Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02141074
Sponsor trial ID:	NN7999-3895
Official title of study:	An Open-label Single-arm Multicentre Non-controlled Phase 3 a Trial Investigating Safety and Efficacy of Nonacog Beta Pegol (N9-GP) in Prophylaxis and Treatment of Bleeding Episodes in Previously Untreated Patients With Haemophilia B (FIX Activity Below or Equal to 2 Percent)
Document date:	05 November 2019

*Document date refers to the date on which the document was most recently updated.

Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

.

Protocol

Trial ID:NN7999-3895

paradigm™6

Safety and Efficacy of nonacog beta pegol (N9-GP) in Previously Untreated Patients with Haemophilia B

An open-label single-arm multicentre non-controlled phase 3a trial investigating safety and efficacy of nonacog beta pegol (N9-GP) in prophylaxis and treatment of bleeding episodes in previously untreated patients with haemophilia B (FIX activity ≤2%)

Includes:
Protocol Amendment no 1 (25-Mar-2015), Protocol Amendment no 2 (15-Jan-2016), Protocol Amendment no 4 (13-Dec-2016), Protocol Amendment no 5 (11-Dec-2017), Protocol Amendment no 6 (29-Jun-2018), Local Protocol Amendment no 7 (31-Jul-2019) (Only applicable for Spain) and Protocol Amendment no 8 (05-Nov-2019).

Trial phase: 3a

Protocol originator:
[redacted], International Trial Manager
Biopharm, Trial Operations 2

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Agreement on Final Protocol
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List of abbreviations

ABAS-3	Adaptive Behavior Assessment System – Third Edition
AE	adverse event
BASC-3	Behavior Assessment System for Children – Third Edition
BRIEF2	Behavior Rating Inventory of Executive Function – Second Edition
BRIEF-P	Behavior Rating Inventory of Executive Function – Preschool Edition.
BP	blood pressure
BU	Bethesda units
BW	body weight
CFR	code of federal regulations
CHMP	committee for medical products for human use
CHO	Chinese hamster ovary
CNS	central nervous system
CLAE	clinical laboratory adverse event
CRF	case report form
CRO	contract research organisation
CTA	clinical trial application
CTR	clinical trial report
DCF	data clarification form
DUN	dispensing unit number
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
ED	exposure day (Definition: One exposure day is defined as each day when a patient is administered coagulation factor IX/blood components for any reason regardless number of doses)
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of trial
FAS	full analysis set
FDA	food and drug administration
FPFV	first patient first visit
FVIIa	activated coagulation factor VII
FIX	coagulation factor IX
FIXa	activated coagulation factor IX
FX	coagulation factor X

GCP	good clinical practice
HCP	host cell protein
HLA	human leucocyte antigen
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IgE	immunoglobulin E
IFU	inhibitor follow up
IND	investigational new drug
IRB	institutional review board
IR_{30min}	incremental recovery 30 min
IU	international unit (1 IU of N9-GP and 1 U of N9-GP are equivalent and can be used interchangeably. In this protocol IU is used, however U may appear in some trial related documents, e.g. IMP labels)
I.V.	intravenous
IWRS	interactive web response system
LAR	legally acceptable representative
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
M	months
MESI	medical event of special interest
N9-GP	nonacog beta pegol, glycopegylated recombinant coagulation factor IX
NIMP	non-investigational medicinal product
OD	on-demand
PDCO	paediatric committee (EMA)
Pd-aPCC	plasma-derived activated prothrombin complex concentrates
PEG	polyethylene glycol
PI	principal investigator
PIP	paediatric investigation plan
PK	pharmacokinetics
PPX	prophylaxis
PUP	previously untreated patient
rFIX	recombinant coagulation factor IX

SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SI	the international system of units
SIF	safety information form
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TMM	trial materials manual
UTN	universal trial number
V	visit
W	weeks
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

1 Summary

Primary Objective

- To evaluate immunogenicity of N9-GP (nonacog beta pegol)

Primary Endpoint

- Incidence of inhibitory antibodies against FIX

Secondary Objectives

- To evaluate safety of N9-GP (nonacog beta pegol)
- To evaluate efficacy of N9-GP (nonacog beta pegol)
    - in long-term prophylaxis treatment
    - in the treatment of bleeding episodes
    - through the surrogate marker: FIX activity
    - through monitoring of number of doses and consumption of N9-GP

Key Secondary Endpoint

- Number and frequency of adverse events, serious adverse events, and Medical Events of Special Interest
- Number of breakthrough bleeding episodes during prophylaxis (annualised bleeding rate)
- Haemostatic effect by 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “poor”)

Time Frame of the Objectives/Endpoint

All objectives/endpoints will be evaluated when minimum 20 PUPs have reached at least 50 exposure days (EDs), when minimum 40 PUPs have reached at least 100 EDs, and at end of trial. End of trial will be 30 Oct 2022.

Trial design

The trial is an open label, single-arm, multinational, non-controlled confirmatory trial investigating safety and efficacy of N9-GP in prophylaxis and treatment of breakthrough bleeding episodes in haemophilia B previously untreated patients with FIX activity ≤ 2%.The trial has one treatment arm in which at least 40 patients should achieve at least 100 exposure days with N9-GP.

The European medicines agency requires submission of safety and efficacy data from a minimum of 50 exposure days in at least 20 patients for approval of the indication in previously untreated patients, with a post-approval extension phase according to guideline to follow-up in at least 40 patients, for a minimum of 100 exposure days. When minimum 20 patients have reached at least 50 exposure days, the analysis and evaluation for the main trial report will be performed. All patients

continue in the extension phase for the purpose of acquiring data for a minimum of 100 exposure days in at least 40 patients.

Trial population
60 patients are planned to be screened and at least 40 patients are expected to complete the trial.

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

Inclusion Criteria
- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male, < 6 years of age at the time of signing informed consent
- Patients with the diagnosis of haemophilia B (FIX activity level ≤ 2%) based on medical records or central laboratory results
- Previously untreated or exposed to FIX containing products less than or equal to 3 exposure days (5 previous exposure days to blood components are acceptable)

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

Assessments

Safety assessments
The following key assessments for safety will be used in the trial:
- Antibody assessment: inhibitory and binding antibodies
- Other adverse events, incl. allergic reactions, anaphylactic reactions and thromboembolic events

Efficacy assessments
The following key assessments for efficacy will be used in the trial:
- Bleeding episodes

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

Pharmacokinetics, pharmacodynamics and other assessments
The following key assessments for pharmacokinetics, pharmacodynamics and other assessments will be used in the trial:

- FIX activity measured as trough and peak

Trial product
The following trial product will be used in the trial:

- nonacog beta pegol hereafter referred to as N9-GP

N9-GP is supplied as a sterile freeze-dried powder for solution for injection in single use vials with a nominal content of 2000 IU/vial or 500 IU/vial to be reconstituted with 4.2 mL Histidine solvent. After reconstitution each vial contains 500 IU/mL or 125 IU/mL N9-GP, respectively.

