Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT01489111
Sponsor trial ID:	NN7088-3860
Official title of study:	Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A (pathfinder™3)
Document date:	06 May 2019

16.1.1 Protocol and protocol amendments

List of contents

Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID: NN7088-3860

pathfinder™ 3

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Trial phase: 3

Author:
Name: [redacted], [redacted]
Department: Haem, ClinOps FVIII

Table of contents

Page

Table of figures

Page

Table of tables

Page

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase (SGPT or serum glutamino-pyruvic-transaminase)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT or serum glutamino-oxaloacetic-transaminase)
BP	blood pressure
BU	Bethesda Units
BW	body weight
CHO	Chinese hamster ovary
CRO	contract research organisation
CTR	clinical trial report
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of trial
EQ-5D	Euroqol 5 dimension self-report questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFP	fresh frozen plasma
FPFV	first patient first visit
FVIIa	activated coagulation factor seven
FVIII	coagulation factor eight
FIX	coagulation factor nine
FU	follow-up
GCP	good clinical practice
GGT	gamma-glutamyl transferase
hr(s)	hour(s)
HAEM-A-QOL	haemophilia-adult-quality of life
HAEMO-QOL	haemophilia-quality of life
HCP	Host cell proteins
HE	Health Economics
HEMO-SAT	haemophilia-satisfaction
HRQoL	Health Related Quality of Life
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	inhibitor follow-up
IMP	Investigational Medicinal Product
INR	Prothrombin time
IRB	institutional review board
IU	international unit
i.v.	intravenous

IV/WRS	interactive voice response system/interactive web response system
LAR	legal acceptable representative
LPFV	last patient first visit
LPLV	last patient last visit
MAA	Marketing Authorisation Application
MCV	mean corpuscular volume
MESI	medical event of special interest
min	minutes
NA	Not Applicable
NDA	New Drug Application
N8-GP	glycopegylated recombinant coagulation factor VIII
NIMP	Non-investigational medicinal product
NN7088-3776	pathfinder™ 1 (phase 1 trial)
NN7088-3859	pathfinder™ 2 (pivotal trial)
NN7088-3860	pathfinder™ 3 (surgery trial)
NN7088-3861	pathfinder™ 4 (extension trial)
NOAEL	No Observed Adverse Effect Level
PCV	packed cell volume
pd-aPCC	plasma derived activated Plasma Coagulation factor Concentrates
pd-PCC	plasma derived Plasma Coagulation factor Concentrates
PEG	polyethylene glycol
PK	pharmacokinetics
PRO	patient reported outcomes
PT	Prothrombin time
PTP	previously treated patients
RBC	red blood cells
rFVIIa	recombinant activated factor VII
rFVIII	recombinant factor VIII
RIA	radioimmunoassay
SAE	serious adverse event
SAS	Safety Analysis Set
TEAE	Treatment emergent AE
$T_{½}$	terminal half-life
TMM	trial materials manual
TVP	trial validation plan
U	Unit
WFH	World Federation of Haemophilia

1 Summary

This trial will provide information on the efficacy and safety profile of NNC 0129-0000-1003, hereafter referred to as N8-GP, when administered before, during and after major surgery, see Section 5.3.1 for definition.

Primary Objective

- To evaluate the haemostatic effect of N8-GP during surgical procedures in patients with haemophilia A

Primary Endpoint

- Haemostatic effect during surgery evaluated by the four-point scale, assessed by the Investigator/surgeon at the day of surgery
  - Four-point response scale: excellent, good, moderate or none

Secondary Objectives

- To evaluate the general safety including immunogenicity of N8-GP when used for prevention and treatment of bleeding throughout the surgical period
- To evaluate the haemostatic effect of N8-GP during the post-operative period
- To evaluate health economic resource use (hospitalisation days) due to surgery

Key Secondary Endpoints

- Average consumption of N8-GP during surgery
- Haemostatic effect of N8-GP during the post-operative period Days 1-6 and 7-14
- Average consumption of N8-GP during the post-operative period Days 1-6
- Incidence rate of inhibitors against factor VIII (FVIII) (≥0.6 BU/mL)

The endpoints will be analysed based on all available information until End of Trial (EOT) Visit and up to approximately 5 weeks for each patient.

Trial design

The trial is a multi-centre, multi-national, open-label, non-randomised, single arm, efficacy and safety trial evaluating N8-GP during surgical procedures in patients with severe (FVIII activity (FVIII:C) <1%) haemophilia A.

This surgery trial NN7088-3860, hereafter referred to as pathfinder™ 3, consists of a Screening Visit (Visit 1), Day of Surgery (Day 0: Visit 2), Post-operative Period (Days 1-6: Visit 3, Days 7-14: Visit 4) and an EOT Visit (Visit 5).

Trial Population

Patients enrolled in pathfinder™ 3 will be recruited from the pivotal trial NN7088-3859, hereafter referred to as pathfinder™ 2 and upon completion of pathfinder™ 3, patients will return to pathfinder™ 2, reentering the prophylactic or on-demand treatment arm as per their prior participation in the trial.

All patients in pathfinder™ 2 will be offered to enter this trial in case they need major surgery. For a definition of major and minor surgeries please refer to Section 5.3.1.

It is expected that approximately 22 patients with severe (FVIII:C <1%) haemophilia A already included in pathfinder™ 2 are to be screened into pathfinder™ 3 in order to ensure evaluation of at least 15 major surgical procedures in 10-15 patients.

If a minimum of 15 major surgeries in minimum 10-15 patients has not yet been performed in this surgery trial by the end of pathfinder™ 2, the trial might be extended to apply for the patients entering from the extension trial NN7088-3861, hereafter referred to as pathfinder™ 4, see Figure 3–1.

The trial population is characterised by the inclusion and exclusion criteria described in pathfinder™ 2 and having the additional key inclusion and exclusion criteria in this trial:

Key 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.)
- Ongoing participation in the pathfinder™ 2 (NN7088-3859) or the pathfinder™ 4 (NN7088-3861) trial and having received ≥5 doses of N8-GP
- Undergoing major surgery (refer to Section 5.3.1 for definition) requiring daily monitoring of FVIII:C and wound status for ≥3 days
- The patient and/or Legally Acceptable Representative (LAR) is capable of assessing a bleeding episode, keeping an eDiary, capable of home treatment of bleeding episodes and otherwise capable of following the trial procedures

Key Exclusion Criteria

- Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products
- Previous withdrawal from the pathfinder™ 2 (NN7088-3859) or the pathfinder™ 4 (NN7088-3861) trial after administration of trial product, except interruption due to inclusion in this pathfinder™ 3 trial (NN7088-3860)
- The receipt of any investigational medicinal product (except N8-GP) 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's discretion)
- FVIII inhibitors ≥ 0.6 BU/mL at screening (refer to Section 8.1.1)
- Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records)
- Immune modulating or chemotherapeutic medication
- 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
- Unwillingness, language or other barriers precluding adequate understanding and/or cooperation

Key Efficacy Assessments

FVIII activity will be measured and clinical efficacy in surgery will be assessed using a 4-point scale of 'excellent, good, moderate or none'. In addition transfusion requirements, haemoglobin, N8-GP consumption and number of doses per procedure will be recorded. The Post-operative Period is important due to that haemophilia patients run a higher risk of re-bleeding, thus several endpoints will be evaluated during this period.

Key Safety Assessments

Adverse events, FVIII antibody assessment, haematology, biochemistry, vital signs and coagulation parameters will be measured.

Trial Products:

The following trial products will be used in this trial:
- N8-GP 2000 U/vial 211µg/vial drug product

N8-GP 2000 U/vial 211µg/vial (N8-GP) drug product is a sterile, freeze-dried 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 reconstituted with 4.3 mL of Sodium Chloride 0.9%. After reconstitution each vial contains 500 U/mL N8-GP at pH 6.9. The trial product will be administered as a slow bolus intravenous (i.v.) injection for all trial product administrations. Sodium Chloride 0.9% will be provided by Novo Nordisk. See Section 9.

Patients undergoing surgery will receive bleeding preventive treatment with N8-GP before, during and after surgery. N8-GP doses will be adjusted based on the FVIII activity levels measured in the individual patient, see Section 5.4.

2 Flow Chart

Table 2–1 Visit Flow Chart

Visit number	1	2	3	4	5	Follow-up Visit FU[4]	Un-scheduled Visit
Time of visit (Day)	Screening[1]	0 Surgery	1-6[2]	7-14[2]	EOT[3]		
Visit window	0-3 w before Visit 2					4 w after EOT ±2 w	
SUBJECT RELATED INFO/ASSESSMENTS							
Informed consent	x						
In/exclusion criteria	x	x[5]					
Withdrawal criteria		x[5]	x	x	x		x
Bleeding treatment history	x[6]						
Concomitant illness	x						
Concomitant medication	x	x	x	x	x		x
Infusions (concom. med.)		x	x	x			
Demography	x[6]						
Genotype (FVIII genotype)	x[6]						
Haemophilia details	x[6]						
History of bleeding episodes	x[6]						
History of surgery	x[6]						
Medical history	x[6]						
Date and time of last coagulation factor administration	x	x			x		x
EFFICACY							
Surgical interventions		x	x	x			
Clinical evaluation of haemostatic response		x	x	x			
Consumption of N8-GP		x	x	x			
Blood product transfusions		x	x	x			
Evaluation of wound haematoma		x	x	x	x		
Drain volume		x	x	x			
Haemoglobin		x	x	x			
Bleeding episodes		x	x	x	x	x	x
SAFETY							
Adverse events	x	x	x	x	x	x	x
ECG	x				x		x
Physical examination	x	x[5]	x[7]	x[8]	x		x
Vital signs	x	x	x[7]	x	x	x	x
Body measurements	x	x[5,9]	x[7,9]	x[9]	x[9]		x
Antibodies							
FVIII inhibitors[10]	x	x			x	x	x
N8-GP binding antibodies[10]	x	x			x		x
IgE, IgG and anti-HCP antibodies							x[11]
Biochemistry[12]	x	x	x	x	x		x
Coagulation parameters[12]							
aPTT	x[13]	x	x	x	x		x
INR (PT)	x[13]	x	x	x	x		x
FVIII activity[14]							
FVIII trough level[12]		x	x	x	x		x
FVIII recovery	x[15]	x	x	x	x		x
Haematology[12]	x	x	x	x	x		x
OTHER ASSESSMENTS							
PRO questionnaires	x[16]						
HE assessments					x		
TRIAL MATERIAL							
Administration of trial product[17]	x	x	x	x			x
IV/WRS call	x	x[5]	x	x	x		x
Drug accountability		x[5]	x	x	x		x

Visit number	1	2	3	4	5	Follow-up Visit FU[4]	Un-scheduled Visit
Time of visit (Day)	Screening[1]	0 Surgery	1-6[2]	7-14[2]	EOT[3]		
Visit window	0-3 w before Visit 2					4 w after EOT ±2 w	
Dispensing trial product	x[18]	x[5]	x	x			x
Dispensing trial card	x						
Dispensing/adjusting eDiaries	x						
REMINDERS/TRAINING							
Affirmation statement					x	x	
End of trial					x	x	
eDiary training	x	x	x	x			x
eDiary review		x[5]	x	x	x		x
Home treatment training	x	x	x	x			x

1. The transfer to pathfinder™ 3 will be performed either on a scheduled or an Unscheduled Visit in pathfinder™ 2. Assessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3. All the assessments pertaining to the Screening Visit must have been done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. These results from pathfinder™ 2 will then be used in pathfinder™ 3. Patients coming from the on-demand treatment arm in pathfinder™ 2 must have FVIII activity recovery level measured at the Screening Visit, see Section 8.1.1. All assessments at Visit 1 and 2 must be performed.
2. Assessments must be done every day during Days 1-6 (Visit 3), once during Days 7-14 (Visit 4) and hereafter once every week until the post-operative control has finalised, as judged by the Investigator. If the late Post-operative Period is extended beyond Day 14, the Investigator/medically qualified person must perform a visit schedule with the patient once every week.
3. The EOT Visit can not be performed earlier than Day 14. If the EOT Visit is performed at Day 14, Visit 4 and 5 may be joined and assessments pertaining to both visits must be performed once.
4. FU Visit is only for patients who have developed inhibitors.
5. To ease the work flow at site, it is allowed to perform the following Visit 2 assessments on the day just prior to the surgery, if necessary.
6. Assessments will only be performed once in pathfinder™ 2 and these results will be used in pathfinder™ 3.
7. Physical examination, Vital signs and Body measurements only to be assessed at Days 1 and 6.
8. Physical examination only to be assessed once during Visit 4 (during Days 7-14).
9. Only body weight will be measured.
10. Antibody sampling is required to be made pre-dose and after minimum 96 hrs wash-out.
11. Conditional assessments, must only be made if a patient experiences an unexpected allergic/anaphylactic reaction, see Section 8.3.6.3.
12. Assessment should be made pre-dose, if dosed.
13. Coagulation parameters are collected pre-dose and additionally post-dose (30 ± 10 min) at Visit 1.
14. FVIII activity tests for central laboratory must be collected in accordance with Section 8.3.8.4. FVIII recovery activity must be measured 30 min ± 5 min post-dose. Additionally all FVIII activity test results from the local laboratory must be recorded in the eCRF, see Section 8.3.7.2.
15. After administration of 50 U/kg BW N8-GP 30 ± 5 min post dose samples must be collected at Visit 1.
16. PROs should preferably be completed before any other trial related activity, except informed consent.
17. Administration of trial product may be repeated during the day, see Section 5.4.1.
18. In order to ensure adequate supply of N8-GP trial drug for the pathfinder™ 3 surgery trial period, IV/WRS must have been notified during the pathfinder™ 2 trial at least 14 days prior to Visit 1.

Table 2–2 Detailed Flow Chart of Visit 2 (Day of Surgery) and Day 1 of Visit 3

Visit		Visit 2 (Day of Surgery)					Visit 3
Day	**-1**	**0**					**1**
Nominal Time[1]	**May be done on the day just prior to surgery**	**Pre-dose[2] 1 hr (± 20 min)**	**0[3]**	**Post-dose 30 min (± 10 min)**	**Post-dose 4 hrs (± 1 hrs)**	**Post-dose 8 hrs (± 2 hrs)**	**Post-dose 24 hrs[4] (± 4 hrs)**
SUBJECT RELATED INFO/ASSESSMENTS							
Concomitant medication[5]		x	x	x	x	x	x
Infusions (concom. med.)				x			x
EFFICACY							
Surgical interventions				x			x
Clinical evaluation of haemostatic response					x[6]		x
Consumption of N8-GP				x			x
Blood product transfusions				x			x
Evaluation of wound haematoma					x[6]		x
Drain volume						x[7]	x[7]
Haemoglobin			x[8]				
SAFETY							
Adverse events		x	x	x	x	x	x
Physical examination	x[10]	x					x
Vital signs		x		x			x
Body measurements	x[10]	x					x
Antibodies		x					
Biochemistry[9]		x					x
Coagulation parameters		x		x	x	x	x[9]
FVIII activity[11]		x		x	x	x	x
Haematology		x		x			x[9]
OTHER ASSESSMENTS							
Administration of trial product		x[12]					

1. Nominal time values refer to time elapsed after administration of the N8-GP loading dose, except for haemoglobin.
2. The time window of 1 hr ± 20 min pre-dose is only applicable for blood samples. Other assessments performed on the Day of Surgery are not restricted to the time window.
3. The actual time of completion of the injection will be recorded and corresponds to trial time point = 0.
4. The 24 ± 4 hrs post-dose sampling at the Day of Surgery equals the sampling time point at Day 1 (Visit 3) in the Post-operative Period, except for haemoglobin.
5. Concomitant medication includes anaesthetics and other haemostatic therapy used during surgery.
6. To be evaluated upon completion of the surgical procedure.
7. Drainage to be evaluated daily within the last 24 hrs ± 4 hrs.
8. Haemoglobin must be measured just prior to, during and following surgery (at 0, 1 hr ± 20 min and 24 ± 4 hrs post start of surgery). "Knife to skin" corresponds to time point = 0. In addition haemoglobin will be assessed by the local laboratory prior to any prescribed RBC transfusion.
9. Assessment should be made pre-dose.
10. To ease the work flow at site, it is allowed to perform the following assessments on the day just prior to the surgery, if necessary.
11. FVIII activity tests for central laboratory must be measured in accordance with Section 8.3.8.4. FVIII activity must be measured 30 min ± 5 min post-dose. Additionally all FVIII activity test results from the local laboratory must be recorded in the eCRF, see Section 8.3.7.2.
12. Pre-loading dose administered no more than 1 hr prior to expected start of the surgical procedure (defined as "knife to skin"). Administration of trial product may be repeated during the day.

