Phase in the country and of patients' next scheduled visit. ~~Please refer to~~

In the Extension phase part 2 patients already included in the pathfinderTM 2 trial will in some countries be offered the opportunity to participate in the pathfinderTM 7 PK trial.

Please refer to Figure 3-1 for an overview of the flow of patients between trials in the clinical development programme.

2.6 Section 8.1.4 Visit 14-n and EOT Visit- visit in the Extension Phase of the trial

...

Blood sampling for central laboratory assessments:

- Biochemistry, see section 8.3.7.1 (not at Visit 14)
- ...
- *Host cell protein (HCP) antibodies, see section 8.3.2.2*

2.7 Section 8.1.8 Transfer of Patients to pathfinderTM7

To enable patients to be transferred to the pathfinderTM7 trial, the Investigator must ensure the following:

- *Order trial product for the pathfinderTM7 to ensure that trial product is available at trial start*

- *At the day of transferring to pathfinder™7 the IV/WRS "PK trial transfer" session must be used in order to transfer the patient into pathfinder™7*
- *The patient must return all drug dispensed in the current trial before entering pathfinder™7*
- *After completion of pathfinder™7 trial the IV/WRS "PK trial transfer session" must be performed in order to transfer the patient into pathfinder™2*

Upon completion of pathfinder™7, patients should return to pathfinder™2 re-entering the treatment regimen as per their prior participation in the trial.

If a patient cannot return to the same treatment regimen as before transferring to pathfinder™7, the investigator must choose the most appropriate regimen for the patient available in pathfinder™2. However, patients in the every 4 day dosing regimen will not be allowed to switch to every 7 day dosing regimen until the 6 month evaluation period have been completed and the requirements fulfilled see section 5.3.1.

The patient will return to the next visit in line in pathfinder™2 and the visit assessments performed at the EOT visit in pathfinder™7, will be used.

2.8 Section 8.3.2 Antibody assessments

...

The samples will be analysed both using the Bethesda assay identifying inhibitory antibodies towards FVIII and using an assay capable of identifying the occurrence of any antibodies towards N8-GP.

In addition an analysis for antibodies developed against HCP, i.e., HCP-antibodies, will be performed. HCP are small pieces of protein remaining from the synthesis of recombinant FVIII in CHO cells. These proteins are removed during the purification, however very small amounts may be present in the drug product and could potentially cause an immune response.

2.9 Section 8.3.2.3 HCP antibodies

A selection of the samples collected for the N8-GP binding antibody analysis will be analysed for HCP antibodies. This analysis will be performed depending on the amount of sample available.

The analysis of HCP antibodies is planned to include samples taken at the following time points: pre-dose prior to first N8-GP exposure and hereafter approximately every 6-12 months.

If deemed necessary more samples may be analysed to fully characterise the individual patient's HCP antibody profile.

2.10 Section 8.3.7 Central Laboratory Assessments

...

For pathfinderTM2 main phase: All blood samples including genotyping blood sample will be destroyed after finalisation of the trial report. ~~Blood samples of patients who are suspected of inhibitors or who have developed inhibitors will be stored at least until evaluation of the clinical trial data by the authorities in the patient's country.~~

For pathfinderTM2 extension phase: Laboratory samples will be destroyed after trial completion.

If allowed by local law and consented to, in pathfinderTM2 extension phase addendum 'Storage of blood samples from pathfinderTM2', samples drawn for analysis of antibodies in pathfinderTM2 main and extension phase will be stored until market authorisation in case further characterisation of the samples should be required by authorities.

However, if allowed according to local law all blood samples might be stored for a maximum of 15 years from end of trial after which they will be destroyed see section 25.2.

2.11 Section 8.3.7.3 FVIII Activity (central Laboratory)

The analysis of plasma FVIII activity will be performed at laboratory selected by Novo Nordisk by ~~two three~~ different assays (*one stage clot and chromogenic assay see below*), but only one FVIII activity result is reported to the site.