Patients are treated with 40 IU/kg N9-GP for:

- bleeding episodes
- pre-prophylaxis or
- prophylaxis

A bleeding episode should be treated with a single dose of 40 IU/kg, unless the bleeding episode is severe in which case it should be treated with 80 IU/kg.

2 Flow chart

Table 2–1 Flow chart visits and assessments

Visit number	**0[15]**	**1-20[13, 15]**	**21-22**	**23**	**24-27**	**28**	**29-X[17]**	**IFU**	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**End of Main**	**Dosing**	**End of extension**	**Dosing (until EOT)**	**ONLY for inhibitor patients**	**End of Trial**
Time of visit (ED(s))[19]	**0**	**1-20**	**30,40**	**50**	**60, 70, 80, 90**	**100**	**124, 148, 172, …**		
Visit interval [19]		**±1 Day**	**10 ± 2 weeks**	**10+2 Weeks**	**10 ± 2 weeks**	**10+2 weeks**	**24 ± 4[17] weeks**		
PATIENT RELATED INFORMATION									
Informed consent [10]	X								
Assent form, if applicable[1]	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Inclusion / Exclusion criteria	X								
Eligibility evaluation		X							
Withdrawal criteria		X	X	X	X	X	X		
Demography	X								
Concomitant illness & medical history	X								
Details on haemophilia and haemophilia treatment history	X								
Concomitant medication	X	X	X	X	X	X	X	X	X
ADVERSE EVENTS									
Adverse events[2]	X	X	X	X	X	X	X	X	X
CLINICAL ASSESSMENTS									
Body measurements[3]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]		X[21]
Physical examination	X			X		X			X
Neurological examination[24]		Visit 1 and 20		X	Visit 26	X	X		X
Neurocognitive assessments[25]		Visit 1 and		X	Visit 26	X	X		X

Visit number	**0[15]**	**1-20[13, 15]**	**21-22**	**23**	**24-27**	**28**	**29-X[17]**	**IFU**	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**End of Main**	**Dosing**	**End of extension**	**Dosing (until EOT)**	**ONLY for inhibitor patients**	**End of Trial**
Time of visit (ED(s))[19]	**0**	**1-20**	**30,40**	**50**	**60, 70, 80, 90**	**100**	**124, 148, 172, …**		
Visit interval [19]		**±1 Day**	**10 ± 2 weeks**	**10+2 Weeks**	**10 ± 2 weeks**	**10+2 weeks**	**24 ± 4[17] weeks**		
		20							
Vital signs[4]	X	Visit 1[4]		X		X			X
CENTRAL LABORATORY ASSESSMENTS									
FIX activity – trough[7]	(X)[5]	Visit 1, 5,10,15, 20	X	X	X	X	X	X	X
FIX activity – recovery 30 min post-dose[6]		Visit 1,10, 20		X		X			
N9-GP binding antibodies[7]		Visit 1, 5,10,15,20	X	X	X	X	X	X	X
FIX inhibitor test[7, 16]		Visit 1,5,10,-15,20	X	X	X	X	X	X	X
HCP antibodies[7]	X			X		X			X
HIV antibodies	(X)[8]								
CD4+ lymphocyte count and HIV viral load	(X)[8]								
Haematology	X	(Visit 1)[9]		X		X			X
Biochemistry	X	(Visit 1)[9]	Visit 21	X	Visit 26	X	X		X
F9 + *HLA* genotype testing	(X)[10]	(X)[10]							
Allergic reaction testing[20]	(X)	(X)							
Plasma PEG levels	X[22]		Visit 21	X	Visit 26	X	X		X
Urinalysis[23]		Visit 1 and 20		X	Visit 26	X	X		X
TRIAL PRODUCT ADMINISTRATION									
N9-GP administration		X	X	X	X	X	X		

Visit number	**0**[15]	**1-20**[13, 15]	**21-22**	**23**	**24-27**	**28**	**29-X**[17]	**IFU**	**EOT**
Visit purpose	**Screening**	**Dosing**	**Dosing**	**End of Main**	**Dosing**	**End of extension**	**Dosing (until EOT)**	**ONLY for inhibitor patients**	**End of Trial**
Time of visit (ED(s))[19]	**0**	**1-20**	**30,40**	**50**	**60, 70, 80, 90**	**100**	**124, 148, 172, …**		
Visit interval [19]		**±1 Day**	**10 ± 2 weeks**	**10+2 Weeks**	**10 ± 2 weeks**	**10+2 weeks**	**24 ± 4**[17] **weeks**		
N9-GP dispensing for home treatment		(X)[13]	X	X	X	X	X[18]		
N9-GP accountability		X	X	X	X	X	X		X
TRAINING AND REMINDERS									
Trial card dispensing	X								
Home treatment training		X	X	X	X	X	X		
eDiary training		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]		
Compliance check of eDiary data, protocol requirements, used drug and bleeding episode evaluation		X	X	X	X	X	X		X
Contact with patients/parent/LAR[12]		(X)[12]					(X)[12]		
IWRS[14]	X	X	X	X	X	X	X		X
End of trial form									X