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 care.[1]

With a deficiency or absence of FVIII, activation of coagulation factor X becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis.[2] The haemostatic plug formed in these patients is, if formed, fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis, prolonged bleeding episodes and re-bleeding. Bleeding episodes in patients with severe haemophilia A are typically spontaneous or after mild trauma in joints, muscles and soft tissues. The bleeding episodes often occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis. In repeated cases this is followed by synovitis in the affected joint. Recurrent bleeding episodes in the same location, may lead to chronic arthropathy, muscular atrophy and deformities.[3] Bleeds may occur in all parts of the body including life-threatening bleeds in the central nervous system, throat, neck, gastrointestinal tract, retroperitonaeum 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 previously treated patients (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.

Haemophilia care is based on treatment of an active bleeding with a haemostatic agent (on-demand use) or haemostatic agents are administered for longer periods to prevent bleeding (bleeding prophylaxis). The standard treatment of patients with haemophilia A is replacement of the FVIII protein. Currently available FVIII products are all lyophilised products for 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.

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-polyethylene glycol (PEG) 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 Chinese hamster ovary (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.

For further information on medicinal aspects, non-clinical data and quality of N8-GP, please refer to the current version of the Investigator's Brochure (IB)[7] and any updates thereof.

In accordance with the European Medicines Agency (EMA) Guidelines[8], 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.

3.1.3 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 terminal half-life ($T_{½}$). 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 product. 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.

Participation in pathfinder™ 3 is offered to the patients in pathfinder™ 2 in need of major surgery, ensuring that the patients can undergo surgery without having to switch product.

To minimise the switching between FVIII products the patient will furthermore be offered to continue in pathfinder™ 4, if approved in country, after completion of pathfinder™ 2. In this way patients will have the opportunity to continue with N8-GP treatment until the product is commercially available.[a]

3.2 Rationale for the Trial

This trial is part of a clinical development programme that at present includes a preceding phase 1 trial NN7088-3776, hereafter referred to as pathfinder™ 1, a pivotal phase 3 pathfinder™ 2 trial, an extension phase 3 pathfinder™ 4 trial and the present phase 3 pathfinder™ 3 trial. The phase 3 trials will be offered to each investigational site to ensure that patients are offered to continue on N8-GP until commercially available[a] and to ensure that patients in need of surgery can undergo surgery without having to switch product.

If a minimum of 15 major surgeries in minimum 10-15 patients has not yet been performed in this trial by the end of pathfinder™ 2, the trial might be extended to apply for the patients entering from pathfinder™ 4. The pathfinder™ clinical trial programme is illustrated in Figure 3–1. Arrows indicate possible transfer of patients between trials.

The rationale for this trial is to investigate efficacy and safety of N8-GP during surgery and in the Post-operative Period in patients with haemophilia A at and above 12 years of age.[b] A surgery trial is in accordance with the CHMP guideline on Clinical investigation of recombinant and human plasma-derived Factor VIII products.[8] This trial will provide information on the bleeding-preventive

[a] For UK patients only: the end of the extension trial will be defined be exact date and not when commercially available.
[b] For Croatia only: the lower age limit will be 18 years.

effect during surgery, the haemostatic effect during and after these procedures and the safety profile of N8-GP in patients with haemophilia A.

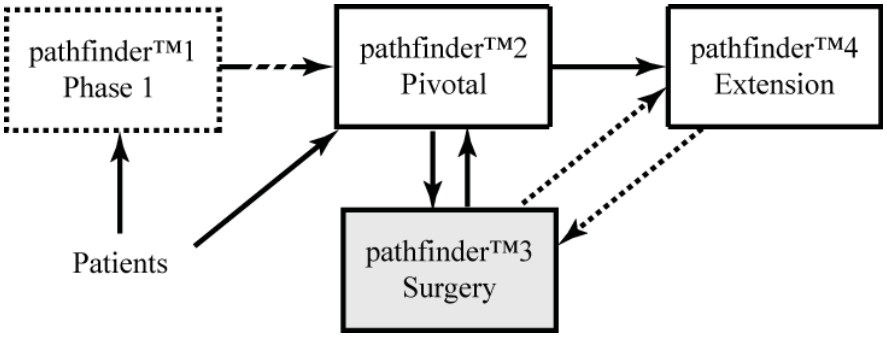


Figure 3–1 Overview of the pathfinder™ Clinical Trial Programme

4 Objectives and Endpoints

4.1 Objectives

4.1.1 Primary Objective

- To evaluate the haemostatic effect of N8-GP during surgical procedures in patients with haemophilia A

4.1.2 Secondary Objectives

- To evaluate the general safety including immunogenicity of N8-GP when used for prevention and treatment of bleeding throughout the surgical period
- To evaluate the haemostatic effect of N8-GP during the post-operative period
- To evaluate health economic (HE) resource use (hospitalisation days) due to surgery

4.2 Endpoints

4.2.1 Primary Endpoint

- Haemostatic effect during surgery evaluated by the four-point scale, assessed by the Investigator/surgeon at the day of surgery
  - Four-point response scale: excellent, good, moderate or none

4.2.2 Secondary Endpoints

4.2.2.1 Efficacy Endpoints

- Estimated blood loss during surgery
- Average consumption of N8-GP during surgery
- Haemostatic effect of N8-GP during the post-operative period Days 1-6
- Average consumption of N8-GP during the post-operative period Days 1-6
- Number of transfusions during the post-operative period Days 1-6
- Haemostatic effect of N8-GP during the post-operative period Days 7-14

4.2.2.2 Safety Endpoints

- AE and SAEs reported during the trial period
- Incidence rate of inhibitors against FVIII (≥0.6 BU/mL)

4.2.2.3 Health Economics Endpoints

Length of stay in the hospital and days in intensive care will be assessed at the end of the trial.

4.3 Time Frame of the Objectives and Endpoints:

- During surgery is defined as the time from "knife to skin" until "last stitch"
- Day of Surgery is defined as Day 0
- The Post-operative Period is defined as the time from Day 1 to Day 14 (this period can be extended as judged be the Investigator)
- The last visit is defined as the EOT Visit. The EOT Visit cannot be performed sooner than Day 14

5 Trial Design

5.1 Type of Trial

The trial is a multi-centre, multi-national, open-label, non-randomised, single arm, efficacy and safety trial evaluating N8-GP during surgical procedures in patients with severe (FVIII:C<1%) haemophilia A.

Patients enrolled in pathfinder™ 3 will be recruited from pathfinder™ 2 and only when having received ≥ 5 doses of N8-GP. Upon completion of pathfinder™ 3, patients will return to pathfinder™ 2, reentering the prophylactic or on-demand treatment arm as per their prior participation in the trial.

All patients in pathfinder™ 2 will be offered to enter this trial in case they need major surgery. For a definition of major and minor surgeries please refer to Section 5.3.1.

It is expected that approximately 22 patients with severe haemophilia A are to be screened into pathfinder™ 3 in order to ensure evaluation of at least 15 major surgical procedures in 10-15 patients.

The trial will for the individual patient consist of Visit 1-5 and the trial period is estimated to have a total duration of 2-5 weeks, see Figure 5–1:

- Visit 1 (Screening Visit)
- Visit 2 (Day of Surgery, Day 0)
- Visit 3 (Post-operative Period, Days 1-6). Assessments must be done every day at the site during Days 1-6
- Visit 4 (Post-operative Period, Days 7-14). Assessments must be done once at the site during Days 7-14 (if the late Post-operative Period is extended beyond Day 14, the Investigator/medically qualified person must perform a visit schedule with the patient once every week until the post-operative control has finalised)
- Visit 5 (EOT Visit)

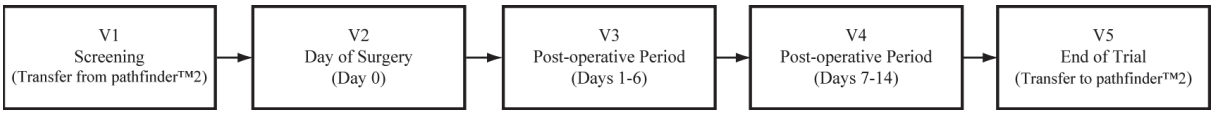


Figure 5–1 Visit Diagram

Recruitment into pathfinder™ 3 will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pathfinder™ 2 trial.

In the US: the surgery trial will not be initiated until at least 20 bleeding episodes in at least 10 patients have been treated with N8-GP.

5.2 Rationale for Trial Design

This trial will provide information on the bleeding-preventive efficacy and safety profile of N8-GP when administered before, during and after surgery in patients with severe haemophilia A (FVIII:C <1%). The trial design and population of patients with severe haemophilia A is consistent with the recommendations in the EMA guideline on the clinical investigation of recombinant and human plasma-derived Factor VIII products.[8] Availability of the product also for surgery is important to avoid unnecessary switching between different products.

The trial population is identical to that intended to be treated with N8-GP when marketed. Efficacy of N8-GP during surgery will be assessed using a 4-point scale of "excellent, good, moderate or none". In addition transfusion requirements, haemoglobin, consumption of N8-GP and number of doses per procedure will be recorded. The Post-operative Period is important since patients with haemophilia are at high risk of re-bleeding, hence several end-points will be evaluated during that period. There is no control treatment in the trial and the trial is open-label regarding treatment given. The rationale for choosing a multi-centre design is to ensure a sufficient number of patients for the trial.

5.3 Surgery

Surgical procedures should be performed in coordination with a team experienced in the management of haemophilia in a centre with adequate laboratory support for reliable monitoring of the FVIII level. Surgery should preferably be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed. Availability of sufficient quantities of N8-GP should be ensured before undertaking surgery for haemophilia patients.

Emergency Surgery

- To minimise switching between FVIII products, patients are able to undergo emergency surgery in this trial whilst still participating in pathfinder™ 2 allowing these patients to proceed directly to Visit 2, Day of Surgery, provided there are sufficient supplies of pathfinder™ 3 trial product at site. The site must ensure that adequate supply of pathfinder™ 3 N8-GP trial product is present to cover the unplanned surgery period without compromising the continuation of any other enrolled patients at the site. The site must notify the IV/WRS in conjunction with the emergency surgery. Furthermore the screening information including the FVIII activity recovery assessment and FVIII inhibitor test data must be available from the preceding visit in the pathfinder™ 2 trial. If these data are available from the preceding trial then these can be used in the present trial. All assessments at Visit 2 must be performed.

Re-surgery

It is allowed to perform more than one surgery in a patient and, if needed, re-surgery are allowed. If a patient, because of complications, is re-operated at the same site during the course of the surgery trial, the surgery does not count as a new surgery. This should be recorded as an AE, see section 12. If a patient is re-operated after the EOT Visit, the surgery counts as a new surgery and the same assessments/evaluations will take place as from Visit 1. Multiple sites, like joints, can be operated at the same time if this is feasible, but will only count as one surgery.

5.3.1 Definition of Major and Minor Surgery

Major Surgery

Any invasive operative procedure (requiring several days of substitution therapy) and/or where any one or more of the following occur:

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

This definition includes both circumcision and port insertions since they require several days of substitution therapy but do not include simple drainage procedures that take place bedside.

The surgical procedures may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation, local anaesthesia or with a combination of these modalities.

Minor Surgery

Any invasive operative procedure where only the skin, mucous membranes, or superficial connective tissue is being manipulated. Examples of minor surgery include implanting pumps in subcutaneous tissue, skin biopsies or simple dental procedures. Minor surgery can be performed concomitant to major surgery or post-operatively during the trial but are not counted as surgeries.

5.4 Treatment of Patients

Major Surgery

Patients undergoing major surgery will receive bleeding preventive treatment with N8-GP before, during and after surgery.

The dose level of N8-GP will be chosen so that FVIII activity at least as recommended by WFH Guidelines (Table 1A)[1] is targeted, and higher levels may be necessary depending on type of surgery and standard practice at site. The rationale is to replace the FVIII activity in these patients up to FVIII activity levels that are effective in preventing bleeding during and after surgery. N8-GP

doses will be adjusted if necessary based on the FVIII activity recovery level measured in the individual patient at Visit 1 (Screening Visit) and the FVIII activity will be monitored daily during Visit 2 and 3.

The maximum dose to be administered to a patient within 24 hours (hrs) is 200 U/kg body weight (BW). The dose is recommended to be divided and only considered under exceptional circumstance such us serious trauma or severe bleed. The $T_{½}$ time of N8-GP has a mean value of 18.4 hrs.

The trial product should be administered as a slow bolus i.v. injection for all trial product administrations.

The administrations in this trial will be performed both at home and in hospital. All patients and/or parents/caregivers will be instructed by the Investigator how to handle home administration before first dose administration at home.

Minor Surgery

Minor surgery performed post-operatively during the trial are not counted as surgery. Minor surgery can be performed while participating in this trial by administering an additional dose of 50-75 U/kg BW N8-GP or a dose sufficient to increase the FVIII level to 100% prior to the minor surgery to prevent peri-operative bleeding.

The following medications are not allowed during the course of the trial:

- Bypassing products: activated recombinant factor VII (rFVIIa), plasma-derived prothrombin complex concentrates (pd-PCC) and activated pd-PCC (pd-aPCC)
- Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma (FFP) or cryoprecipitate

The following medications are not allowed unless clinically warranted:

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

5.4.1 Dose Adjustments

Dosing during the pre-surgery period

Upon confirmation of eligibility at Visit 1 the patient must be administered once with a dose of 50 U/kg BW N8-GP at the site. The FVIII recovery level at this visit, as measured by the central laboratory, will be used to determine the N8-GP dosing level maintained during and after surgery.

Between Screening (Visit 1) and Day of Surgery (Visit 2) the patients entering this trial from the prophylaxis treatment arm in pathfinder™ 2 will continue on the preventive dosing of 50 U/kg BW N8-GP every four days (96 hours interval) or twice weekly and patients entering this trial from the

on-demand treatment arm in pathfinder™ 2 will continue the on-demand treatment (20-75 U/kg BW at Investigator's discretion), unless Investigator decides otherwise.

Dosing during the Day of Surgery (Day 0)

On the Day of Surgery (Visit 2), all patients must receive a planned pre-operative loading dose of N8-GP, no more than 1 hour prior to expected start of the surgical procedure ("knife to skin") and before any procedures are undertaken including anaesthesia to avoid bleeding when being anaesthetised. Therapeutic dose level of N8-GP should be calculated to aim for a FVIII plasma level of approximately 80-100 %, depending upon the results of the mandated recovery assessment, and should be administered by a slow bolus i.v. injection. Subsequent dosing on the day of surgery should be considered approximately 12 hrs after the loading dose to maintain plasma levels of FVIII above 50%.

Dosing during the Post-operative Period (Days 1-14)

During days 1 to 6 the patients dose level of N8-GP should be adjusted at the Investigator's discretion as needed depending on the type of surgery, in general aiming for a FVIII plasma level above 50%.