2.12 Section 8.4.5. PRO Questionnaires and Health Economics

PROs will be collected at screening visit (Visit 1), *at Visit 13 (end of main phase)*, at Visit 17 (end of part 1) and *approximately every year during Extension Phase part 2 (Visit 21, 25...)* and at the End of Trial visit for all patients.

2.13 Section 10 Interactive Voice/Web Response System (IV/WRS)

...

As a minimum, the system will be used for:

- screening of patients
- ...
- *PK trial transfer session*

2.14 Section 12.2.1 Follow-up of Adverse Events

...

After access to update the AE form in EDC is removed the Investigator must record any SAE and MESI follow-up information, if required, on the paper CRFs provided at trial closure.

Details on how to handle AEs that were not Recovered/Recovering in the pathfinder^{TM3} Surgery & pathfinder^{TM7} PK Trials when patients are ~~included in~~ returning to the pathfinder^{TM2} Trial

An AE (including SAEs and MESIs), that is not recovered/recovering in the Surgical Trial pathfinder^{TM3} when the patient is ~~enrolled into~~ returns to the present trial (pathfinder^{TM2}), will be followed up in the preceding Surgical Trial (pathfinder^{TM3}) and entered by the Investigator as concomitant illness in the present trial. *An AE (including SAEs and MESIs), that is not recovered/recovering in the PK trial (pathfinder^{TM7}) will upon return of the patient be followed up in the present trial (pathfinder^{TM2}).*

Non-serious AEs that are reported as not related and not severe in the Surgery and PK Trials will not be followed-up when ~~enrolling into~~ returning to the pathfinder^{TM2} trial. Details on how to handle unresolved non-serious AEs when patients are transferred from the pathfinder^{TM3} & 7 (Surgery and PK Trials) into the present trial (pathfinder^{TM2}) are described below and in table 12.1 and table 12.2.

Table 2–1 Table 12-1 Handling of Not Recovered/recovering Non-Serious AEs from pathfinder^{TM3}

Severity		Outcome Categories		Relationship		AE follow-up in:	AE in NN7088-3859 (Present)	Concomitant illness in NN7088-3859 (Present)
Mild/Moderate	Severe	Recovered/Recovered with sequelae/Fatal/Unknown	Not recovered/Recovering	Probable/Possible	Unlikely	NN7088-3860 (Surgery)		
X			✗	X		Yes	No*	Yes
	X		✗	X		Yes	No*	Yes
X			✗		X	No	No*	No
	X		✗		X	Yes	No*	Yes

* Unless worsened during participation in pathfinder^{TM2} (Present Trial)

Table 2–2 Table 12-2 Handling of Not Recovered/recovering Non-Serious AEs from pathfinder™7

Severity		Relationship		AE follow-up in: NN7088-4033 (PK)	AE in NN7088-3859 (Present)	Concomitant illness in NN7088-3859 (Present)
Mild/Moderate	Severe	Probable/Possible	Unlikely			
X		X		No	No	Yes
	X	X		No	No	Yes
X			X	No	No	Yes
	X		X	No	No	Yes

2.15 Section 18.5 Interim Analysis

...

All main conclusions from the trial will be based on this reporting. Furthermore, an interim analysis will be performed when the patients enrolled in the randomised part of the Extension have completed part 1.

In addition interim analyses including data from the extension phase part 2 are planned prior to submission of Biologics License Application and Marketing Authorisation Application.

2.16 Section 25 Retention of Clinical Trial Documentation and Human Biosamples

25.1 Retention of Clinical Trial Documentation

...

Novo Nordisk will maintain Novo Nordisk’s documentation pertaining to the trial as long as the product is on the market plus 20 years. The files from the Investigator site/institution will be retained 15 years after the completion of the trial, or longer if required by national regulations.

25.2 Retention of Human Biosamples

If allowed according to local law leftover blood samples may be retained for later analysis for further characterisation until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action may evolve the analyses may also include biomarkers that are unknown at present or have not been included in the scientific hypothesis at initiation of the trial. The samples will be stored at a Novo Nordisk designated central laboratory. Samples might be transferred to other countries, if not prohibited by local regulations. The patient’s identity will remain confidential and samples will only be marked and identified by a unique sample ID. No direct identification of the patient will be stored together

with the samples. The analyses will not have any medical consequences for the patients or their relatives.