Table 2–2 Flow chart explanatory descriptions

Footer	Description
1	Any patient above the age of 3 years should sign a child assent form, if capable, and if required by local requirements. This can be performed on a separate day. As this is a long term trial the investigator should check the progressing maturation of the child and its ability to assent throughout the trial
2	When Informed consent has been obtained all adverse events must be reported in the eCRF
3	For practical purposes, when dispensing trial drug, the body weight from an earlier measurement (or visit) can be used if the measurement was performed within the previous 12 weeks (in children < 3 years of age, within 6 weeks). After visit 29, a body weight measured within the previous 12 weeks for all age groups can be used. Please refer to Section 8.3.1.
4	Vital signs should be measured prior to dosing at screening, V1, V23, V28 and EOT. In addition vital signs should also be measured 30±10 minutes after the first injection with N9-GP at V1
5	FIX activity should only be measured at V0 if diagnosis of haemophilia B (FIX≤2%) has not been documented in the patients' medical record. FIX activity at V0 can either be measured at local or central laboratory depending on the urgency of receiving the result i.e. in case V0 and V1 are combined
6	FIX recovery activity is measured 30 min ±10 min after dosing at the following EDs: 1, 10, 20, 50 and 100. For details please refer to Section 8.4.2.1
7	Blood samples must be collected within 1 hour prior to dosing at dosing visits
8	HIV antibodies are only to be assessed, if status is unknown (i.e. previous test older than 6 months). Tests for CD4+ lymphocyte count and HIV viral load are only required for HIV positive patients. Sampling can be postponed to the earliest convenient visit to ensure that the allowed blood volume is not exceeded
9	In case V1 is more than a month after V0, haematology and biochemistry need to be retaken at V1 prior to dosing. Biochemistry also needs to be retaken at visit 1 if biochemistry at V0 was a local assessment. Please refer to Section 8.4.2.4 and 8.4.2.5
10	*F9* and *HLA* genotype sample should be taken prior to administrating the first dose of N9-GP or at a visit as soon as possible thereafter taking the limitation of the allowed blood sampling volume into account.
11	eDiary training prior to initiating home treatment to ensure that the patient's parent(s)/LAR(s) are comfortable entering data in the eDiary. Retrain in the use of the eDiary as applicable at V21-VX to ensure entry of correct eDiary data
12	When site visits are more than 3 months apart the Investigator must contact the patient's parents/LAR at least every 12 weeks ± 1week to ensure the patients well-being. For details please refer to Section 8.8.4. Primarily expected to be applicable for patients treated according to pre-prophylaxis (V1-V20) and who visit the trial site less frequent than every 3 months. In addition all visits from V29 –VX will be scheduled every 24 weeks.
13	It will be possible to administer ED 11-20 outside the trial site (except ED 15 and 20 since blood sampling is needed). This is only allowed if the trial site can ensure presence of a relevant health care professional qualified of handling anaphylactic reactions
14	IWRS to be used for screening, visit registration, trial drug dispensing, drug accountability and completion. Refer to Section 10 for more information.
15	V0 and V1 can be combined to one visit, if the patient fulfils the in- and exclusions criteria
16	Blood sampling for FIX .inhibitor testing must be performed prior to administrating the first dose of N9-GP to the patient at visit 1. An inhibitor test must be performed before surgery if the previous inhibitor test was performed more than 30 days prior to surgery.
17	V29 to VX will be performed every 24 weeks ± 4 weeks until End of Trial

18	At every dosing visit from V29-VX, drug will be dispensed to cover up to 3 months of treatment
19	When the patient has commenced prophylaxis, visits can for practical purposes be planned according to the predicted number of EDs based on the patient's prophylaxis regimen. A visit does not need to be re-scheduled even if the actual EDs between visits turn out higher due to treatment of bleeding episodes during the home treatment period
20	Allergic reaction testing can be taken at visit 0 or visit 1 pre-dose, taking the limitation of the allowed blood sampling volume into account.
21	Height will be collected at visit 0, visit 21, visit 23, visit 26, and at all visits from visit 28 to EOT visit. In case visit 1 is more than a month after visit 0, height needs to be redone at visit 1. For patients who have already attended visit 23 and 28 height at these two visits ± 1 month will be collected retrospective if available in medical records upon parent(s)/LAR(s) consent.
22	Blood samples for PEG analysis should be taken at visit 0 taking the limitation of the allowed blood sampling volume into account. If not taken at visit 0, the blood sample should be taken at visit 1 pre-dose, if the blood volume allows.
23	Urine sample should be obtained if possible. It can be collected at home same day and brought to site if transported cold according to Section8.4.2.8.
24	The neurological examination can for all visits be made within ±1 month of the visits, except for the visit 1 and EOT visit where it can be made at visit date or up to 1 month ahead of the visit.
25	The neurocognitive assessments can for all visits be made within ±1 month of the visits, except for visit 1 and EOT visit where it can be made at visit date or up to 1 month ahead of the visit. For details see Table 8-1 and Table 8-2.

3 Background information and rationale for the trial

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

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

3.1 Background information

Haemophilia B is a recessive X-linked congenital bleeding disorder characterised by increased bleeding tendency due to either a partial or complete deficiency or dysfunction of the essential blood coagulation factor IX (FIX). It is caused by mutations in the *F9* gene, located in the distal part on the long arm of the X-chromosome. The incidence of haemophilia B is approximately 1 per 25,000 male births. Haemophilia care is based on prevention (prophylaxis) and/or "on-demand treatment" of bleeding episodes with a haemostatic agent.

With a deficiency or absence of FIX, activation of coagulation factor X (FX) becomes severely impaired, and consequently, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug formed in these patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis, prolonged bleeding and rebleeding[3]. Haemophilia B is classified according to the plasma activity of FIX as severe (<1%), moderate (1-5%) or mild (>5-40%).

The predominant treatment for patients with haemophilia B is factor replacement therapy where concentrates of FIX are injected intravenously to replace the deficient and/or dysfunctional FIX. Haemophilia care is based on treatment of a bleeding episode with a haemostatic agent or - during recent decades - haemostatic agents are administered for longer periods to prevent bleeding (bleeding prophylaxis).

The most commonly used products for the treatment of haemophilia B are plasma derived FIX and recombinant FIX (rFIX). Both have half-lives of 18-19 hours requiring 2-3 weekly injections for prophylaxis of bleeding episodes.[4]

The clinical manifestations of haemophilia B are bleeding episodes due to impaired haemostasis. The bleeding episodes in patients with severe haemophilia B typically occur spontaneously or after mild trauma in joints, muscles and soft tissues. The bleeding episodes often occur in muscles and weight bearing joints (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, most commonly a weight-bearing joint, may lead to chronic arthropathy, muscular atrophy and disabling deformities. Bleeding may occur in all parts of the body including rare, but life-

threatening events such as: e.g. bleeding in the central nervous system (CNS), throat, neck or retroperitoneum.

3.2 Rationale for the trial

The rationale for performing this trial is to investigate safety and efficacy of N9-GP in the treatment of previously untreated patients (PUP) with haemophilia B, hereby supporting anticipated marketing authorisation of N9-GP and line extension in the PUP population.

EMA requires separate investigation of PUPs as part of the development programme initiated before market authorisation (MA) gets obtained. A final guideline on the clinical investigation of recombinant and human plasma-derived factor IX products[5] from the Committee for Medical Product for Human Use (CHMP), describes the mandatory components for trials in PUP. In some countries outside the EU, PUP Paediatric investigation is necessary to achieve labelled indication for all children.

3.3 N9-GP (nonacog beta pegol)

Novo Nordisk A/S is developing a recombinant coagulation factor IX, N9-GP (nonacog beta pegol), with a prolonged half-life for treatment of haemophilia B patients. The steady state half-life based on PK from the phase 3 trial of previously treated adults and adolescents haemophilia B was determined to 111 hours.

The long half-life is achieved by site-directed glycopegylation that makes it possible to attach a 40 kilodalton polyethylene glycol (PEG) molecule to the FIX activation peptide.[6] Upon activation by FIX's physiological activators, the activation peptide – with the attached PEG – is cleaved off, thereby leaving wild type activated FIX (FIXa).