From days 7 to 14 post-surgery N8-GP should be dosed at the investigator discretion, considering the WFH guidelines.[1] FVIII activity level should be monitored by daily measurements of FVIII activity locally in the Post-operative Period until and through Day 6 (a reference standard provided by Novo Nordisk must always be used when running the assay), see Section 8.3.7.2.

The Post-operative Period may be extended beyond Day 14 if the patient is judged by the Investigator, not to be ready to continue either the prophylactic or on-demand treatment as previously decided upon in pathfinder™ 2. The patient's dose level of N8-GP should be adjusted at the Investigator's discretion.

5.4.2 Treatment of Bleeding Episodes

If a patient experiences a treatment requiring bleeding episode at home, treatment with N8-GP should be initiated as soon as it is identified and the patient must contact the Investigator immediately and irrespectively of severity of the bleeding episode, please refer to Section 8.2.2. When the patient is in contact with the Investigator, it is the responsibility of the Investigator to assess the severity of the bleeding episode. Patients with severe bleeding episodes must visit the site within 24 hrs. For definition of the severity of a bleeding episode please refer to Section 8.2.2.1.

For the treatment of bleeding episodes, doses will be based on WFH guidelines (Table 1A)[1]. For treatment of a bleed all patients will be treated with doses between 20-75 U/kg BW (the recommended standard dose will be 50 U/kg). 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.

Dose level, number of doses and frequency of dosing are decided by the Investigator in relation to the particular bleeding episode. The maximum dose to be administered to a patient within 24 hours (hrs) is 200 U/kg body weight (BW). The dose is recommended to be divided and only considered under exceptional circumstance such us serious trauma or severe bleed.

If a haemostatic response cannot be achieved after 48 hrs 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.

During the entire trial period all treatment requiring bleeding episodes will be entered by the patient or caregiver in the patient's eDiary. When the patient is hospitalised or otherwise unable to enter a severe bleeding episode, the site personnel can enter this information in the patient's medical record and hereafter in the eCRF, please refer to Section 8.1.6, 8.2.2 and 8.4.7.

5.5 Rationale for Treatment

In the preceding phase 1 pathfinder™ 1 trial, 26 PTPs 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 serious adverse events were reported. The half-life was prolonged with approximately 1.6-fold compared to the patient's 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 activities.[9] The longer half-life of N8-GP will allow for prophylaxis with fewer injections and presumably better compliance.

The dosing guidelines from the WFH[1] for treatment of bleeding episodes and during surgery describes injections 1-2 times a day for up to 7-14 days, depending on the severity of bleed and the type of surgery. The longer half-life of N8-GP is expected to translate into a reduced frequency of doses and duration of therapy compared with existing treatments. A long acting product is expected to give a more steady plasma profile ensuring significant increased FVIII trough activity levels with fewer injections, an advantage both during surgery and especially in the Post-operative Period.

6 Trial Population

6.1 Number of Subjects 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 subjects to be screened (i.e. documented informed consent) approximately: 22

Planned number of subjects to be started on trial product approximately: 18

Planned number of subjects to complete the trial: 10-15

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. Ongoing participation in the pathfinder™ 2 (NN7088-3859) or the pathfinder™ 4 (NN7088-3861) trial and having received ≥5 doses of N8-GP
3. Undergoing major surgery (refer to Section 5.3.1 for definition) requiring daily monitoring of FVIII:C and wound status for ≥3 days
4. The patient and/or Legally Acceptable Representative (LAR) is capable of assessing a bleeding episode, keeping an eDiary, capable of home treatment of bleeding episodes and otherwise capable of following the trial procedures

6.3 Exclusion Criteria

1. Known or suspected hypersensitivity to trial product including allergy to hamster protein or related products
2. Previous withdrawal from the pathfinder™ 2 (NN7088-3859) or the pathfinder™ 4 (NN7088-3861) trial after administration of trial product, except interruption due to inclusion in this pathfinder™ 3 trial (NN7088-3860)
3. The receipt of any investigational medicinal product (except N8-GP) 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's discretion)
4. FVIII inhibitors ≥ 0.6 BU/mL at screening (refer to Section 8.1.1)

5. Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records)
6. Immune modulating or chemotherapeutic medication
7. 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
8. 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 Rescheduling Criteria

1. Subjective signs of illness or fever within 48 hours prior to Screening Visit
2. In a bleeding state (Screening Visit and EOT Visit)
3. Less than 96 hrs wash-out prior to Screening Visit and EOT Visit

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 bleeding episode cannot be controlled after 48 hrs 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, see Section 8.3.6.3 and 12.1.2
4. Usage of Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like FFP or cryoprecipitate. Bypassing products: rFVIIa, pd-PCC and pd-aPCC
5. Significant thromboembolic event prior to Day of Surgery (Visit 2)
6. Incapacity or unwillingness to follow the trial procedures

7. The planned major surgical procedure is cancelled or postponed

Patients withdrawn from this trial due to cancelled or postponed planned major surgery or unwillingness to perform the surgical procedure are not excluded from continuing in pathfinder™ 2 unless pathfinder™ 2 withdrawal criteria are met.

6.6 Patient Replacement

All patients in pathfinder™ 2 will be offered to enter this trial in case they need major surgery. If a minimum of 15 major surgeries in minimum 10-15 patients has not yet been performed in this surgery trial by the end of pathfinder™ 2, this trial might be extended to apply for the patients entering from pathfinder™ 4, see Figure 3–1. Patients withdrawn from the trial prior to completion of Day 2 (Visit 3) will not count as a surgery and will be replaced.

6.7 Rationale for Trial Population

The phase 3 pathfinder™ 2 trial and this phase 3 pathfinder™ 3 trial will enrol patients with haemophilia A aged ≥12 years who are likely to benefit from the treatment in the trial.[c] 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 prophylactic treatment. Adherence to current prophylaxis regimens drops dramatically during the teenage years where the compliance rate may be as low as 13%.[9] Fewer injections are therefore likely to improve compliance.

All patients in the trial or their LAR(s) must be capable of giving informed consent prior to any trial related activity.

The trial population are characterised through the inclusion criteria:

- Criterion no. 1 is included in accordance with ICH GCP[10]
- Criteria no. 2 and 3 are included to enable patients to undergo surgery without switching FVIII product while they participate in pathfinder™ 2
- Criterion no. 4 is included to ensure compliance with treatment and protocol requirements

The trial population are characterised through the exclusion criteria:

- Criterion no. 1 and 2 is selected to exclude patients who have previously demonstrated adverse reactions to or insufficient compliance with N8-GP trial regimen
- Criteria no. 1, 4, 5, 6, 7, and 8 is chosen to avoid exposing potentially fragile patients to a new compound and to prevent exposure of N8-GP to patients with FVIII inhibitors
- Criteria no. 3 and 6 are selected to minimise any effect of external compounds on the patient's coagulation and immune system

[c] For Croatia only: the lower age limit will be 18 years.

- Criterion no 8 serves to prevent patient exposure to the risk of not following prescribed dosing of the drug product

7 Trial Schedule

Planned date for first patient first visit (FPFV): 02.Apr.2012

Planned completion of the last patient (LPLV): 02.Sep.2013

Planned duration of recruitment period: 16 months

The end of the clinical trial is defined as LPLV

Planned completion of clinical trial report (CTR): 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)[11], the Food and Drug Administration Amendments Act (FDAAA)[12] - as reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

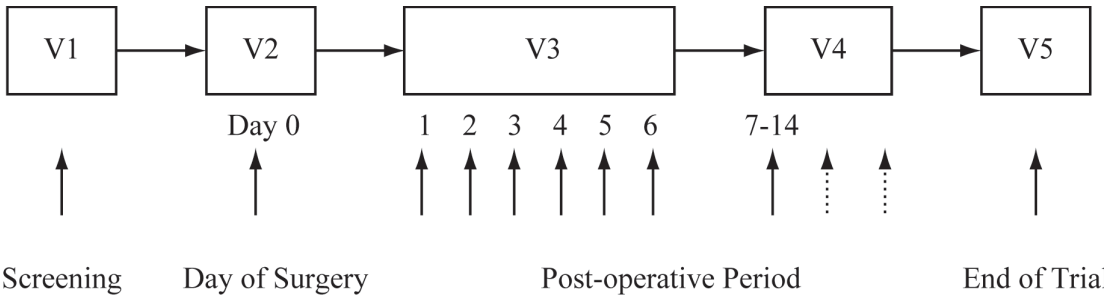
8 Methods and Assessments

8.1 Visit Procedures

Procedures for the scheduled visits are described in the sections below and in the flow charts, see Section 2, Table 2–1 and Table 2–2.

In order to ensure adequate supply of N8-GP pathfinder™ 3 trial drug for the surgery period, IV/WRS must have been notified during pathfinder™ 2 at least 14 days prior to Visit 1.

The trial consists of Visit 1-5 and the trial period is estimated to have a total duration of 2-5 weeks. Assessments at the site are done every day during Days 1-6 (Visit 3), once during Days 7-14 (Visit 4) and hereafter once every week until the post-operative control has finalised, as judged by the Investigator. If the late Post-operative Period is extended beyond Day 14, the Investigator/medically qualified person must perform a visit schedule with the patient once every week, see Figure 8–1.



Mandatory assessments and blood sampling performed at the site. The EOT Visit must not be scheduled before Day 14.

The Post-operative Period can be extended as judged by the Investigator.

Figure 8–1 Detailed Overview of Visits

The transfer to pathfinder™ 3 will be performed either on a scheduled or an Unscheduled Visit in pathfinder™ 2.

Assessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3. All the assessments pertaining to the Screening Visit must have been done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. These results from pathfinder™ 2 will then be used in pathfinder™ 3. Patients coming from the on-demand treatment arm in pathfinder™ 2 must have FVIII activity recovery level measured at the Screening Visit. All assessments at Visit 1 and Visit 2 must be performed.

The patient can attend the EOT Visit earliest at Day 14. This includes minimum 96 hrs of wash-out before the inhibitor sampling at the EOT Visit.

If the patient is ready for the EOT Visit at Day 14, Visit 4 and the EOT Visit may be joined and all assessments pertaining to Visit 4 and EOT Visit must be done once.

Before the EOT Visit and re-entering pathfinder™ 2 the patient should be judged by the Investigator to be ready to continue the treatment as previously decided upon in the pathfinder™ 2 trial (either the prophylactic or on-demand treatment). If not, the Post-operative Period must be extended as judged by the Investigator beyond Day 14 and the Investigator/medically qualified person must perform a visit schedule with the patient once every week.

Trial Participation:

Patients enrolled in the trial should be provided with a Trial Card stating that the patient is participating in the trial and whom to contact (site address, Investigator name and telephone number). The patients must keep the card with them at all times. The patients should be instructed to return the card to the Investigator at the last visit of the patient or destroy the card after the last visit. It must be stated in the medical record that the patient is participating in the trial.

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 LAR(s) 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 patient's LAR(s) will be requested to sign and date the Informed Consent Form. If the patient is a minor, they can in addition sign a child assent form, as per local regulations.

Screening Failures:

Screening failures are defined as patients who have signed the informed consent, but fail to comply with the inclusion and exclusion criteria or patients withdrawing 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 within 3 days after data are available. A Screening failure call must be made in IV/WRS. Serious and non-serious AEs from screening failures will be entered by the Investigator into 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 in pathfinder™ 3 are not excluded from continuing in pathfinder™ 2 unless pathfinder™ 2 withdrawal criteria are met.

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 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 EOT 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 8.3.6.

EOT Visit:

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

Before enrolment in the trial and prior to conduct of any trial related procedures/activities the patient and/or the patient's LAR(s) must have signed the Informed consent form after having received written and verbal information about the trial. This should be done prior to the Surgery transfer visit in pathfinder™ 2.

If the patient is enrolled in the trial, the patient will receive a unique subject number, which will be assigned to the patient throughout the trial.

The Screening Visit must be scheduled 0-3 weeks prior to Visit 2 (Day of Surgery). All results necessary for confirming the inclusion and exclusion criteria at Visit 2, from local and central laboratory analyses must be available before determining whether or not the patient can continue in the trial.

Prior to any assessments at Visit 1, except informed consent, baseline PRO data must be completed.

A wash-out period of minimum 96 hrs is necessary prior to FVIII inhibitor and N8-GP binding antibodies sampling at Visit 1. Sampling must be collected prior to dosing.

The patient must be administered once with a fixed dose of 50 U/kg BW N8-GP at the site. The FVIII activity recovery level, as measured by the central laboratory, will be used to calculate and determine the dosing level maintained during and after surgery.

The samples taken 30 min (± 5 or 10 min) post-dose must not be taken from the same vein as previously used for administration of N8-GP.

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

- Informed consent form, signed and dated, see Section 19.1
- In/exclusion criteria, see Sections 6.2 and 6.3
- Adverse events, see Section 12.1
  - Ongoing AEs from the pivotal trial or the extension trial should be recorded as concomitant illness, please see Section 12.2.1 for details
- Concomitant medication, see Section 11
- Concomitant illness, see Section 11
- ECG, see Section 8.3.2
- Physical examination, see Section 8.3.3
- Vital signs, see Section 8.3.4
- Body measurements, see Section 8.3.5
- Check date and time of last coagulation factor (N8-GP) administration, see Section 8.4.4
- PRO questionnaires, see Section 8.4.5
- Administration of trial product (50 U/kg BW), see Section 8.5.1

Blood sampling for local laboratory assessments:

- Haematology, see Section 8.3.7.3

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see Section 8.3.6.1
- N8-GP binding antibodies, see Section 8.3.6.2
- Biochemistry, see Section 8.3.8.2
- Coagulation parameters, see Section 8.3.8.3
- FVIII activity, recovery of a fixed N8-GP dose, see Section 8.3.8.4

Trial material, training and reminders:

- Dispensing trial card, see Section 8.5.2
- Dispensing/adjusting eDiaries, see Section 8.5.3
- Home treatment/eDiary entry training, see Sections 8.5.4 and 8.4.7

- It is of utmost importance that the patient is carefully instructed in how to complete the eDiary and trial product administration at home. The trial personnel must monitor treatment compliance carefully
- Enrolment session in IV/WRS, see Section 10
- Dispensing trial product in IV/WRS, see Section 9.4 and 10
  - Handout sufficient amount of N8-GP for home treatment prior to Visit 2, see Section 8.5.4
  - Remind the patient only to use the dispensed medication of this pathfinder™ 3 trial whilst enrolled in the surgery trial and not the medication from the pathfinder™ 2 trial

8.1.2 Visit 2 - Day of Surgery

All results necessary for confirming 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.

A wash-out period of minimum 96 hrs is necessary prior to FVIII inhibitor and N8-GP antibodies sampling at Visit 2. Patients should withhold treatment with N8-GP unless they have a bleeding episode. In case of a bleeding episode occur prior to Visit 2, the patient should still attend the visit as scheduled. Sampling must be collected prior to dosing.

To ease the work flow at site, it is allowed to perform some of the assessments on the day prior to the surgery, if necessary, see Table 2–1 Visit Flow Chart.

All patients must receive bleeding preventive treatment during and after the surgery with N8-GP in doses calculated based on the FVIII activity level of N8-GP measured in the individual patients at the Screening Visit, see Section 8.1.1. Patients must receive a pre-loading dose of N8-GP administered no more than 1 hr prior to expected start of the surgical procedure (defined as “knife to skin”). For dosing during surgery and the Post-operative Period, please see Section 5.4.1.

Some assessments will be made prior to, during and following surgery, please refer to Table 2–2 for a detailed overview of assessments made during the Day of Surgery.