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

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

Protocol Amendment
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UTN: U1111-1119-7416
EudraCT No.: 2011-001142-15

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Novo Nordisk

Protocol Amendment
no 20
to Protocol, final version 12.0
dated 02 May 2016

Trial ID: NN7088-3859
pathfinder™ 2

A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC 0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients with Haemophilia A

Trial phase: 3

Applicable to: Denmark, Italy, Netherlands and Switzerland

Amendment originator:



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1 Introduction including rationale for the protocol amendment

The rationale for this protocol amendment is the introduction of N8-GP in 3000 IU vials instead of 2000 U vials. The change is evaluated to be convenient for the patients since the use of N8-GP in 3000 IU vials will reduce the required injection volume compared to the use of N8-GP in 2000 U vials. In addition the number of N8-GP vials required for each injection will be reduced for some patients depending on the patient's bodyweight.

In this protocol amendment:

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

2 Changes to section 9 Trial supplies

9.1 Trial Product(s)

The following trial products will be supplied by Novo Nordisk:

- ~~N8-GP 2000 U/vial 211 µg/vial as a sterile, freeze-dried powder in a 2-8 °C (36-46°F) stable formulation single use vial of 2000 U/vial to be reconstituted with 4.3 mL of 0.9% Sodium Chloride (NaCl) for i.v. injection.~~
- *N8-GP 3000 IU/vial as a sterile, freeze-dried powder in a 2-8 °C (36-46°F) stable formulation single use vial of 3000 IU/vial to be reconstituted with 4.3 mL of 0.9% Sodium Chloride (NaCl) for i.v. injection. The strength is given as IU, however, for N8-GP the strength IU equals U and these units can be used interchangeably.*

~~N8-GP 2000 U/vial 211 µg/vial powder must be reconstituted prior to administration. After reconstitution with 4.3 mL Sodium Chloride 0.9% solution each 2000 U vial contains 500 U/mL of N8-GP (4 mL can be withdrawn from the vial).~~ *N8-GP 3000 IU/vial powder must be reconstituted prior to administration. After reconstitution with 4.3 mL Sodium Chloride 0.9% solution each 3000 IU vial contains 750 IU/mL of N8-GP (4 mL can be withdrawn from the vial).* Sodium Chloride 0.9% will be provided by Novo Nordisk.

...

9.4 Storage, Handling, Accountability and Destruction of Trial Product(s)

~~N8-GP 2000 U/vial 211 µg/vial must be stored at 2-8 °C, protected from light.~~ *N8-GP 3000 IU/vials must be stored at 2-8 °C, protected from light*

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Novo Nordisk

Protocol Amendment

no 21

**to Protocol, version 12
dated 02 May 2016**

**(for Denmark, Italy, Netherlands and Switzerland:
Amendment to Protocol, version 13
dated 24 January 2017)**

Trial ID: NN7088-3859

pathfinder™ 2

**A Multi-national Trial Evaluating Safety and Efficacy, including Pharmacokinetics, of NNC
0129-0000-1003 when Administered for Treatment and Prophylaxis of Bleeding in Patients
with Haemophilia A**

**Trial phase: 3
Applicable to all countries**

Protocol Amendment no 21
Trial ID:NN7088-3859
UTN: U1111-1119-7416
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1 Introduction including rationale for the protocol amendment

The purpose of this amendment is to clarify when patients participating in pathfinder2 (NN7088-3859) can complete the trial.

From May 2018, patients will be offered to complete their visit schedule in NN7088-3859 and transfer to a new trial (NN7088-4410), where treatment with N8-GP can be continued. Transfer can take place when local authority approvals for the new trial have been obtained.

The planned LPLV date for NN7088-3859 remains unchanged.

In this protocol amendment:

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

2 Changes

Section 7 Trial Schedule

.....

Planned date for FPFV: 01-Feb-2012

Planned date for LPLV: 03-Dec-2018*

**Patients may successfully complete the trial from May 2018, irrespective of their last scheduled visit.*

.....