The product is intended for FIX replacement therapy in adults and children with haemophilia B. N9-GP is under development for both the control and prevention of bleeding episodes, including routine prophylaxis, and for treatment and prevention of bleeding during surgery.

For full information on medical aspects, non-clinical data and quality of N9-GP, please refer to the current version of the Investigator's Brochure (IB)[7] and any updates hereof.

For an overview of the trials in the clinical development programme of N9-GP, please refer to Table 3-1

Table 3-1 The clinical development programme of N9-GP

Trial ID	Trial description		Status
NN7999-3639 (paradigm™1)	A multi-centre, multi-national, open-label, dose escalation trial evaluating safety and pharmacokinetics of ascending intravenous doses of N9-GP in non-bleeding patients with haemophilia B	Phase 1 (PK trial)	Completed
NN7999-3747 (paradigm™2)	A multi-centre, single-blind trial evaluating safety and efficacy, including pharmacokinetics, of N9-GP when used for treatment and prophylaxis of bleeding episodes in patients with haemophilia B	Phase 3a (safety and efficacy trial)	Completed
NN7999-3773 (paradigm™3)	An open-label, multi-centre, un-controlled trial to assess efficacy and safety of N9-GP during surgical procedures in patients with haemophilia B	Phase 3a (surgery trial)	Completed
NN7999-3775 (paradigm™4)	An open-label, multi-centre, multinational trial evaluating safety and efficacy of N9-GP in treatment of bleeding episodes and long-term prophylaxis in haemophilia B patients	Phase 3b (extension trial)	Completed
NN7999-3774 (paradigm™5)	An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and pharmacokinetics of N9-GP in prophylaxis and treatment of bleeding episodes in children with haemophilia B with extension phase	Phase 3 (paediatric, safety and efficacy trial)	On-going (main phase completed)
NN7999-3895 (paradigm™6)	An open-label, single-arm, multicentre non-controlled trial investigating safety and efficacy of N9-GP in prophylaxis and treatment of bleeding episodes in previously untreated patients with haemophilia B	Phase 3a (safety trial)	Current trial

3.4 Risk and benefits

Children are among those who might benefit significantly from prophylaxis with N9-GP. The most commonly used products for the treatment of haemophilia B have short half-life of 18-19 hours demanding frequent dosing for prophylaxis of bleeding episodes, with 2-3 injections a week[8]. The prolonged half-life of N9-GP offers an expected advantage of once weekly or potentially even less frequent injections, which reduces the burden of treatment while maintaining effective haemostasis. Likewise it may promote adherence to therapy due to less frequent injections.[6] The pivotal phase 3 trial (NN7999-3747) demonstrated a prophylactic protection of 40 IU/kg N9-GP once weekly and showed that 99% of bleeding episodes in the 40 IU/kg arm were stopped with a single dose of N9-GP.

N9-GP is manufactured in a serum-free process. The recombinant FIX part of N9-GP has an amino acid sequence identical to human FIX and is produced from the Chinese hamster ovary (CHO) cell-line, a mammalian cell line shown to be free of known infectious agents.

The primary concern in PUPs is the risk of development of neutralising antibodies to FIX (inhibitors). Development of binding antibodies and inhibitors will be monitored closely throughout the trial.

Hypersensitivity reactions may occur with the administration of N9-GP, as with any protein injected intravenously. Patients will be closely monitored for development of hypersensitivity reactions, in relation to the first 20 exposures with N9-GP.

Correlation between allergic reactions and the development of inhibitors have been observed with FIX treatment. If patients develop inhibitors, they will be carefully instructed how to react if an allergic reaction occurs following N9-GP administration.

Pegylation of proteins is a well-established technology which is used in the treatment of a variety of clinical disorders.[9] In repeat dose toxicity studies in animals, PEG was shown to be bio-distributed to blood in connective tissue and cytoplasm of epithelial cells of the choroid plexus of the brain, for further information refer to the current version of the Investigator's Brochure (IB)[7]. The potential clinical implications of these animal findings are unknown. No adverse neurological effects of PEG have been reported in infants, children, and adolescents exposed to N9-GP during clinical trials. The potential consequences of long term exposure have not been fully evaluated. Due to this theoretical safety concern regarding PEG, potential clinical effects of longer-term exposure to N9-GP with special emphasis on the choroid plexus and the two major excretion organs (liver and kidney) will be investigated in more detail (neurological examination, age-appropriate neurocognitive assessments and laboratory analyses of plasma PEG levels, liver and kidney parameters).

No safety issues have been identified in the completed and ongoing clinical trials with N9-GP and the risk/benefit ratio for N9-GP is therefore expected to be favorable. For further information refer to the current version of the IB[7].

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary Objective

- To evaluate immunogenicity of N9-GP (nonacog beta pegol)

Secondary Objectives

- To evaluate safety of N9-GP (nonacog beta pegol)
- To evaluate efficacy of N9-GP (nonacog beta pegol)
    - in long-term prophylaxis treatment
    - in the treatment of bleeding episodes
    - through the surrogate marker: FIX activity
    - through monitoring of number of doses and consumption of N9-GP

4.2 Endpoint(s)

4.2.1 Primary Endpoint

- Incidence of inhibitory antibodies against FIX

4.2.2 Secondary Endpoint

- Number and frequency of adverse events (AEs), serious AEs (SAEs) and Medical Events of Special Interest (MESI)*
- Number of breakthrough bleeding episodes during prophylaxis (annualised bleeding rate)*
- Haemostatic effect by 4-point haemostatic response scale (“excellent”, “good”, “moderate” and “poor”)*
- Incremental recovery at 30 minutes (IR30min), FIX activity at 30 minutes (C_{30min}) and trough level
- Amount of drug administered and number of doses needed to treat a bleeding episode

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

5 Trial design

5.1 Type of trial

This is an open label, single-arm, multinational, non-controlled confirmatory trial investigating safety and efficacy of N9-GP in prophylaxis and treatment of breakthrough bleeding episodes in haemophilia B PUPs with FIX activity ≤ 2%.

The trial has one treatment arm in which at least 40 patients should achieve 100 exposure days of 40 IU/kg N9-GP.

The trial consists of four parts: screening, main (i.e. core) phase, extension phase and a prophylaxis period until EOT, see Table 5-1.

EMA requires submission of safety and efficacy data from a minimum of 50 EDs in at least 20 patients for approval of indication in PUPs, with a post-approval extension phase according to guideline to follow in at least 40 patients, for a minimum of 100 EDs. Sixty (60) patients are planned to enter screening.[5] When minimum 20 patients have reached a minimum of 50 EDs the analysis and evaluation for the main report will be performed. All patients will continue in the extension phase for the purpose of acquiring data for a minimum of 100 EDs in at least 40 patients. Results from all patients, in all parts of the trial, will be reported in a final report when the last patient has completed the trial.