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

At the Day of Surgery the following assessments will be performed and/or recorded in the eCRF:

- Confirmation of In/exclusion criteria, see Sections 6.2 and 6.3
- Withdrawal criteria, see Section 6.5
- Adverse events, see Section 12.1
- Concomitant medication, see Section 11

- Bleeding episodes and/or eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Surgical Interventions, see Section 8.2.1
  - Clinical evaluation of haemostatic response, see Section 8.2.1.1
  - Consumption of N8-GP, see Section 8.2.1.2
  - Blood product transfusions, see Section 8.2.1.3
  - Evaluation of wound haematoma, see Section 8.2.1.4
  - Drain volume, see Section 8.2.1.5
- eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Physical examination, see Section 8.3.3
- Vital signs, see Section 8.3.4
- Body measurements (weight only), see Section 8.3.5
- Check date and time of last coagulation factor (N8-GP) administration, see Section 8.4.4
- Infusions, see Section 8.4.6
- Administration of trial product, see Section 8.5.1

Blood sampling for local laboratory assessments:

- Haemoglobin, see Section 8.2.1.6
- FVIII activity, see Section 8.3.7.2
- Haematology, see Section 8.3.7.3

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see Section 8.3.6.1
- N8-GP binding antibodies, see Section 8.3.6.2
- Biochemistry, see Section 8.3.8.2
- Coagulation parameters, see Section 8.3.8.3
- FVIII activity, see Section 8.3.8.4

Trial material, training and reminders

- eDiary review and rating severity of bleeding episodes, see Section 8.4.7 and 8.2.2
- Home treatment/eDiary entry training, see Sections 8.5.4 and 8.4.7
  - It is of utmost importance that the patient is carefully instructed in how to complete the eDiary and trial product administration at home. The trial personnel must monitor treatment compliance carefully
- Drug accountability and dispensing in IV/WRS, see Section 9.4 and 10

Assessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3. All the assessments pertaining to the Screening Visit must have been done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. These results from pathfinder™ 2 will then be used in pathfinder™ 3. Patients coming from the

on-demand treatment arm in pathfinder™ 2 must have FVIII activity recovery level measured at the Screening Visit. All assessments at Visit 1 and 2 mentioned above must be performed/evaluated.

Furthermore patients are able to undergo emergency surgery in this trial whilst still participating in pathfinder™ 2 allowing these patients to proceed directly to Visit 2, Day of Surgery, provided there are sufficient supplies of pathfinder™ 3 trial product at site. The site must ensure that adequate supply of pathfinder™ 3 N8-GP trial product is present to cover the unplanned surgery period without compromising the continuation of any other enrolled patients at the site. The site must notify the IV/WRS in conjunction with the emergency surgery. Furthermore the screening information, including the FVIII activity recovery assessment and FVIII inhibitor test must be done and data must be available from the proceeding visit in the pathfinder™ 2 trial.

For patients undergoing emergency surgery the following assessments for Visit 2 should additionally be performed and/or recorded in the eCRF:

- Informed consent form, signed and dated, see Section 19.1
- In/exclusion criteria, see Sections 6.2 and 6.3
- Concomitant illness and medication, see Section 11
- ECG, see Section 8.3.2
- Body measurements (as at Visit 1), see Section 8.3.5
- PRO questionnaires, see Section 8.4.5
- Dispensing trial card, see Section 8.5.2
- Dispensing/adjusting eDiaries, see Section 8.5.3

8.1.3 Visit 3 to Visit 4 - Post-operative Period

The Post-operative Period consists of Day 1 to Day 14. The following assessments must be performed daily during Visit 3 (Days 1-6) and once during Visit 4 (Days 7-14). The EOT Visit cannot be scheduled earlier than Day 14.

Before the EOT Visit and re-entering the pathfinder™ 2 trial the patient should be judged by the Investigator to be ready to continue either the prophylactic or on-demand treatment as previously decided upon in the pathfinder™ 2 trial. If not, the Post-operative Period must be extended as judged by the Investigator beyond Day 14 and the Investigator/medically qualified person must perform this visit schedule with the patient once every week.

When the patient is discharged from the hospital, the patient must record bleeding episodes, dosing of N8-GP etc., in the eDiary (refer to Section 8.4.7 for details).

During the Post-operative Period it is recommended to administer N8-GP according to Section 5.4.1.

The samples taken 30 min (± 5 or 10 min) post-dose should not be taken from the same vein as previously used for administration of N8-GP.

In the Post-operative Period (Visit 3 and 4) the following assessments will be performed and/or recorded in the eCRF:

- Withdrawal criteria, see Section 6.5
- Adverse events, see Section 12.1
- Concomitant medication, see Section 11
- Surgical Interventions, see Section 8.2.1
  - Clinical evaluation of haemostatic response, see Section 8.2.1.1 and 8.2.2.2
  - Consumption of N8-GP, see Section 8.2.1.2
  - Blood product transfusions, see Section 8.2.1.3
  - Evaluation of wound haematoma, see Section 8.2.1.4
  - Drain volume, see Section 8.2.1.5
- Bleeding episodes and/or eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Physical examination, see Section 8.3.3
- Vital signs, see Section 8.3.4
- Body measurements (weight only), see Section 8.3.5
- Infusions, see Section 8.4.6
- Administration of trial product, see Section 8.5.1

Blood sampling for local laboratory assessments:

- Haemoglobin, see Section 8.2.1.6
- FVIII activity, see Section 8.3.7.2
- Haematology, see Section 8.3.7.3

Blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.3.8.2
- Coagulation parameters, see Section 8.3.8.3
- FVIII activity, see Section 8.3.8.4

Trial material, training and reminders

- An appointment for the next visit should be made.
- Home treatment/eDiary entry training, see Sections 8.5.4 and 8.4.7
  - It is of utmost importance that the patient is carefully instructed in how to complete the eDiary and trial product administration at home. The trial personnel must monitor treatment compliance carefully
- eDiary review and rating severity of bleeding episodes, see Section 8.4.7 and 8.2.2
- Drug accountability and dispensing in IV/WRS, see Section 9.4 and 10

– Handout sufficient amount of N8-GP for possible home treatment following to Visit 3, 4 and EOT

8.1.4 Visit 5 – EOT

The patient can attend the EOT Visit earliest at Day 14. This includes minimum 96 hrs of wash-out before the inhibitor sampling at the EOT Visit.

If the patient is ready for having the EOT Visit at Day 14, Visit 4 and the EOT Visit may be joined and all assessments pertaining to Visit 4 and EOT Visit must be performed once.

Before the EOT Visit and re-entering the pathfinder™ 2 trial the patient should be judged by the Investigator to be ready to continue either the prophylactic or on-demand treatment as previously decided upon in the pathfinder™ 2 trial. If not, the Post-operative Period must be extended beyond Day 14 as judged by the Investigator.

After having the EOT Visit, patients will return to pathfinder™ 2, reentering the prophylactic or on-demand treatment arm as per their prior participation in the trial.

A wash-out period of minimum 96 hrs is necessary prior to FVIII inhibitor and N8-GP antibodies sampling at EOT.

If a patient is prematurely withdrawn from the trial the Investigator must ensure that the procedures for Visit 5 (EOT Visit) are undertaken, if possible. A withdrawal session must be completed in the IV/WRS. The primary reason (AE, noncompliance with protocol or other) for discontinuation must be specified in the eCRF. If a subject is discontinued due to an ongoing AE from pathfinder™ 2, the primary reason for discontinuation must be entered under ‘other’ in the end of trial form. Even if the subject is not able to attend the visit, trial drugs should be returned, the end of trial form must be completed, a withdrawal call and drug accountability must be performed in the IV/WRS and the affirmation statement in the case book must be electronically signed off. The patient has been withdrawn from trial treatment and treated according to Investigator’s discretion.

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 at central laboratory, preferably prior to initiation of treatment with another FVIII product.

At EOT Visit the following assessments will be performed and/or recorded in the eCRF:

- Withdrawal criteria, see Section 6.5
- Concomitant medication, see Section 11
- Adverse events, see Section 12.1

- Bleeding episodes and/or eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Evaluation of wound haematoma, see Section 8.2.1.4
- ECG, see Section 8.3.2
- Physical examination, see Section 8.3.3
- Vital signs, see Section 8.3.4
- Body measurements (weight only), see Section 8.3.5
- Check date and time of last coagulation factor administration, see Section 8.4.4
- HE assessments, see Section 8.4.5

Blood sampling for local laboratory assessments:

- Haematology, see Section 8.3.7.3

Blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.3.8.2
- Coagulation parameters, see Section 8.3.8.3
- FVIII activity, see Section 8.3.8.4
- FVIII inhibitors, see Section 8.3.6.1
- N8-GP binding antibodies, see Section 8.3.6.2

Trial material, training and reminders

- eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Return eDiary
- Drug accountability for all trial products dispensed or any product returned from the previous visits, see Section 9.4 and 10
- Make completion call in IV/WRS, see Section 10
- Make withdrawal call in IV/WRS, see Section 10
- Affirmation statement
- End of trial

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, the patient should be scheduled for an EOT Visit as soon as possible and within 1 week after a positive inhibitor test is confirmed via re-testing, preferably prior to initiation of treatment with another FVIII product. One month (4 weeks ± 2 weeks) after the EOT Visit the patient should 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 ± 2 week as long as clinically warranted up until 3 months after confirmation of the FVIII inhibitor.

A wash-out period of minimum 72 hrs is necessary prior to FVIII inhibitors sampling at FU Visit.

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

- Bleeding episodes since last visit
- Vital signs, see Section 8.3.4

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see Section 8.3.6.1

Reminder

- Follow up on any AEs according to Section 12.1
- End of trial
- Affirmation statement

8.1.6 Unscheduled Visits

It is possible to perform Unscheduled Visits during the trial. The Unscheduled Visit can be performed at any time after the enrolment to and until the EOT Visit as either a telephone contact 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. If the patient has any concerns regarding surgery (no improvement/worsening), the patient should contact the Investigator/Surgeon.

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

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

- Withdrawal criteria, see Section 6.5
- Concomitant medication, see Section 11
- Adverse events since previous visit, see Section 12.1
- eDiary review and rating severity of bleeding episodes, see Section 8.2.2 and 8.4.7
- Bleeding episodes (including date, severity and location) and eDiary compliance review, see Section 8.2.2 and 8.4.7
- ECG, see Section 8.3.2
- Physical examination, see Section 8.3.3
- Vital signs, see Section 8.3.4
- Body measurements, see Section 8.3.5
- Antibodies (FVIII inhibitors and N8-GP binding antibodies), see Section 8.3.6.1
- N8-GP specific IgE, IgG and anti-HCP (Host Cell Proteins) antibodies (conditional test), see Section 8.3.6.3
- FVIII activity, see Section 8.3.7.2 and 8.3.8.4
- Haematology, see Section 8.3.7.3

- Biochemistry, see Section 8.3.8.2
- Coagulation parameters, see Section 8.3.8.3
- Check date and time of last coagulation factor administration (N8-GP) prior to Unscheduled Visit, see Section 8.4.4
- Administration of trial product, see Section 8.5.1
- Home treatment/eDiary training, see Sections 8.5.4 and 8.4.7
- Dispensing of N8-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10
- Drug accountability of N8-GP, see Section 9.4 and 10
- IV/WRS call, se Section 10

8.2 Assessments for Efficacy

8.2.1 Surgical Interventions

Surgical procedure and duration:

- Type of surgery (e.g. arthroscopy)
- Indication (e.g. haemarthrosis)
- Location of surgery (e.g. left knee joint)
- Elective or emergency surgery
- Duration of surgical procedure
  - Start of surgery: date and time of first incision ("knife to skin")
  - Stop of surgery: date and time of skin closure ("last stitch")
- Clinical narrative incl. description of any complication, anticipated blood loss before surgery and estimation of blood loss after surgery, re-operation etc
  - Summary of surgery (through day 0)
  - Summary of Post-operative Period (Day 1-6)
  - Summary of Post-operative Period (Day 7-14)

8.2.1.1 Clinical Evaluation of Haemostatic Response

After completion of surgery (defined as "last stitch") (Day 0, Visit 2) a clinical evaluation of haemostatic response during surgery will be assessed by the Surgeon or Anaesthesiologist or Investigator using a 4-point scale based on experience as follows:

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

Clinical evaluation of haemostatic response during the Post-operative Period, Days 1-6 and 7-14 will be assessed by the definitions described in section 8.2.2.2.

8.2.1.2 Consumption of N8-GP

Consumption of N8-GP (U/kg BW) during Surgery, Day 0 and Post-operative Period, Days 1-6 and 7-14 must be recorded, see Section 8.5.1.

8.2.1.3 Blood Product Transfusions

The following must be recorded for blood product transfusions during Day of Surgery, Visit 2 and hospitalised days in the Post-operative Period:

- Type (e.g red blood cells (RBC) or platelets
- Haemoglobin (g/dL) prior to RBC transfusion and platelet count (x 10^9/L) prior to platelets transfusion
- Quantity (number of units and mL)
- Start date and time

RBC, platelets and other transfusion products can be administered as clinically warranted. See Section 11 for medications not allowed during this trial.

8.2.1.4 Evaluation of Wound Haematoma

To be evaluated upon completion of the surgical procedure at Day of Surgery (Visit 2). Furthermore to be evaluated daily during the Post-operative Period Days 1-6 (Visit 3), once during Days 7-14 (Visit 4) and at EOT Visit.

- Wound haematoma, if assessable: yes /no
  - Estimate volume of wound haematoma (mL), cross sectional area on skin (cm^2)
  - Has the wound haematoma been evacuated: yes/no
  - Text description of wound haematoma evacuation procedure

8.2.1.5 Drain Volume

Drainage to be evaluated daily (within the last 24 hrs ± 4 hrs) during Day of Surgery, Visit 2 and hospitalised days in the Post-operative Period:

- Yes /no
  - Estimate Volume of drainage (mL)

8.2.1.6 Haemoglobin

At Day of Surgery, Visit 2, haemoglobin must be measured just prior to, during and following surgery, see definition in section 4.3 (at 0, 1 hr ± 20 min and 24 hrs ± 4 hrs post start of surgery). Exact date and time of sampling must be documented. “Knife to skin” corresponds to time point = 0.

In addition haemoglobin will be assessed by the local laboratory prior to prescribed RBC blood product transfusion.

8.2.2 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. When the patient is hospitalised or otherwise unable to enter a bleeding episode, the Investigator will have to report in the eCRF, please refer to Section 8.1.6. It is always 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.

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 bleeding episode at home, treatment with N8-GP should be initiated as soon as it is identified and the patient must contact the Investigator immediately and irrespectively of severity of the bleeding episode, please refer to Section 8.2.2. When the patient is in contact with the Investigator, it is the responsibility of the Investigator to assess the severity of the bleeding episode. Patients with severe bleeding episodes must visit the site within 24 hrs. For definition of the severity of a bleeding episode please refer to Section 8.2.2.1.

Joint bleeds are either categorised as target joint or non-target joint bleeds. Target joints are defined as 3 or more bleeds 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.

From Visit 1 to Visit 2 (Day of Surgery)
All treatment requiring bleeding episodes and any haemostatic treatment administered at home must be recorded in the eDiary.

Day of Surgery
All bleeding episodes and any haemostatic treatment administered must be recorded in the eCRF.

During the Post-operative Period (Days 1-14)
All bleeding episodes occurring during the Post-operative Period (Days 1-14) must be recorded in the eCRF by the investigator/medically qualified person, while the patient is hospitalised. When the patient is discharged from the hospital all bleeding episodes and any haemostatic treatment administered must be recorded in the eDiary by the patient, see Section 8.4.7.

If the late Post-operative Period is extended beyond Day 14
The Investigator/medically qualified person must maintain the visit schedule with the patient every week. It is important that the Investigator/medically qualified person reminds the patient or the patient's caregiver to record details on bleeding episodes, their treatment and assessment thereof in the eDiary, see Section 8.4.7.

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

- Onset of each bleeding episode (date and time)
- Cause of bleed (spontaneous, traumatic, surgery (minor/major))
- Location of the bleed
- Haemostatic drug used for treatment, dose(s) and time(s) of administration
- Pain relieving medication
- Other therapy used (compression, ice or other)
- Categorisation of bleed (mild/moderate or severe), in the eCRF
- Clinical evaluation of the haemostasis effect (excellent, good, moderate or none)
- Stop of bleed (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.

8.2.2.1 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 hospitalised or unable to fill in the eDiary, the Investigator or trial personnel can enter the data in the eCRF. Traumatic bleeds at other locations than described above can always be considered severe at the investigators discretion.

8.2.2.2 Definition of Haemostatic Response

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

The assessment for haemostatic response will be made by the patient or patient's caregiver and discussed with the Investigator during visits to the site.

8.2.2.3 Classification of a Bleeding Episode

- spontaneous, traumatic, surgery (minor/major) or re-bleed

A re-bleed is defined as when after an initial period of improvement, there is a worsening of the bleeding site conditions in the same location, either on treatment or *within* 72 hr after stopping treatment. It is considered as a new bleed if worsened >72 hrs after stopping of treatment. Classification of re-bleeds will be done by the trial statistician based on collected trial data at the time of statistical analysis.

8.3 Assessments for Safety

Clinical assessments should preferably be performed prior to blood sampling and trial product administration (where applicable). All assessments/measurements will be recorded in the eCRF unless stated otherwise.

8.3.1 Adverse Events

Monitoring of AEs will be performed from screening to EOT visit, according to the procedures described in Section 12.

For recording of bleeding episodes please refer to Section 12.1.3.

8.3.2 ECG

Electrocardiograms (ECGs) will be performed at Screening and EOT Visit. ECG should preferably be performed prior to blood sampling and prior to trial product administration at Screening Visit. Electrocardiograms will be performed using a 12-lead 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 and reported as specified in Section 12.

8.3.3 Physical Examination

Physical examination will be performed at Visit 1, 2, 3 (Days 1 and 6 only), Visit 4 (only once during Visit 4 (during Days 7-14)) and EOT Visit. The physical examinations will be performed according to local procedure and should preferably be performed prior to blood sampling and prior to trial product administration, where applicable.
Physical examinations should include:

- General appearance
- Head, Ears, Eyes, Nose, Throat and Neck
- Respiratory System
- Cardiovascular System
- Gastrointestinal System, including mouth
- Musculoskeletal System
- Central and Peripheral Nervous System (general evaluation)
- Skin
- Lymph node palpation

Clinically significant findings present at screening must be documented as concomitant illness and during the trial as AEs and reported as specified in Section 12.

8.3.4 Vital Signs

Vital signs will be performed at Visit 1, 2, 3 (Day 1 and 6 only), Visit 4 (once during Days 7-14 and hereafter once weekly) and EOT Visit. Vitals signs should preferably be performed prior to blood sampling and prior to trial product administration, where applicable, and are additionally assessed pre-dose and post-dose (30 min ± 10 min) at the Day of Surgery (Visit 2).

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.

Vital signs include assessment of:

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

BP and pulse rate will be measured using standard techniques. Measurements will be reported in the eCRF.

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

Any clinically significant worsening from baseline must be reported as an AE (see section 12).

8.3.5 Body Measurements

Body measurements will be performed at Visit 1, Visit 2, Visit 3 (Day 1 and 6 only), Visit 4 (once during Days 7-14 and hereafter once weekly) and EOT Visit. Body measurements should preferably be performed prior to blood sampling and prior to trial product administration, where applicable and include:

- Weight, wearing light clothing only and without shoes (kg/pounds)
- Height, without shoes (cm/inches) (Visit 1 only)
- Body mass index calculation (kg/m^2) (Visit 1 only)

8.3.6 Antibodies

Blood samples for assessment of FVIII inhibitor and N8-GP binding antibodies will be drawn pre-dose of N8-GP administration at Visit 1, 2 and EOT Visit. A wash-out period of minimum 96 hrs is necessary prior to FVIII inhibitor and N8-GP binding antibodies sampling. 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.

8.3.6.1 FVIII Inhibitors

All patients will be examined for the development of FVIII inhibitors at Visit 1, 2 and EOT Visit. 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, peak levels 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 FU Visit must be scheduled 4 weeks ± 2 weeks after the EOT Visit, if possible and additional monthly FU Visits may be arranged at intervals of 4 weeks ± 2 weeks 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 assay.[13]. 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. Residual drug levels of N8-GP >0.015 IU/mL can interfere with the modified Bethesda assay and may in some instances result in false negative inhibitor tests. Therefore N8-GP binding antibodies will be closely monitored throughout the trial. A significant increase and a negative Bethesda assay (and the recovery value is not evaluated as normal (guidance < 60%)) will result in a new inhibitor sample collected after 7 days wash-out.

When inhibitor results are negative and there is clinical suspicion that inhibitor may be present FVIII levels will be measured. FVIII levels <0.015 IU/mL will confirm a negative inhibitor test. FVIII levels >0.015 IU/ml can result in the need for collection of sampling for inhibitor testing following a 7 days wash out period.

A patient that tests negative for inhibitors following a 7 days wash out and with FVIII levels <0.015 IU/mL will confirm a negative inhibitor test and the patient will continue in the trial.

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 (≥0.6BU) – 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 made, see Section 12.6.3.

8.3.6.2 N8-GP Binding Antibodies

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 (RIA) 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 binding 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 characterised 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 develop N8-GP binding antibodies and the incremental recovery value at this 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 hrs wash-out is not sufficient to avoid drug interference in the inhibitor assay.

8.3.6.3 N8-GP specific IgE, IgG and anti-HCP Antibodies (Conditional Test)

Any patient who experiences an unexpected allergic/anaphylactic reaction will be assessed for inhibitors and antibodies against drug product content, such as IgE/IgG against N8-GP and anti-HCP antibodies. 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.

8.3.7 Local Laboratory Tests

The local laboratory will analyse and report all laboratory safety tests related to haematology 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 2-5 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 results (reports) are considering source data and should be kept in 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 min ± 5 min after administration of N8-GP.

Storage, handling, and disposition of samples analysed at local laboratories, will be performed according to local laboratory procedures. The laboratory test results provided by the local laboratory should be recorded in the below units or in other predefined units specified in the eCRF.

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

8.3.7.1 Haemoglobin

See Section 8.2.1.6.

8.3.7.2 FVIII Activity and FVIII Inhibitors

The Investigator/Surgeon can at any time during the trial perform additional FVIII activity and inhibitor assessments at his/her discretion.

- FVIII activity (% or U/mL)
- FVIII inhibitor test

The Investigator/Surgeon should perform local laboratory assessments of FVIII activity in parallel with the central laboratory assessments (see Section 8.3.8.4) during surgery and the post-operative days in order to be able to adjust the dose level of N8-GP and aim for the recommended FVIII plasma level, see Section 5.4.1. All FVIII activity tests, time of the sample and the results from the local laboratory, must be recorded in the eCRF. When FVIII activity measurements are made, one-stage clot and/or chromogenic activity assays must be used. Moreover a reference standard provided by Novo Nordisk must be used when running the assays. The reference standard will be provided by Novo Nordisk together with a description of how to handle, store and use it.

If an Investigator suspects lack of efficacy e.g. due to inhibitor formation an Unscheduled Visit must be scheduled and a blood sample must be sent to the central laboratory for confirmatory analysis (please also refer to Section 8.3.6 regarding details on inhibitor formation. Only the laboratory results from the central laboratory will be reported to Novo Nordisk.

8.3.7.3 Haematology

Blood samples for analysis of haematology will be collected at the Screening Visit, daily during Visit 2 (Day 0) and 3 (Days 1-6), once during Days 7-14 and hereafter once every week of Visit 4 and at the EOT Visit. Haematology are drawn pre-dose and additionally post-dose (30 min ± 10 min) at Day of Surgery (Visit 2), and include assessment of:

- Platelet count (thrombocytes) (x 10^9/L)

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

Platelet count will be assessed prior to any prescribed platelet blood product transfusion and haemoglobin will be assessed prior to RBC transfusion, see Section 8.2.1.3.

8.3.8 Central Laboratory Tests

A central laboratory will analyse and report all laboratory safety tests performed in this trial related to coagulation parameters, biochemistry 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. Investigators will receive test results by fax or e-mail. Upon review of the central laboratory results the investigator must sign and date the laboratory reports.

Clinically significant values must be recorded as an AE or if present at the Screening visit it should be recorded as Concomitant illness.

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 in the Central Laboratory Manual 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 laboratory. 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, 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.

8.3.8.1 Antibodies

See Section 8.3.6.

8.3.8.2 Biochemistry

Blood samples for analysis of biochemistry will be drawn pre-dose, if applicable at the Screening Visit, daily during Visit 2 (Day 0) and 3 (Days 1-6), once during Days 7-14 and hereafter once every week of Visit 4 and at the EOT Visit and include assessments of:

- 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)

8.3.8.3 Coagulation Parameters

Blood samples for coagulation parameters will be collected pre-dose at the Screening Visit, daily during Visit 2 (Day 0) and 3 (Days 1-6), once during Days 7-14 and hereafter once every week of Visit 4 and at the EOT Visit. Additionally coagulation parameters will be collected post-dose (30 min ± 10 min) at Visit 1 and post-dose (30 min ± 10 min, 4 hrs ± 1 hr and 8 hrs ± 2 hrs) at Day of Surgery, Visit 2.

- Activated partial thromboplastin time (aPTT) (sec)
- INR (Prothrombin time (PT)) (sec)

8.3.8.4 FVIII Activity

Blood samples for analysis of FVIII activity (FVIII:C) is analysed using one-stage clot and chromogenic assay. Recovery is the FVIII level 30 min after trial product administration relative to

the dose administered. The trough level is defined as the lowest level of FVIII measured immediately prior to dosing.

Blood samples for analysis of FVIII activity will be collected at the Screening Visit, daily during Visit 2 (Day 0) and 3 (Days 1-6), once during Days 7-14 and hereafter once every week of Visit 4 and at the EOT Visit.

Pre-dose and 30 min ± 5 min post dose samples must be collected at Visit 1 after administration of 50 U/kg BW N8-GP and at the Day of Surgery (Visit 2) additional samples will be taken post-dose (loading dose), and include: 30 min ± 5 min, 4 hrs ± 1 hr and 8 hrs ± 2 hrs.

Blood samples for analysis of FVIII activity pre-dosing (trough) and 30 min ± 5 min post dosing (recovery) will be collected from all patients at each dose given when hospitalised/at visits. The sampling time points are relative to completion of N8-GP administration, and actual time must be documented. For the scheduled visits where dosing will not occur there will only be one sample as only trough will be measured.

The analysis of plasma FVIII activity will be performed at a central laboratory selected by Novo Nordisk by the use of two different assays:

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.

One-stage Clot Activity Assay

A bioassay (FVIII:C clot assay), which measures the activity of the compound in a specific process (clot formation). The FVIII:C assay is a validated 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.

8.4 Other Assessments

8.4.1 Demography

Demography will be obtained from the baseline data recorded on the patient in pathfinder™ 2.

8.4.2 Genotype

FVIII genotype will be obtained from the data recorded on the patient in pathfinder™ 2, if done and the patient has consented to that the result can be used for this trial purpose.

8.4.3 Medical History

The following Medical history data will be obtained from the baseline data recorded on the patient in pathfinder™ 2, including:

- Medical history
- Haemophilia details
- Bleeding treatment history
- History of bleeding episodes
- History of surgery

8.4.4 Date and Time of Last Coagulation Factor Administration

Check date and time of last administration of coagulation product at Visit 1, 2 and EOT Visit in the data from the patients eDiary.

8.4.5 PRO Questionnaires and Health Economic Assessments

PRO Questionnaires

Different Patient Reported Outcome (PRO) questionnaires will be used to measure health related quality of life and treatment satisfaction prior to surgery. These measurements will be used to adjust PRO measurements from the pivotal trial for surgery confounding.

The following questionnaires should be completed at Visit 1 by the patients and, where relevant, also by the parent/LAR, preferably before any other trial related activity, except informed consent.

For trial patients aged 12-16:

- HAEMO-QOL: Questionnaire for adolescents (8-12 years, 13-16 years)
- EQ-5D: Questionnaire (13 years and above) and EQ-5D VAS
- HAEMO-QOL: Parents proxy; Questionnaire for parents/LARs of 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) and EQ-5D VAS

These PRO instruments are designed to minimise the burden on the patient/parent/LAR in providing the information. They were 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 this case the questionnaire is not to be completed.

It is the responsibility of the Investigator to review the subject PRO questionnaires regarding possible AEs, see Section 12.

Health Economics (HE) Variables

The following HE assessments will be recorded in the eCRF at the EOT Visit:

- Length of stay (days) in the hospital and days in intensive care

8.4.6 Infusions

Intravenous fluid infusions (e.g. NaCl, albumin etc.) must be recorded during Day of Surgery, Visit 2 and hospitalised days in the Post-operative Period. Infusions are recorded in concomitant medication, see Section 11:

- Type (crystalloid or colloids)
- Quantity (number of units or mLs)
- Start date and time

8.4.7 eDiaries

In this trial electronic diaries (eDiaries) will be used. The patient or the patient's caregiver must bring the eDiary whenever the patient visits the site.

The following information will, as a minimum, be captured by the patient or the caregiver in the eDiary:

Treatment

- FVIII product used
- Prophylaxis or treatment of bleed
- Dose level
- Date and time of dose administration

Bleeding episodes

- Onset of each bleeding episode (date and time)
- Cause of bleed (spontaneous, traumatic, surgery (minor/major))
- Location of bleed
- Haemostatic drug used for treatment (dose and time of administration)
- Pain relieving medication
- Other therapy used (ice, compression, or other)
- Evaluation of haemostasis effect (excellent, good, moderate, none)
- Stop of bleed (date and time)

The Investigator must carefully instruct the patient in how to evaluate a bleeding episode, the haemostasis 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 the visit to ensure consistency/compliance. The information in the patient's eDiary is regarded as source data. In case of information missing from the eDiary is available in the medical records, then this information can be used.

It is the Investigator's responsibility to rate the severity of all reported bleeding episodes in the eCRF.

Between Visit 1 and Visit 2 (Day of Surgery) and when the patient is discharged from hospital following surgery, the patient or the patient's caregiver must ensure that all bleeding episodes, their treatment and assessment thereof is captured in the eDiary. Trial product administration performed at the site should also be entered in the eDiary by the patient before Visit 2 and when discharged from hospital. Bleeding episodes and trial product administration performed while the patient is hospitalised will not be entered in the eDiary but in the eCRF.

8.5 Trial Material, Training and Reminders

8.5.1 Administration of Trial Product

N8-GP will be administered while the patient is in a comfortable position.

The samples taken 30 min (± 5 or 10 min) post dose, should not be taken from the same vein as previously used for administration of N8-GP (please refer to Section 8.1 and Table 2–1 for details on sampling at each visit).

The injection should be performed as a slow bolus i.v. injection. The date and the actual time of completion of the injection must be recorded in the eCRF. The actual time of completion of the injection will be recorded and corresponds to trial time point = 0.

Trial product administration for the Screening Visit, Visits 2 – 4 and Unscheduled Visit include:

- Dose of N8-GP administered (U/kg BW)
- Trough level (if applicable)
- Recovery (if applicable)

8.5.2 Dispensing Trial Card

At the Screening Visit the patient will receive a trial card stating that the patient is participating in a clinical trial. Phone numbers and contact persons at the investigational site will be listed.

8.5.3 Dispensing/adjusting eDiaries

The eDiary will either be dispensed to the patient at the first visit or their current eDiary will be adjusted for participation in this surgery trial. For details regarding entry of patient eDiary data into the eDiary, please refer to Section 8.4.7.