The trial design is based on the guideline on clinical investigation of recombinant and human plasma-derived factor IX products developed by CHMP in EU.[5]

For Japan only: The NN7999-3895 trial will be classified as a post-marketing clinical trial if obtaining marketing approval in Japan. Therefore, the term ‘chiken’, which is a term for a clinical trial conducted for getting marketing approval, is replaced in the protocol and other related materials/documents with the term ‘post-marketing clinical trial.’

5.2 Rationale for trial design

The trial is designed to investigate immunogenicity of N9-GP in PUPs who are known to have the highest risk of inhibitor formation.[10] A minimum of 100 EDs will provide the required exposure to N9-GP in order to investigate the immunogenicity, safety other than immunogenicity and efficacy of N9-GP.

A multinational design has been chosen to ensure a sufficient screening pool of patients with this rare disorder, to meet local regulatory requirements and to reflect the anticipated patient population. There will be no randomisation or stratification.

5.3 Treatment of patients

The duration of a patient's treatment with N9-GP in the main phase of the trial is until Visit 23 (50 EDs) has been reached.

The duration of N9-GP treatment in the extension phase is at least 50 EDs or until global LPLV (30-Oct-2022). Thereafter treatment with N9-GP will continue until LPLV. Trial overview will be as shown in Figure 5–1.

60 patients are planned to be screened and at least 40 patients are expected to complete the trial.

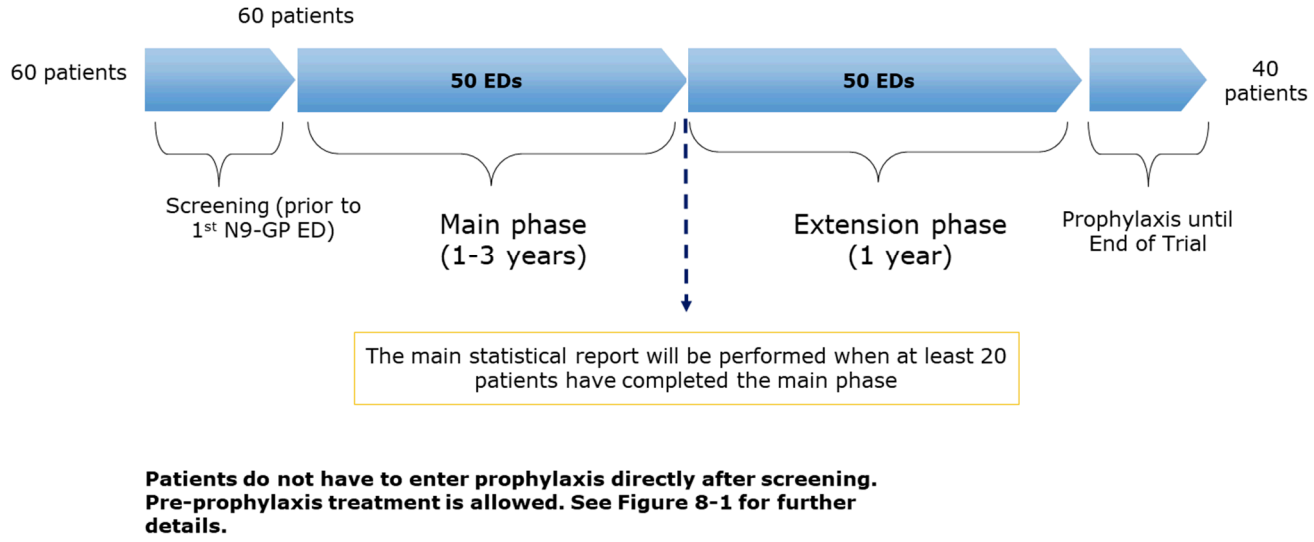

Figure 5–1 Patient flow chart

The trial is designed to reflect common practice in haemophilia treatment centres. Most children will initially receive on-demand (episodic) treatment for minor skin/mucosa bleeding episodes, and after the first joint and/or muscle bleed, switch to prophylaxis in order to prevent bleeding episodes and musculoskeletal damage. This is usually done when the child is between 1 and 2 years of age. Prior to starting treatment at Visit 1, the family and investigator will choose between prophylaxis and pre-prophylaxis treatment. One exposure day is defined as each day when a patient is administered N9-GP for any reason regardless of number of doses.

5.3.1 Previous exposure to FIX products

Due to the rarity of the condition, recruitment for clinical trials of PUPs with severe or moderate Haemophilia B is highly challenging. According to EMA guidelines only PUPs are eligible for

participation. However, patients that are 'minimally exposed' (up to 3 EDs of commercial FIX) can enter this trial in agreement with PDCO at EMA.

In addition to the above, maximum 5 previous blood product (e.g. plasma, cryoprecipitate, erythrocyte concentrate or platelets) EDs are allowed.

5.3.2 Pre-prophylaxis treatment

If it is decided by the investigator and family not to initiate regular once weekly prophylaxis immediately after Visit 0, the patient can instead, until he is 24 months of age or until 20 ED, be treated on-demand for bleeding episodes and/or have a slow start-up of prophylaxis (i.e. pre-prophylaxis) with a dose of 40 IU/kg at intervals longer than a week.

The decision regarding pre-prophylaxis treatment will be made at visit 0. Pre-prophylaxis treatment will be administered as a dose of 40 IU/kg N9-GP (or 80 IU/kg for a severe bleed), see Section 5.3.4.
Pre-prophylaxis treated patients will have regular contact with trial site at least every 12 weeks, if dosing with N9-GP is not planned and/or required, until initiation of prophylaxis.

5.3.3 Prophylaxis treatment

Regular prophylaxis must be initiated no later than 24 months of age or upon reaching 20 EDs whichever comes first, with a dose of 40 IU/kg N9-GP administered every 7th day (± 1 day).

If considered relevant, the investigator is permitted to prescribe administration of extra N9-GP bleeding preventive doses before demanding physical activities (e.g. sports). The next regular prophylaxis dose should not be postponed but be administered on the usual dosing day.

5.3.4 Treatment of bleeding episodes

The patient's parent(s)/LAR(s) will be instructed by the trial site on how to treat a bleeding episode at home and record this in the eDiary, see Sections 8.1.12.1 , 8.6 and 8.6.1.

In case of a treatment requiring bleeding episode, immediate treatment with N9-GP as intravenous injection of 40 IU/kg in case of mild or moderate bleeding or 80 IU/kg in case of a severe bleeding episode can be administered. The investigator must always be contacted in case of a severe bleeding episode. These doses can be repeated, but not exceeding 200 IU/kg per 24 hours Table 5-1.