8.5.4 Home Treatment Training

Home treatment with administration of N8-GP starts after the N8-GP administration has been performed in the site at Visit 1. Home treatment may be given by the patient, patient's caregiver or a home nurse as applicable. They should be comfortable with the reconstitution and administration process prior to the home treatment period. Patients should treat themselves at home between Visit 1 and Visit 2 and when discharged from the hospital after surgery. All patients must be carefully instructed in recognising and dealing with signs and symptoms of an anaphylactic reaction. This includes knowledge of which medical facility to contact in this situation. Training should be documented in the medical records.

If a patients experience bleeding episodes due to exceeding the time between doses, the Investigator must retrain the patient and/or the patient caregiver(s) (a close person who helps the patient in their daily life. It is not the Investigator or the site staff). The training must be documented in the medical records.

8.6 Patient Compliance

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

Failure to comply with scheduled visits and N8-GP administration may result in withdrawal in accordance with the protocol withdrawal criteria (please refer to Section 6.5). Treatment with FVIII concentrates other than N8-GP during the trial is not allowed and violation of this will lead to withdrawal due to non-compliance (please refer to Section 11).

9 Trial Supplies

9.1 Trial Products

The following trial product (IMP) 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 (N8-GP) powder must be reconstituted prior to administration. After reconstitution with 4.3 mL Sodium Chloride 0.9% each 2000U/4mL vial contains 500U/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 than Sodium Chloride 0.9%.

9.2 Trial Product Administration

The trial product should be administered as a slow bolus i.v. for all trial product administrations.

The administrations in this trial will be performed both at home and in hospital. All patients and/or parents/caregivers will be instructed by the Investigator how to handle home administration before first dose administration at home.

9.3 Packaging and Labelling of Trial Products

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

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. Detailed information will be provided in the TMM. Each drug product vial will have a unique Dispensing Unit Number (DUN) for drug identification.

Labelling will be in accordance with Annex 13[14], local law and trial requirements.

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

9.4 Storage, Handling, Accountability and Destruction of Trial Product

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 hrs at room temperature (below 30°C) or 24 hrs 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 and monitor, record and evaluate the temperature. The storage facilities must be checked daily using a calibrated temperature logging device. A temperature log for temperature recording (actual, minimum, and maximum temperature on working days) must be kept at the Investigator site. The Investigator must contact the Monitor in case of deviation outside the acceptable temperature range.

The temperature recorder should be either:
- electronic with minimum interval of logging of 1 hr 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 DUN 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 on the 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 trial site rests with the head of the trial site. The head of the trial site should assign some or all of the responsibilities for accountability of the trial products at the 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 trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary Supply

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

10 Interactive Voice/Web Response System

A trial specific Interactive Voice/Web Response System (IV/WRS) will be set-up, and can be accessed at any time by 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

In order to have drug shipped and available at site for the pathfinder™ 3 trial surgery period, a planned date of surgery must be entered in IV/WRS in the pathfinder™ 2 at least 14 days in advance of Visit 1.

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).

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

Details of all concomitant illnesses and medication must be recorded at trial entry (i.e. at the first visit). 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 includes preferably generic name and dose, and at a minimum start date, stop date or continuation and indication.

Concomitant medication at Day of Surgery includes anaesthetics and other haemostatic therapy used during surgery.

If any other haemostatic medication/therapy is used during and after surgery, please indicate this as concomitant medication and in the clinical narrative (see Section 8.2.1).

Vaccinations from time of screening should be recorded as concomitant medication at the time of vaccination. If at all possible, planned vaccination should be postponed beyond the first 3 months after this surgery trial.

The following medications are not allowed during the course of the trial:

- Bypassing products: rFVIIa, pd-PCC and pd-aPCC
- Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like FFP or cryoprecipitate

The following medications are not allowed unless clinically warranted:

- 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, Technical Complaints 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-subject 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 subject 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 subject 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"* 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.

c) The term "*disability/incapacity*" means that following the event the subject or clinical investigation subject 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 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 subject 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 Complaints

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 as for SAEs (see Section 12.2), irrespective of the MESI fulfils a SAE criterion.

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.

The following events are defined as MESIs in this trial:

1. **Medication errors concerning trial product:**

- Administration of wrong drug or use of wrong device
- Wrong route of administration, such as intramuscular instead of subcutaneous

- Administration of a high dose with the intention to cause harm, e.g. suicide attempt
- Administration of an accidental overdose i.e. dose which may lead to significant health consequence as judged by the investigator irrespective of whether a SAE criterion is met

2. **Inhibitor formation against FVIII**
   Blood samples for measurement of FVIII inhibitors will be analysed at the central laboratory selected by Novo Nordisk and if *positive* (BU ≥0.6/mL) should be reported as a MESI. A subject is only considered to be inhibitor positive if the inhibitor test is positive (BU ≥0.6/mL) at two consecutive tests - sampled preferably within 2 weeks

3. **Allergic reaction including Anaphylactic reaction as defined by Sampson et al.[15] (see below).** Allergic reactions included but 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.[15]. 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. **Suspected transmission of an infectious agent via a trial product**

MESIs are reported by completing an AE form and safety information forms. 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[15]

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, wheese-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   - Reduced blood pressure (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 subject (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (eg, dyspnea, wheese-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 subject (minutes to several hours):
   - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (low systolic blood pressure for children is defined as <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, Peak expiratory flow; BP, blood pressure.

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 ≥ 0.2mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)
   - 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 hrs 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.

12.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an AE must be collected and reported.

During each contact with the trial site (visit or telephone, excluding the follow up visits due to inhibitor development or safety visits where the subject is not seeing the Investigator or his staff e.g. visit to the laboratory) the subject 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 subject, must be recorded by the Investigator and evaluated.

Novo Nordisk' assessment of expectedness is done according to the reference documents:

- Investigator's Brochure, 40K PEG-N8.[7]

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 SAEs complete a safety information form for each event. However, if several symptoms or diagnosis occur as part of the same clinical picture only one set of safety information form pages can be used to describe all the 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 GCP.[10]

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.

Investigators will be notified of trial-related SAEs in accordance with the local requirements in force and ICH GCP.[10]

The monitor must be informed accordingly.

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 GCP.[10]

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.

Non-serious AEs must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. 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".

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 form 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.

Follow-up on AEs that were not Recovered in the Preceeding Trial

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

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

A non-serious AE that is reported as not related and not severe in the preceding pathfinder™ 2 trial will not be followed-up when enrolling into the present pathfinder™ 3 trial. Details on how to handle unresolved non-serious AEs when patients transfer from the pathfinder™ 2 trial into the present pathfinder™ 3 trial are described below and in Table 12–1.

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

Table 12–1 Handling of Not Recovered Non-Serious AEs from pathfinder™ 2

Severity		Outcome Categories		Relationship		AE follow- up in: pathfinder™ 2 (Pivotal)	AE in pathfinder™ 3 (Surgery)	Concomitant illness in pathfinder™ 3 (Surgery)
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™ 3 (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 on the technical complaint form why it was not collected.

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

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 details on the shipment conditions of technical complaint samples please contact the monitor.

12.4 Pregnancies in Partners of Trial Subjects

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.

12.5 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 blood pressure.

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

12.6 Safety Committees

12.6.1 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.

12.6.2 Data Monitoring Committee

As this is an open label trial, the subject 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 subjects enrolled in the trial.

12.6.3 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 one of the below mentioned stopping criteria is fulfilled in trial, enrolment of additional subjects will be put on hold. All Investigators will be informed in writing. An urgent Safety Committee meeting will be called for to decide whether or not the trial can continue with or without modifications. During the evaluation of the stopping rules the trial will be on hold meaning no new subject will be recruited. Dosing of subjects on treatment may continue while further evaluation of the SAE/MESI is made by the Safety Committee unless otherwise decided by the Safety Committee. The evaluation of fulfilment of the below stopping

rules by the Safety Committee will take into consideration whether or not the subject was dosed according to protocol.

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

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

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 CRFs

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 CRFs

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 CRF 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 CTR is available the data will be archived by Novo Nordisk.

13.4 eDiaries

Novo Nordisk will provide patients with an eDiary for electronic recording of details of their bleeding episodes, see Section 8.2.2. 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 1, 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 Novo Nordisk clinical database at defined intervals. For details on eDiary flow see Figure 13–1.

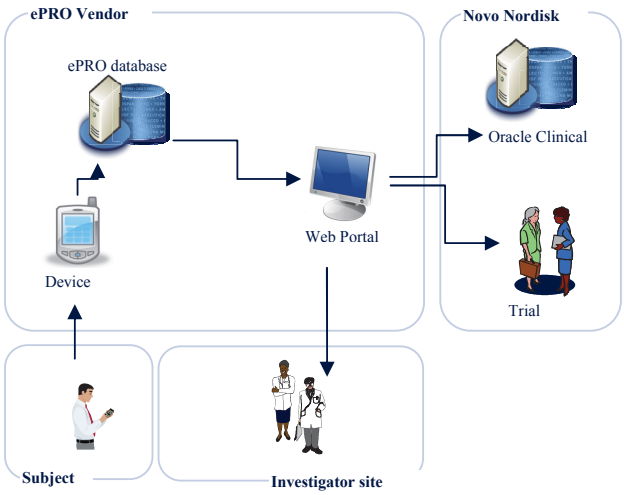


Figure 13–1 eDiary Data Flow

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 contact the site regularly. Monitoring visits to the site should be performed within 2 weeks after a patient has been screened. Time between 2 visits must not exceed 8 weeks, provided there is an active patient.

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 subjects: All data collected in the period the subject participated in the trial will be entered into the eCRF.

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

eDiaries will be provided by Novo Nordisk. Information on treatment and bleeding episodes will be collected in the eDiaries (please refer to Section 8.4.7).

The completed eDiaries are considered source data. The Monitor will verify and ensure that the eCRFs and eDiaries 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 subject and biological material obtained from the subject will be identified by subject number, trial site and trial identification number. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects 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 if an electronic medical file system is used. 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 Subjects for Analysis

17.1 Safety Analysis Set

The Safety Analysis Set (SAS) will consist of all patients exposed to trial drug (N8-GP).

17.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all patients exposed to trial drug.

18 Statistical Considerations

18.1 Sample Size Calculation

Sample size is based on recommendations in the EMEA guideline on the clinical investigation of recombinant and human plasma-derived Factor VIII products.[8]

18.2 Statistical Methods

18.2.1 General Considerations

Novo Nordisk A/S will be responsible for the statistical analysis.

18.2.2 Primary Endpoint

The primary efficacy endpoint of assessment of haemostatic effect during surgery (none, moderate, good, excellent) will be summarised and listed.

18.2.3 Confirmatory Secondary Endpoints

NA

18.2.4 Supportive Secondary Endpoints

18.2.4.1 Secondary Safety Endpoints

Treatment emergent AEs (TEAEs are defined as adverse events with onset after exposure to trial product) and SAEs will be summarised by frequency of events and frequency of patients with any event. Similar summaries for AEs cross-classified by severity and by causal relation to trial product will also be made.

Furthermore, listings will be provided displaying all AEs and SAEs (including MESIs) including relevant information.

N8-GP/rFVIII inhibitor development will be summarised and listed.

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

18.2.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarised and listed:

- Estimated blood loss during surgery
- Average consumption of N8-GP during surgery

- Haemostatic effect of N8-GP during the post-operative period Days 1-6
- Average consumption of N8-GP during the post-operative period Days 1-6
- Number of transfusions during the post-operative period Days 1-6
- Haemostatic effect of N8-GP during the post-operative period Days 7-14

18.3 Interim Analysis

In order to obtain regulatory permission to start surgery treatment in US, prophylaxis treatment in US and paediatric trial in 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.

Furthermore an interim analysis is planned to include data from at least 5 severe haemophilia A patients, undergoing 10 major surgeries in the initial New Drug Application (NDA) and Marketing Authorisation Application (MAA).

18.4 Sequential Safety Analysis/Safety Monitoring

NA

18.5 Explorative Statistical Analysis for Pharmacogenetics and Biomarkers

NA

18.6 PK and/or PD Modelling

NA

18.7 Health Economics and Patient Reported Outcome

Health economic endpoints will be summarised and listed using descriptive statistics. PRO endpoints, collected at the screening visit, will be used to adjust PRO endpoints collected in the pivotal trial for confounding due to surgery.

19 Ethics

The trial will be conducted in compliance with ICH GCP[10], applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[16]

To minimise switching between FVIII products, patients are able to undergo elective and emergency surgery in this trial whilst participating in pathfinder™ 2.

Upon completion of pathfinder™ 3, patients will return to pathfinder™ 2, reentering the prophylactic or on-demand treatment arm as per their prior participation in the trial. If a patient is prematurely withdrawn from the trial the Investigator must ensure that the procedures for EOT Visit are undertaken, if possible. In case of withdrawal due to FVIII inhibitor development, the patient should be scheduled for an EOT Visit as soon as possible and within 1 week after a positive inhibitor test is confirmed via re-testing, preferably prior to initiation of treatment with another FVIII product. One month (4 weeks ± 2 weeks) after the EOT Visit the patient must attend a FU Visit.

The patient will be offered to continue in pathfinder™ 4, if approved in country, after completion of pathfinder™ 2 where patients have the opportunity to continue with N8-GP treatment until the product is commercial available[d].

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 in question. If the patient does not wish to continue in pathfinder™ 4, the patient will consult with the Investigator to decide on the best available treatment.

19.1 Informed Consent Form for Trial Subjects

In seeking and documenting informed consent, the Investigator must comply with the applicable regulatory requirement(s), and adhere to the ICH GCP[10] and the requirements in the Declaration of Helsinki.[16]

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, informed consent form will be obtained from the subject and/or the subject's LAR prior to any trial-related activity.

[d] For UK patients only: the end of the extension trial will be defined be exact date and not when commercially available.

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, by the person who seeks the informed consent.

If information becomes available that may be relevant to the subject'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 subject's partner when collecting data from the subject's partner, if subject's partner becomes pregnant during the trial.

Collection of Previous FVIII Genotype Documentation (Not applicable for Brazil)

If documentation of the patients' genotype already exists from pathfinder™ 2, the patient should give their consent before the data is collected for this trial purpose. Prior to any trial-related activity, the Investigator must provide the patient the possibility to abstain from the genetic 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, 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 subjects if not mentioned in the patient information, the Investigator's current curriculum vitae (CV) 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 subjects, new information that may affect adversely the safety of the subjects 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 subjects), 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 subjects.

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.

19.4 Regulatory Authorities

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

For Japan: 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 subjects 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 subjects who have participated in the trial. If so, the actions needed to protect the subjects 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 subjects and/or the trial except for protocol deviations where no corrections are required as described in the trial specific validation checks in the approved trial validation plan (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 subjected 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 subjects), 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 Interest.[17]

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 NN7088-3860 (pathfinder™ 3) (US sites):

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

Protocol NN7088-3860 (pathfinder™ 3) (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 GCP[10], applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[16]

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 Criteria[18]).

24.1.2 Publications

The results of this trial will be subjected 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 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 Publications by Investigators

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 subjects; 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 Investigators will have their own research participants' data.

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: 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 is 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.

For France only: 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".

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

References

1 Guidelines for the Management of Hemophilia. 2005.

2 Vander AJ, Sherman JH, Luciano. Hemostasis:The Prevention of Blood Loss. In: Vander AJ, Sherman JH, Luciano DS, editors. Human Physiology. McGraw-Hill, Inc., 1994: 741-750.

3 Mancojohnson MJ, Nuss R, Geraghty S, Funk S, Kilcoyne R. Results of secondary prophylaxis in children with severe hemophilia. Am J Hematol 1994; 47(2):113-117.

4 Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007; 357(6):535-544.