An additional dose of 40 IU/kg for a mild/moderate bleeding episode is only allowed after consultation with the investigator. If a mild/moderate bleeding episode has not improved within 24 hours, the patient's parent(s)/LAR(s) should contact the investigator.

For treatment of bleeding episodes prior to reaching the first 20 EDs please refer to Section 5.3.5.

5.3.5 Requirements for the first 20 injections

The risk of anaphylaxis and allergic reactions is evaluated as being highest during the first 20 EDs.[8, 10] For this reason it is a requirement in this protocol to administer the first 10 N9-GP injections at the trial site and it is recommended to administer at least the first 20 injections at the site. If the Investigator in accordance with local practice or guidelines decides to allow treatment outside the trial site prior to reaching 20 EDs this must be with a health care professional present that will be able to manage an anaphylactic reaction and could for example be at the emergency room, local paediatrician or at home, see Section 8.1.3.1.

5.3.6 Treatment of bleeding episodes in low titre inhibitor (<5 BU) patients

Low titre inhibitor patients who do not respond sufficiently to N9-GP treatment may be treated with bypassing agents according to local label for a period of up to 2 years. It is recommended to avoid FIX containing bypassing agents. Bypassing agents are not considered trial medication. Patients will stay in the trial and continue the N9-GP treatment 40 IU/kg once weekly.

5.3.7 Treatment of suspected severe bleeding episodes

In case of an abdominal or head trauma where there is a risk of a severe traumatic bleeding episode it is allowed to initiate treatment before clinical symptoms arise. This is defined as preventive treatment of suspected severe traumatic bleeding episode. The recommended dose is 80 IU/kg. The site must be contacted and the event documented either in the eDiary or in the eCRF as treatment of bleeding episode.

5.3.8 Surgery

Minor surgery

Minor surgeries (procedures where only one dose of N9-GP is considered sufficient prior to the surgery) can be performed while participating in this trial by administering a dose of 40 IU/kg N9-GP, see Table 5-1.

Definition of minor surgery

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

- Implanting and removing ports in subcutaneous tissue (see * in Table 5-1)
- Skin excisions
- Drainage of abscess
- Simple dental procedures

- Circumcision

Major surgery

Major surgery may be performed after 20 EDs in the current trial.

In a separate completed N9-GP surgery trial (NN7999-3773/paradigm™3) 13 adults and adolescent patients underwent major surgery where the haemostatic effect in all study participants was reported as either good or excellent and the N9-GP appeared to have a safe and well tolerated profile.

Major surgery in the current trial should be planned and conducted in accordance with the recommendations in the WFH Guidelines for the management of haemophilia.[8] Determination of dose and dose intervals to achieve adequate haemostasis should include close monitoring of FIX activity trough and peak levels, taken into consideration the half-life of N9-GP and ongoing clinical evaluation of the haemostatic effect.

Major surgery may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation, local anaesthesia or with a combination of these modalities. The used sedative products should be listed in the concomitant medication.

Further details and requirements when performing major surgery are provided in Section 8.7.

Definition of major surgery

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

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

Treatment with N9-GP during surgery will be included in the overall count of N9-GP EDs. Upon completion of the surgical/invasive procedure the patient will continue prophylactic treatment with N9-GP as before the surgery.

Table 5-1 Intravenous N9-GP treatment

Indication	Dosage*	Frequency
Pre-prophylaxis during main phase (prior to 20EDs) (pt. less than 24 months of age)	40 IU/kg	On-demand or intervals longer than once weekly
Prophylaxis during main phase	40 IU/kg	Once weekly (±1 day)
Prophylaxis during extension phase	40 IU/kg	Once weekly (±1 day)
Mild/moderate bleeding episode	40 IU/kg	Single dose for bleeding episodes. Additional doses only after consultation with the investigator
Severe bleeding episode (The investigator must be contacted)	80 IU/kg, not exceeding 200 IU/kg per 24 hours	Single dose for bleeding episodes. Severe bleeding episodes can be treated with further dose if instructed by the investigator
Minor surgery	40 IU/kg (*Port implantation: 80 IU/kg)	Single dose prior to surgery
Major surgery, only allowed after 20 EDs	In accordance with the WFH Guidelines[8] and local standard of practise	In accordance with the WFH Guidelines[8] and local standard of practise
Low titre inhibitor	40 IU/kg	Once weekly (±1 day)

*The dose to administer will be calculated by IWRS and defined in whole mL for doses above 3mL.

5.3.9 Vaccinations

Vaccinations are allowed before entering the trial but should preferably not take place until 3 months after the first N9-GP exposure, as vaccination activates the immune system, thereby potentially increasing the risk of inhibitor development.

5.4 Treatment after end of trial

After trial end the investigator will agree with the patient's parent(s)/LAR(s) upon the best available treatment for the patient. Novo Nordisk will not provide any trial product to a patient after the end of the trial unless required in accordance with local law or regulation.

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

It is expected that N9-GP will be granted marketing authorisation and is commercially available when the patients complete this trial. However, this cannot be guaranteed.

5.5 Rationale for treatment

Lack of compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with coagulation factor treatment[6]. The increased half-life of N9-GP will allow for prophylaxis with fewer injections than currently available products and will most likely result in improving compliance.

The dose levels for this trial are based on PK data from the phase 1 PK trial (NN7999-3639), PK data from 10 IU/kg and 40 IU/kg in the pivotal trial (NN7999-3747) and PK data from children participating in the paediatric trial (NN7999-3774).

Please refer to the IB[7] and any updates hereof for further non-clinical and clinical data.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 60

Number of patients planned to be started on trial product: 60

Number of patients expected to complete the trial: 40

6.2 Inclusion criteria

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. (Note: By consenting to this trial, the parent(s)/LAR(s) accepts that genotype of the patient's haemophilia B mutation is analysed/recorded and used for trial purposes).
2. Male, < 6 years of age at the time of signing informed consent.
3. Patients with the diagnosis of haemophilia B (FIX activity level ≤ 2%) based on medical records or central laboratory results.
4. Previously untreated or exposed to FIX containing products less than or equal to 3 EDs (5 previous exposure days to blood components are acceptable).

6.3 Exclusion criteria

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

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

6.4 Withdrawal criteria

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

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

The patient must be withdrawn if the following applies:

1. Dosed in the trial, but not fulfilling the inclusion and/or exclusion criteria
2. Development of FIX inhibitors ≥ 5 BU confirmed by two consecutive tests (central laboratory) and associated with N9-GP binding antibodies (the patient must be withdrawn from N9-GP treatment upon confirmation of FIX inhibitor ≥ 5 BU and attend three inhibitor follow-up visits)
3. Anaphylactic reaction to the trial product, for definition see section 11.1
4. Major surgery prior to 20 EDs. see section 5.3.8
5. Significant thromboembolic event, see Section 11.1
6. Incapacity or unwillingness to follow trial procedures
7. Participation in another clinical trial while participating in this trial

If a patient experiences treatment failure where haemostatic response is rated as poor according to Section 8.6, the investigator should consider if it is in the patient's best interest to continue in the trial.