5 Ehrenforth S, Kreuz W, Scharrer I, Linde R, Funk M, Gungor T et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet 1992; 339(8793):594-598.

6 White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001; 85(3):560.

7 Investigator's Brochure. 40K PEG-N8, 1st edition. Novo Nordisk A/S. 2010.

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

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

10 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4. 10-6-1996.

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

12 Food and Drug Administration Amendments Act. 2007.

13 Giles AR, Verbruggen B, Rivard GE, Teitel J, Walker I. A detailed comparison of the performance of the standard versus the Nijmegen modification of the Bethesda assay in detecting factor VIII:C inhibitors in the haemophilia A population of Canada. Association of Hemophilia Centre Directors of Canada. Factor VIII/IX Subcommittee of Scientific and

Standardization Committee of International Society on Thrombosis and Haemostasis. Thromb Haemost 1998; 79(4):872-875.

14 European Union; The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Medicinal Products - Brussels, July 2003. 2010.

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

16 World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects - Last amended by the 59th WMA General Assembly, Seoul. 2008.

17 Food and Drug Administration: Code of Federal Regulations, 21 CFR Part 54, Financial Disclosure by Clinical Investigators. 2006.

18 Clever L, Colaianni LA, Davidoff F, Horton R, Kassirer JP, Angell M et al. Uniform requirements for manuscripts submitted to biomedical journals. New Engl J Med 1997; 336(4):309-315.

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

no 1

to Protocol, Final version 1.0 dated 30-Sep-2011 and Sample Subject Information Informed Consent Form Final version 2.0 dated 15-Nov-2011

Trial ID: NN7088-3860

pathfinder™ 3

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:

Name: [redacted], [redacted]

Department: Haem, ClinOps FVIII

Table of Contents

Page

Table of tables

Page

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 counts the CTA submission of the NN7088-3859 (pathfinder™ 2) and NN7088-3860 (pathfinder™ 3) protocol in 8 European countries.

- VHP has required a more detailed guidance regarding the treatment of bleeding episodes in the pathfinder™ 2 protocol. Section 5.4.2 has therefore been updated accordingly to reflect the updated Section 5.3.2 of the pathfinder™ 2 protocol
- To clarify for VHP that 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 and therefore UK requirement on contraception deleted in Section 6.3
- VHP has required that the US condition of when to start the surgery trial described in Section 5.1 is made applicable for all member states. The condition will therefore be made applicable for all participating countries

Further minor adjustments have concurrently been made to the pathfinder™ 3 protocol

- In order for the pathfinder™ 3 design to work (allowing patients to go directly to Day of Surgery, if lab results are no more than 4 weeks old from Day of Surgery), the results from Coagulation parameter assessment from pathfinder™ 2 Visit 2a will always need to be re-used at pathfinder™ 3 Visit 1.The Flow chart in Section 2, footer no. 13, Section 8.1.1 and 8.3.8.3 has been corrected to reflect this
- Planned number of sites in Section 6.1 have been updated to reflect the current plan for number of sites in the trial. Furthermore Russia has been added to planned participating countries.
- Local pathfinder™ 2 substantial amendment criteria for Netherlands has been included in Section 3.2 and 6.7
- Addition of requirement for decimal specification on weight have been added in Section 8.3.5 to comply with resent audit finding
- Section 8.4.7 updated to reflect current set-up of eDiary
- Section 22 updated to reflect SOP deviation no. 2681 to comply with FDA requirement
- Some inconsistencies and minor corrections have made to the Flow Chart in Section 2

The following changes have been made to the pathfinder™ 3 Subject Information/Informed Consent forms and are therefore reflected in this global substantial amendment

- Number of sites have been updated and Russia has been added to planned participating countries.
- Total blood volume collection have been updated
- Precaution in connection to the reconstitution of trial product have been added (when not to take the trial product if the solution has solid particles)

- Error in the flowchart has been corrected
- Section 1.7 regarding follow-up visit in case of inhibitor detection has been clarified

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 ~~strike through~~.

The Protocol version 2 incorporates all changes.

The Sample Subject Information Informed Consent form version 3.0 and the The Sample Subject Information Informed Consent form for minor version 3.0 incorporates all changes

2 Changes to Protocol

2 Flow Chart

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

- FVIII trough level to be assessed at Screening Visit
- FVIII recovery not to be assessed at EOT Visit
- Footer 1 has been updated: The transfer to pathfinder™ 3 will be performed either on a scheduled or an Unscheduled Visit in pathfinder™ 2. *Laboratory* ~~A~~*a*ssessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3~~. All the assessments pertaining to the Screening Visit must have been~~ *if* done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation.
- Footer 13 has been updated: *The results from* ~~C~~coagulation parameters ~~are co~~*assessed* ~~llected~~ pre~~- dose~~ and ~~additionally~~ post-dose (30 ± 10 min) at Visit ~~1~~*2a in pathfinder™ 2, will be used in pathfinder™ 3*.

5 Trial Design

…

Figure 5-1 Visit Diagram

~~Recruitment into pathfinder™ 3 will begin after successful treatment of bleeding episodes with N8-GP in at least 5 patients in the pathfinder™ 2 trial.~~

Recruitment into pathfinder™ 3 ~~**In the US:** the surgery trial~~ will not be initiated until at least 20 bleeding episodes in at least 10 patients have been treated with N8-GP *in the pathfinder™ 2 trial*.

5.4.2 Treatment of Bleeding Episodes

…

~~For the treatment of bleeding episodes, doses will be based on WFH guidelines (Table 1A)[1].~~ For treatment of a bleed*ing episode,* all patients will be treated with doses between 20-75 U/kg *body weight (BW), 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%. Further guidance on the treatment of bleeding episodes may be found in WFH guidelines (Table 1A)[1].* ~~(the recommended standard dose will be 50 U/kg). 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.~~

The dosage is calculated by multiplying the patient's BW 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 = 1000 units of N8-GP).*

Table 2–1 Guide for Dosing in Bleeding Episodes

Type of hemorage	***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 in WFH guidelines.[1]

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 (hrs) 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.

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

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

6 Trial Population

6.1 Number of Subjects 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): ~~55~~*75*

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.~~

6.7 Rationale for Trial Population

Footer c: For Croatia *and Netherlands* only: the lower age limit will be 18 years.

8 Methods and Assessments

8.1.1 Visit 1 - Screening Visit

…

Blood sampling for central laboratory assessments:

…

- ~~Coagulation parameters, see Section 8.3.8.3~~

8.3.5 Body Measurements

…

- Weight, wearing light clothing only and without shoes (kg/pounds) *(registered with one decimal)*

8.3.8.3 Coagulation Parameters

Blood samples for coagulation parameters will be collected ~~pre-dose at the Screening Visit, daily during~~*at* Visit 2 (Day 0), ~~and~~ *daily during Visit* 3 (Days 1-6), once during Days 7-14 and hereafter once every week of Visit 4 and at the EOT Visit. Additionally coagulation parameters will be collected post-dose ~~(30 min ± 10 min) at Visit 1 and post-dose~~ (30 min ± 10 min, 4 hrs ± 1 hr and 8 hrs ± 2 hrs) at Day of Surgery, Visit 2.

8.4.7 eDiaries

The following information will, as a minimum, be captured by the patient or the caregiver in the eDiary:

Treatment

- ~~FVIII product used~~
- *Instructed doses (p*~~P~~rophylaxis *treatment and doses related to the major surgery)* ~~or~~, treatment of bleed*ing epsiode (not related to the major surgery) or minor surgery*

22 Critical Documents

…

For US:

~~Signed and dated~~ FDA form 1572 *must be completed and signed by*~~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)~~.

3 Changes to Sample Subject Information Informed Consent Form

1 Information about the surgery trial and trial product

…

In this surgery trial we will expect that approximately 15 patients will complete the trial in ~~55~~*75* centres worldwide. 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.

1.2 Procedures during the trial conduct

…

Flow chart for visits and assessments in the surgery trial

Assessments	**Visit 1** **Screening**	**Visit 2** **The day of surgery**	**Visit 3** **Day 1-6 daily**	**Visit 4** **Day 7-14 weekly**	**End of trial visit** **Any time between 2- ~~6~~*5* weeks after surgery**

1.5 How to handle trial medication, N8-GP

…

The trial medication must be stored refrigerated and handled as described on 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 is any solid particles to be seen.*

1.7 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 ~~at least monthly in the following three month~~ *monthly up to three month after the end of trial visit.*

2 Information about the Risks/Benefits

…

The total estimated ml of blood that will be taken from you during this trial will be maximal ~~250~~*200* ml which is less than one unit of a blood transfusion.

3.1 Changes to Sample Subject Information Informed Consent Form for minor

3 Visits

…

Visits and test during the trial

Tests	**Visit 1** **Screening**	**Visit 2** **The day of surgery**	**Visit 3** **Day 1-6 daily**	**Visit 4** **Day 7-14** **weekly**	**Last trial visit** **Any time between 2- *5* weeks after surgery**

Substantial Protocol Amendment

no 2-ES

to Protocol, final version 1.0

dated 30-Sep-2011

Trial ID: NN7088-3860

pathfinder™ 3

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Trial phase: 3

Applicable to Spain

Amendment originator:

Name: [redacted]

Department: Clinical Operations, CMR

Table of Contents

Page

1 Introduction including rationale for the substantial protocol amendment

This local substantial amendment is being issued to include a new site in Spain (Hospital Regional Universitario Carlos Haya).

The Substantial Amendment No. 2-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:~~ *National Coordinating Investigator:*	Name:	[redacted]
Investigator:	*Name:*	[redacted]
	Title:	*MD, PhD*
	Address:	*UGC Hematología y Hemoterapia* *Hospital Regional Universitario Carlos Haya* *Avda. Carlos Haya s/n* *Pabellón General A* *29010 Málaga*
	Tel:	[redacted]
Local laboratory(ies):	*Name:*	*Laboratorio de Biología Molecular*
	Address:	*Hospital Regional Universitario Carlos Haya* *Avda. Carlos Haya s/n* *Pabellón General* *29010 Málaga*
	Tel:	

Substantial Protocol Amendment

no 3

to Protocol, final version 2.0 dated 08-Dec-2011 and Sample Subject Information Informed Consent Form Final version 3.0 dated 08-Dec-2011

Trial ID: NN7088-3860

pathfinder™ 3

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:

Name: [redacted], [redacted]

Department: Haem, ClinOps FVIII

Table of Contents

Page

1 Introduction including rationale for the substantial protocol amendment

This global substantial protocol amendment is issued primarily to change the requirement for the timing of the pre-operative loading dose and secondarily to align with the NN7088-3859 (pathfinder™2) substantial protocol amendment issued simultaneously. In conjunction other minor clarifications to the protocol has also been included.

The following clarifications to the protocol have been made:

- Sections 2, 5.4.1 and 8.1.2: the timing requirements of the pre-operative loading dose changed to adjust to local surgical settings
- Sections 2 and 8.1.5: N8-GP binding antibodies sampling added to FU visit according to the EMA immunogenicity guideline
- Sections 3.2 and 6.7: France added in the footer, listing the countries that will not allow adolescents to participate in the trial
- Sections 5.4.2 and 8.4.7: requirement for documentation of Investigators' review of the patient's eDiary at every visit has been added
- Sections 8.1, 8.1.1 and 8.1.2: text regarding re-use of laboratory assessments from pathfinder™ 2 has been aligned to flow chart footer 1. Furthermore the text has been deleted from section 8.1 and moved to section 8.1.1
- Section 8.1.1: subject number allocation rule added
- Section 8.1.2: clarification of requirements for emergency surgery
- Sections 8.2.2 and 8.4.7: text added to guide Investigators and patients how to determine the stop time of a bleeding episode
- Section 8.3.8: text added to be in accordance with the SI/IC regarding storage of blood samples
- Other editorial corrections have been made to the protocol
- Attachment I of the protocol has been updated due to changes in key personnel

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

- Section 3.3: 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 3.0 incorporates all changes.

The Sample Subject Information/Informed Consent Form version 4.0 incorporates all changes.

2 Changes to Protocol

List of Abbreviations

…

INR	~~Prothrombin time~~ *international normalised ratio*

…

pd-aPCC	plasma derived activated ~~Plasma Coagulation factor~~ *prothrombin complex* ~~C~~*c*oncentrates
pd-PCC	plasma derived ~~Plasma Coagulation factor~~ *prothrombin complex* ~~C~~*c*oncentrates

Section 2 Flow Chart

Flow Chart table 2-1 has been updated: N8-GP binding antibodies to be assessed at the Follow-up Visit.

Flow Chart table 2-2, Footer 12 has been updated: Pre-*operative* loading dose administered no more than *2* ~~+~~ hr*s* prior to expected start of the surgical procedure (defined as "knife to skin"). *Subsequent* ~~A~~*a*dministration of trial product may be *considered approximately 12 hrs after* ~~repeated during the day~~ *the pre-operative loading dose.*

Section 3.2 Rationale for the Trial

Footer b: For Croatia*, France* and Netherlands only: the lower age limit will be 18 years.

Section 5.4.1 Dose Adjustments

…

On the Day of Surgery (Visit 2), all patients must receive a planned pre-operative loading dose of N8-GP, no more than ~~+~~ *2* hour*s* prior to expected start of the surgical procedure ("knife to skin") and before any procedures are undertaken, including anaesthesia to avoid bleeding when being anaesthetised. Therapeutic dose level of N8-GP should be calculated to aim for a FVIII plasma level of approximately 80-100 %, depending upon the results of the mandated recovery assessment, and should be administered by a slow bolus i.v. injection. Subsequent dosing on the day of surgery should be considered approximately 12 hrs after the loading dose to maintain plasma levels of FVIII above 50%. *Local laboratory FVIII activity measurements may be used for dosing guidance.*

Section 5.4.2 Treatment of 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. *The Investigator must review the eDiary data and rate the bleeding episodes at every visit. The review of the eDiary must be documented.*

Section 6.7 Rationale for Trial Population

Footer c: For Croatia*,* *France* and Netherlands only: the lower age limit will be 18 years.

Section 8.1 Visit Procedures

…

In order to ensure adequate supply of N8-GP pathfinder™ 3 trial drug for the *elective* surgery period, IV/WRS must have been notified during pathfinder™ 2 at least 14 days prior to Visit 1.

…

~~Assessments performed in pathfinderTM 2 may be used as the Screening Visit assessments in pathfinderTM 3. All the assessments pertaining to the Screening Visit must have been done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. These results from pathfinder™ 2 will then be used in pathfinder™ 3. Patients coming from the on demand treatment arm in pathfinderTM 2 must have FVIII activity recovery level measured at the Screening Visit. All assessments at Visit 1 and Visit 2 must be performed.~~

Section 8.1.1 Visit 1 - Screening Visit

...

~~If the~~ *All* patient*s* ~~is~~ enrolled in the trial~~, the patient~~ will receive a unique subject number, which will be assigned to the patient throughout the trial. *The assigned subject number will be the same as in pathfinder™ 2. If the patient is enrolled into pathfinder™ 3 more than once, the 4th digit in the subject number is incremented by one.*

Example for patient with subject number 101001 in pathfinder™ 2:

- *101001 (in pathfinder™ 2)*
- *101001 (Surgery no. 1 in pathfinder™ 3)*
- *101001 (return to pathfinder™ 2)*
- *101**1**01 (Surgery no. 2 in pathfinder™ 3)*
- *101001 (return to pathfinder™ 2)*
- *101**2**01 (Surgery no. 3 in pathfinder™ 3) etc.*

…

Laboratory assessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3 if done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. Patients undergoing emergency surgery must have the results available from the preceding visit. These results from pathfinder™ 2 will then be used in pathfinder™ 3. Patients coming from the on-demand treatment arm in pathfinder™ 2 must have FVIII activity recovery level measured at the Screening Visit. All assessments at Visit 1 and Visit 2 must be performed.