All data collected prior to withdrawal will be used in the trial analyses.

Temporary or permanent discontinuation of treatment with trial product will not lead to withdrawal from the trial.

6.4.1 Only applicable for Spain: Temporary discontinuation of trial treatment

Temporary treatment discontinuation is allowed at the discretion of the investigator and the reason for discontinuation must be recorded in the eCRF. Treatment with trial product may be resumed if the circumstances later allow. Date and last trial product dose should be recorded in the eCRF. Resupply status in the IWRS should be put on hold when a patient is on treatment pause. The eDiary will not be used during temporary discontinuation of trial product.

6.5 Patient replacement

Withdrawn patients may be replaced to ensure that at least 40 patients complete the trial with a minimum of 100 ED.

6.6 Rationale for trial population

The selection of the trial population is based on the specific requirements found in the final guideline on the clinical investigation of recombinant and human plasma-derived factor IX products[5] from the CHMP and in the Paediatric Investigation Plan (PIP) in agreement with the Paediatric Committee (PDCO).

Children are among those who might benefit significantly from prophylaxis. Less frequent injections with N9-GP as compared to other treatment options are likely to improve compliance, avoid interruptions of daily life and thereby increase the quality of life of the patients.

6.6.1 Rationale for inclusion criteria

- Criterion no. 1 is included in accordance with International Conference on Harmonisation/Good Clinical Practice (ICH-GCP).
- Criterion no. 2 is included due to Novo Nordisk A/S has decided to use an age cut-off of 6 years.
- Criterion no. 3 is included to select the patient group based on the CHMP guideline[5].
- Criterion no. 4 is included to select the patient group based on the CHMP guideline and in accordance with recent PIP modification allowing inclusion of minimally treated patients.

6.6.2 Rationale for exclusion criteria

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

6.6.3 Rationale for withdrawal criteria

- Criteria nos. 1-7 are included to protect the patient's safety and reliability of the data.

7 Milestones

Planned duration of recruitment period: First patient first visit (FPFV) to last patient first visit (LPFV): 75 months

First Patient First Visit: 02-Jul-2014
Planned Last Patient First Visit: 30-Sep-2020
End of trial is defined as Last Patient Last Visit: 30-Oct-2022

The duration of N9-GP treatment in the trial is a minimum of 100 EDs for at least 40 patients and will continue until Last Patient Last Visit for the trial, which will be 30 October 2022.

Planned completion of clinical trial report (CTR): Q2 2023

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

All subjects included in the screening period and eligible for the trial will enter the trial.

Trial registration
Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, it will also be disclosed according to other requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[11], the Food and Drug Administration Amendment Act (FDAAA)[12], European Commission Requirements[13] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

Specific procedures, assessments and methods for the scheduled visits are described in the section below, and the list of assessments for each visit is presented in the flow chart, see Table 2–1 and visit flow diagram Table 8-1.

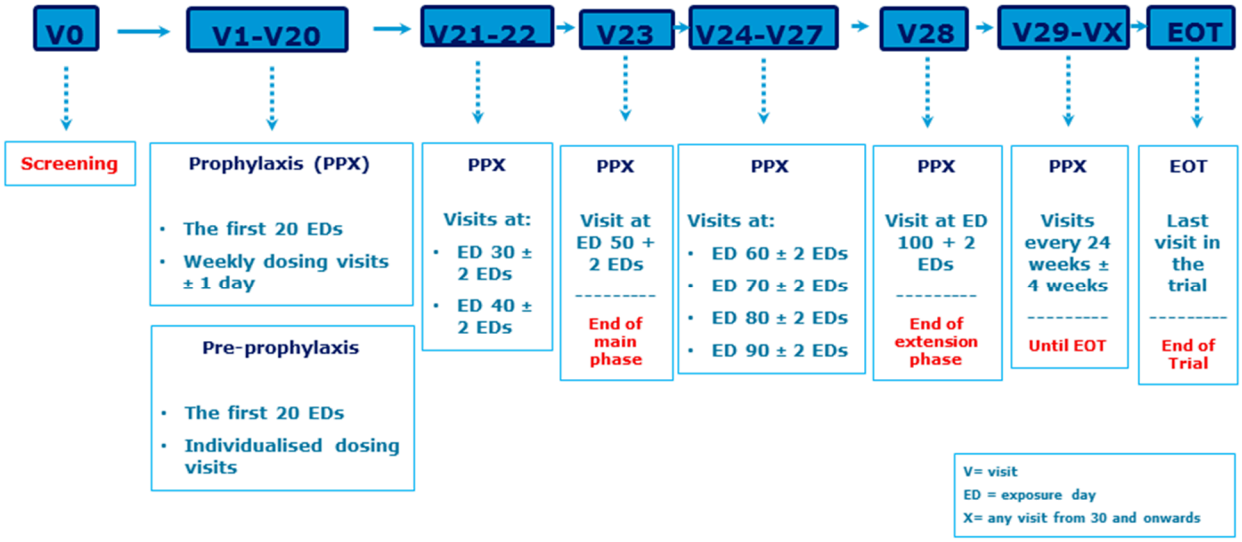

Figure 8–1 Visit flow diagram

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

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

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

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

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

Informed consent including haemophilia B mutation genotyping at screening must be obtained.

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

For screening failures, the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.

Serious and non-serious adverse events (AE) from screening failures must be transcribed by the investigator into the case report form (eCRF). Follow-up of SAEs must be carried out according to Section 11.3. A screening failure session must be made in the IWRS. The case book must be signed.

Re-screening is **not** allowed after the first dose of trial product – see excl. criteria no. 2 in Section 6.3.

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

If a patient is withdrawn from the trial, the investigator must aim to perform the end of trial visit, as soon as possible except for patients with a high titre inhibitor.

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

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

Although a patient or patient's parent(s)/LAR(s) is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s),

while fully respecting the patient's rights. Where the reasons are obtained, the primary reason(s) for discontinuation must be specified on the end-of-trial form in the eCRF e.g.:

- Adverse events (AEs)
- Protocol violation
- Lack of efficacy
- Lost to follow up
- Withdrawal by patient or parent(s)/LAR(s)
- Technical problems
- Other

End of trial
The end of trial (EOT) form should be filled in at the End-of-Trial visit or the last visit of the patient. If a patient is withdrawn prior to completion of the trial, all attempts must be made to schedule the end of trial visit for the patient.
For a patient with high titre inhibitor the EOT visit should be performed in connection with the third follow-up visit.