Section 8.1.2 Visit 2 – Day of Surgery

…

Patients must receive a pre-*operative* loading dose of N8-GP*,* administered no more than ~~1~~ *2* hr*s* prior to expected start of the surgical procedure (defined as "knife to skin").

…

Laboratory ~~A~~assessments performed in pathfinder™ 2 may be used as the Screening Visit assessments in pathfinder™ 3~~. All the assessments pertaining to the Screening Visit must have been~~ *if* done within maximum 4 weeks of the Day of Surgery and the results must be available for evaluation. *Patients undergoing emergency surgery must have the results available from the preceding visit.*

…

Furthermore the screening information, including the FVIII activity recovery assessment and FVIII inhibitor test must *have* be*en* done and data must be available from the pr~~o~~*e*c~~c~~eding visit in the pathfinder™ 2 trial.

For patients undergoing emergency surgery the following assessments for Visit ~~2~~ *1* should additionally be performed and/or recorded in the eCRF:

…

- *FVIII inhibitors, see Section 8.3.6.1*
- *N8-GP binding antibodies, see Section 8.3.6.2*
- *Haematology, see Section 8.3.7.3*
- *Biochemistry, see Section 8.3.8.2*
- *FVIII activity, see Section 8.3.8.4*

Section 8.1.5 Follow-up Visit (only for patients withdrawn due to development of FVIII inhibitors)

…

Blood sampling for central laboratory assessments:

- FVIII inhibitors, see Section 8.3.6.1
- *N8-GP binding antibodies, see Section 8.3.6.2*

Section 8.2.2 Bleeding Episodes

…

- Stop of bleed (date and time *(e.g. pain reduction with no increase in swelling)*)

Section 8.3.8 Central Laboratory Tests

…
All blood samples 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.

Section 8.4.7 eDiaries

…
- Stop of bleed (date and time *(e.g. pain reduction with no increase in swelling)*)

…
The entries made by the patient in the eDiary will be reviewed by the Investigator together with the patient and/or caregiver during the visit to ensure consistency/compliance. *The review of the eDiary must be documented.*

…
Bleeding episodes and trial product administration performed while the patient is hospitalised will not be entered in the eDiary but *in the patient's medical records and hereafter* in the eCRF.

3 Changes to Sample Subject Information/Informed Consent Form

Front page

…
Author

[redacted], [redacted]

Section 3.3 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 will be identified in the same way.

Substantial Protocol Amendment

no 4-FR

to Protocol, final version 3.0

dated 30 March 2012

Trial ID: NN7088-3860

pathfinder™ 3

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Amendment originator:
Name: [redacted]

Table of Contents

Page

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 NN7088-3860:

Site added:

Investigator:	*Name:*	[redacted]
	Title:	*MD-PhD*
	Address:	*Hôpital Edouard Herriot* *Centre de Traitement des Hémophiles* *Place d'Arsonval* *69003 LYON*
	Tel:	[redacted]
	Fax:	[redacted]
	E-mail:	[redacted]

Protocol Amendment

no 5
to Protocol, final version 3.0 dated 30 March 2012

pathfinder™ 3

Trial ID: NN7088-3860

Efficacy and Safety of NNC 0129-0000-1003 during Surgical Procedures in Patients with Haemophilia A

Trial phase: 3

Applicable to all countries

Amendment originator:

[redacted], [redacted]

Haem, Clin Ops 2

Table of contents

Page

1 Introduction including rationale for the protocol amendment

It has been decided that the NN7088-3860 (pathfinder™3) trial will remain open to ensure that patients participating in the NN7088-3859 (pathfinder™2) trial, including the extension phase part 1 and 2, will have the opportunity to undergo major surgery. Patients are offered to continue on N8-GP until commercially available ensuring that they can undergo surgery without having to switch product. The originally planned NN7088-3861 (pathfinder™4) has been replaced with the pathfinder™2 extension phase part 1 and 2.
Section, List of Abbreviations, 1, 3.1.3, 3.2, 6.1, 6.2, 6.3, 6.6, 7, 18.3 and 19 have been updated to reflect this decision.
In addition, the withdrawal criteria in the current version of the pathfinder™3 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, Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition), BJH, 2013, 160, 153–170). 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., Guidelines for the management of hemophilia, Haemophlia, 2012, 1-47).
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. Section 8.1.5 and 8.3.6.1 are updated to reflect this change of process.

Furthermore a few other updates have been performed concurrently:

- Section 5.3.1 has been updated to align the minor surgery definition with NN7088-3859
- Israel has been added to the country list in section 6.1
- Section 8.3.8 has been updated to reflect what the patient has consented to regarding storage of samples in pathfinder™3 (if allowed by local law)
- Section 9.3 regarding labelling and packaging of trial product
- Text regarding adverse events has been updated in section 12.1

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

2 Changes

List of Abbreviations

....

~~NN7088-3861 pathfinder™4 (extension trial)~~

....

1 Summary

Trial Population

….

It is expected that approximately 22 patients with severe (FVIII:C <1%) haemophilia A already included in pathfinder™2 are to be screened into pathfinder™3 in order to ensure evaluation of at least 15 major surgical procedures in 10-15 patients, see Figure 3–1.

~~If a minimum of 15 major surgeries in minimum 10-15 patients has not yet been performed in this surgery trial by the end of pathfinder™ 2, the trial might be extended to apply for the patients entering from the extension trial NN7088-3861, hereafter referred to as pathfinder™ 4, see Figure 3–1.~~

The trial population is characterised by the inclusion and exclusion criteria described in pathfinder™2 and having the additional key inclusion and exclusion criteria in this trial:

Key Inclusion Criteria

….

Ongoing participation in the pathfinder™2 (NN7088-3859) ~~or the pathfinder™ 4 (NN7088-3861)~~ trial and having received ≥5 doses of N8-GP

….

Key Exclusion Criteria

….

Previous withdrawal from the pathfinder™2 (NN7088-3859) ~~or the pathfinder™ 4 (NN7088-3861)~~ trial after administration of trial product, except interruption due to inclusion in this pathfinder™3 trial (NN7088-3860)

….

3 Introduction

3.1.3 Risk and Benefits

….

Participation in pathfinder™3 is offered to the patients in pathfinder™2 in need of major surgery, ensuring that the patients can undergo surgery without having to switch product.

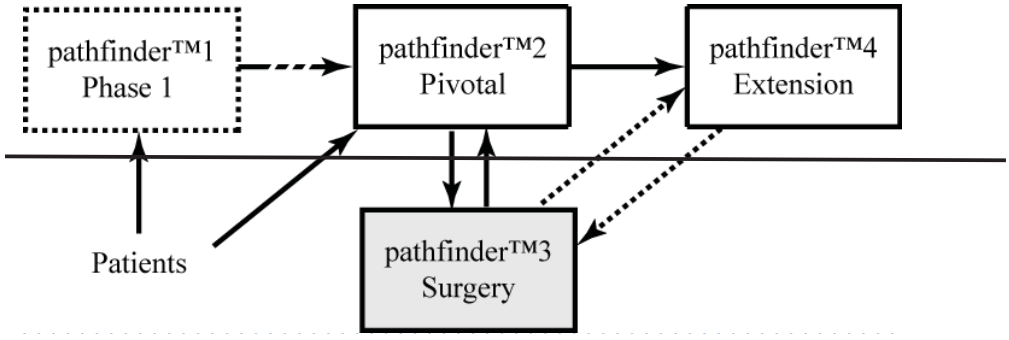
~~To minimise the switching between FVIII products the patient will furthermore be offered to continue in pathfinder™ 4, if approved in country, after completion of pathfinder™ 2.~~ In this way patients will have the opportunity to continue with N8-GP treatment until the product is commercially available.

3.2 Rationale for the Trial

This trial is part of a clinical development programme that at present includes a preceding phase 1 trial NN7088-3776, hereafter referred to as pathfinder™1, a pivotal phase 3 pathfinder™2 trial *including an extension phase part 1 and 2~~, an extension phase 3 pathfinder™ 4 trial~~* and the present phase 3 pathfinder™3 trial. The phase 3 trials will be offered to each investigational site to ensure that patients are offered to continue on N8-GP until commercially available and to ensure that patients in need of surgery can undergo surgery without having to switch product.

~~If a minimum of 15 major surgeries in minimum 10-15 patients has not yet been performed in this trial by the end of pathfinder™ 2, the~~. *The pathfinder™3* trial *will remain open to ensure that patients participating in the pathfinder™2 trial will have the opportunity to undergo major surgery during pathfinder™2*.~~might be extended to apply for the patients entering from pathfinder™ 4.~~ The pathfinder™ clinical trial programme is illustrated in Figure 3–1. Arrows indicate possible transfer of patients between trials.

….



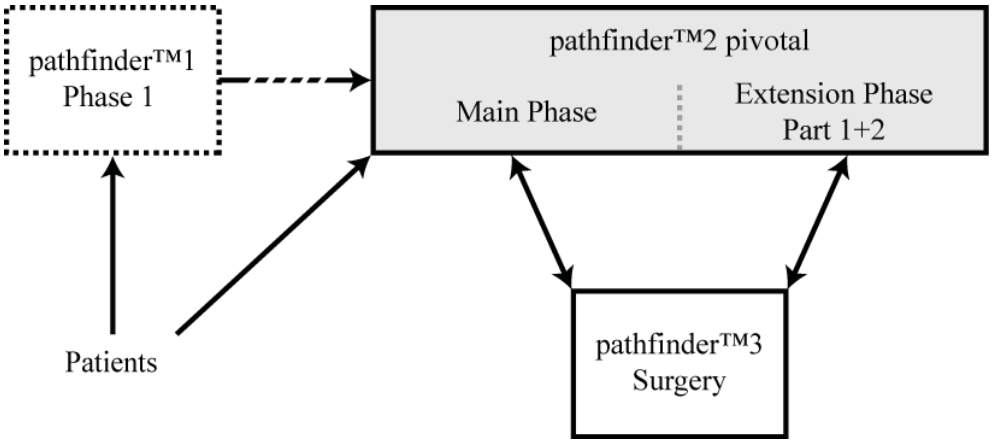


Figure 3–1 Overview of the pathfinder™ Clinical Trial Programme

5 Trial Design

5.3.1 Definition of Major and Minor Surgery

Major Surgery

….

This definition includes *e.g.* ~~both~~ circumcision ~~and port insertions~~ since *this~~ey~~* require*s* several days of substitution therapy but do not include simple drainage procedures that take place bedside.

….

Minor Surgery

….

Examples of minor surgery include implanting pumps *or ports* in subcutaneous tissue, skin biopsies or simple dental procedures.

….

6 Trial Population

6.1 Number of Subjects to be Studied

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

Planned number of subjects to be screened (i.e. documented informed consent) approximately: 22

Planned number of subjects to be started on trial product approximately: 18*

Planned number of subjects to complete the trial: 10-15*

Planned number of trial sites approximately: 75

**These numbers indicate the minimum numbers of required patients.*
The pathfinder™3 trial will remain open to ensure that patients participating in the pathfinder ™2 trial will have the opportunity to undergo major surgery during the pathfinder™2 trial including the extension phase Part 1 and Part 2.

6.2 Inclusion Criteria

….

2. Ongoing participation in the pathfinder™2 (NN7088-3859) ~~or the pathfinder™ 4 (NN7088-3861)~~ trial and having received ≥5 doses of N8-GP

….

6.3 Exclusion Criteria

….

2. Previous withdrawal from the pathfinder™2 (NN7088-3859) ~~or the pathfinder™ 4 (NN7088-3861)~~ trial after administration of trial product, except interruption due to inclusion in this pathfinder™3 trial (NN7088-3860)

….

6.5 Withdrawal Criteria

….

2. FVIII inhibitor (~~≥0.6~~*>5* BU/mL) as confirmed by re-testing by central laboratory

8. 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

….

6.6 Patient Replacement

All patients in pathfinder^{TM}2 will be offered to enter this trial in case they need major surgery. *When* ~~If~~ a minimum of 15 major surgeries in minimum 10-15 patients has ~~not yet~~ been performed in this surgery trial *the* ~~by the end of~~ pathfinder™ ~~2~~*3*~~, this~~ trial *will remain open to ensure that the patients have the opportunity to undergo major surgery during the pathfinder™2 trial* ~~might be extended to apply for the patients entering from pathfinder™ 4~~, see Figure 3–1. Patients withdrawn from the trial prior to completion of Day 2 (Visit 3) will not count as a surgery and will be replaced. *When a minimum of 15 patients have fulfilled this requirement patients will no longer be replaced.*

7 Trial Schedule

….

Planned completion of the last patient (LPLV): ~~02.Sep.2013~~ *03.Dec.2018*

….

8 Methods and Assessments

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.

….

8.3.6.1 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.* The~~is~~*se* ~~second~~ sample*s* 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 N8-GP treatment (prophylaxis or treatment of bleeding episodes) the patients may stay in pathfinder™3 on current treatment or be transferred back to pathfinder™2 for further follow-up.

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 FU Visit must be scheduled 4 weeks ± 2 weeks after the EOT Visit, if possible and additional monthly FU Visits may be arranged at intervals of 4 weeks ± 2 weeks as long as clinically warranted up to 3 months after the EOT Visit.

For patients continuing in pathfinder™3 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. 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. 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 inhibitor tests (performed at 2 visits at least 4 weeks apart) and the FVIII recovery is ≥66% of expected values. A patient with repeated positive inhibitor test result will count only once in the determination of the inhibitor incidence rate.

Patients who develop an inhibitor should be classified as high responders (peak inhibitor titre > 5 BU/mL), low responders (peak inhibitor titre ≤5 BU/mL), and whether the inhibitor is transient

(disappearing (inhibitor titer <0.6 BU/mL on ≥2 measurements at least 4 weeks apart) spontaneously within 6 months without a change in treatment regimen), or not.

….

Residual drug levels of N8-GP >0.0~~15~~*2* U/mL can interfere with the modified Bethesda assay and may in some instances result in false negative inhibitor tests.

….

When inhibitor results are negative and there is clinical suspicion that inhibitor may be present FVIII levels will be measured. FVIII levels <0.0~~15~~*2* IU/mL will confirm a negative inhibitor test. FVIII levels >0.0~~15~~*2* IU/ml can result in the need for collection of sampling for inhibitor testing following a 7 days wash out period.

A patient that tests negative for inhibitors following a 7 days wash out and with FVIII levels <0.0~~15~~2 IU/mL will confirm a negative inhibitor test and the patient will continue in the trial.

….

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 (≥0.6BU) – and the patient ~~should~~ *may* discontinue the trial including an EOT Visit and FU Visits *or remain in pathfinder™3 or transferred back to pathfinder™2 as described above.*

….

8.3.8 Central Laboratory Tests

....

All blood samples 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.

If allowed by local law and consented to, in pathfinder™3 addendum 'Storage of blood samples from pathfinder™3', samples drawn for analysis of antibodies in pathfinder™3 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 Products

Novo Nordisk A/S will ~~label and pack the trial products~~ *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 subject 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

18.3 Interim Analysis

….

Furthermore an interim analysis is planned to include data from at least ~~5~~*10* severe haemophilia A patients, undergoing ~~10~~*15* major surgeries in the initial New Drug Application (NDA) and Marketing Authorisation Application (MAA).
Additional updates, including data from additional patients undergoing major surgeries, may be made prior to submission of the initial MAA and NDA.

19 Ethics

….

The patient will be offered to continue in pathfinder™ ~~4~~*2*, ~~if approved in country,~~ after completion of pathfinder™ ~~2~~*3* where patients have the opportunity to continue with N8-GP treatment until the product is commercial available.

….

If the patient does not wish to continue in pathfinder™~~4~~*2*, the patient will consult with the Investigator to decide on the best available treatment.