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

In accordance with local law a caregiver may take over the responsibilities from the parent(s)/LAR(s) of handling and administrating the trial drug, filling in the eDiary and attending visits at site. The caregiver must be trained to the same extent as the parent(s)/LAR(s) in the relevant responsibilities.

Prior to a visit the investigator must request the patient's parent(s)/LAR(s) to return any trial medication , solvent or injection kits if this would expire during the following home treatment period. The patient's parent(s)/LAR(s) must also be instructed in never using any expired trial materials.

Any corrections made by the investigator to the eDiary entries must be discussed with the patient's parent(s)/LAR(s) and the conclusion documented in the medical record. Care must be taken not to bias the patient's parent(s)/LAR(s).

8.1.1 Visit 0 – screening visit

The patient's parent(s)/LAR(s) must give signed and dated informed consent prior to any trial related activities. Signing of the informed consent can take place before visit 0, if allowed by local

law. All patients will be provided with a copy on the patient information and a copy of the signed and dated Informed Consent Form.

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

A screening period (interval between visit 0 (V0) and V1) is allowed until the first dose of N9-GP is required.

The screening visit (V0) can be combined with the first treatment of N9-GP (V1), hereby allowing patients to be enrolled in the trial and treated for their first bleeding episode immediately after having confirmed inclusion and exclusion criteria.

All results necessary for evaluating the inclusion and exclusion criteria must be available before determining whether or not the patient can continue in the trial and whether it will be possible to receive the first dose of N9-GP at the same day.

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

Assessments for V0 are listed in Table 2–1.

Reminders:

- Dispense trial card, see Section 8.8.1
- Screening call in the IWRS, see Section 10
- Discuss treatment regimen: prophylaxis versus pre-prophylaxis
- In case V1 is not planned or performed within 3 month from visit 0 the investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1 week, See Sections 8.8.4 and 8.1.10.
- During the screening period the patient cannot be treated with commercially available FIX product

8.1.1.1 Pre-prophylaxis treatment

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

During pre-prophylaxis the following dosing regimens applies:

- dosing with 40 IU/kg N9-GP

- individualised prophylaxis dosing intervals but less frequent than once weekly
- on-demand treatment of bleeding episodes
- minor surgery

See further Section 5.3.2 and 5.3.8.

Dosing visits during the pre-prophylaxis period can be performed at any time until ED 20. Visits during the pre-prophylaxis period without dosing should be performed as unscheduled visits, see Section 8.1.10.

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

Visit 1-20 occurs when the patient needs treatment of a bleed and /or is planned individually per patient at the investigator and patient's parent(s)/LAR(s) discretion.

8.1.1.2 Prophylaxis treatment

Prophylaxis treatment can begin at visit 1 or at any time during the pre-prophylaxis period and must be initiated latest when the patient has reached 20 EDs on pre-prophylaxis or has turned 24 months of age, whatever comes first.

The dosing frequency is once weekly ±1 day (preferable the same day of the week).

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

8.1.2 Visit 1 – first dosing with N9-GP

Visit 1 will take place after the screening visit (V0) whenever the first treatment of N9-GP is administered, if not already combined with V0.

Before administrating the first dose of N9-GP the FIX inhibitor test for central laboratory must be taken and sent to central laboratory for analysis. In case of subjective signs of illness and/or fever within 48 hours prior to the first injection of N9-GP the dose should be postponed, if possible.

The patient will continue treatment on either:

- **Pre-prophylaxis treatment**. See Sections 5.3.2 and 8.1.1.1.
- **Prophylaxis treatment.** See Sections 5.3.3 and 8.1.1.2.

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

Reminders

- Next visit should be scheduled if applicable, see Sections 8.1.1.1 and 8.1.1.2
- In case V2 is not planned or performed within 3 months from visit 1 the Investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week. See Sections 8.8.4 and 8.1.10.
- Drug accountability of trial product at V1 must be recorded in the IWRS, see Section 10
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing via IWRS, see Section 10.

8.1.3 Visit 2-20 – main phase

The 10 first N9-GP exposure days (EDs) (V1-V10) must take place at the trial site.

ED11-20 should preferable take place at trial site however administration can take place outside the trial site, if a health care professional qualified of handling anaphylactic reactions is present, see Section 5.3.5. Visit 15 (ED 15 ± 1) and visit 20 (ED 20 ± 1) are mandatory at site due to blood sampling.

All doses should be registered in the eCRF. In case the patient is treated outside the trial site the trial site should be informed and the details hereof should be entered in the eCRF.

Assessments for V2-V20 are listed in Table 2–1.

Reminders

- In case next visit is not planned or performed within 3 months from the previous visit the investigator must contact the patient's parent(s)/LAR(s) at least every 12 weeks ± 1week. See Sections 8.8.4 and 8.1.10.
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- eDiary dispensing, see Section 8.8.3.1
- eDiary training, see Section 8.8.3 and 12.3

8.1.3.1 Treatment outside trial site

It is the responsibility of the investigator to ensure the safety of the patient and adherence to the protocol, ICH, GCP and local regulations also when the patient is treated outside trial site.

Prior to allowing treatment outside trial site at ED 11 to ED 14 and ED 16 to ED 19 the Investigator must have a plan describing how this can be done in a safe and responsible manner.

The plan should be prepared for each individual patient and should describe the circumstances under which the treatment outside trial site is performed, e.g. how it can be ensured that a health care professional qualified to handle anaphylactic reactions can be present, how training is performed, and how appropriate documentation is obtained. The plan must also address that the patient may need trial drug at home/not at home.

The plan should include an instruction for the patient's parent(s)/LAR(s) with the directions for use and describe the importance of having a health care professional present to handle anaphylactic reactions during administration and how to act in case of emergency bleeding episodes.

The process should be discussed with Novo Nordisk, if applicable approved by IRB/IEC, and must always comply with local regulations.

8.1.4 Visit 21-22 – main phase

From V21 all patients (including patients previously on pre-prophylaxis) will be on prophylaxis treatment with N9-GP. Between the visits the patient will receive N9-GP treatment at home if comfortable with home administrations or at the site, see Section 8.1.12

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

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

Assessments for V21 and V22 are listed in Table 2–1.

Reminders

- An appointment for the next visit should be made
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for site dosing/home treatment must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- The Investigator must prior to the visit instruct the patient's parent(s)/LAR(s) in returning any trial medication, solvent or injection kits that would expire during the following home treatment period
- Home treatment training, if the trial site suspects that the patient's parent(s)/LAR(s) is not fully confident with administration and how to deal with safety related signs and symptoms , see Sections 8.5 and Sections 8.6
- eDiary training, see Section 8.8.3 and 12.3
- eDiary compliance review, see Section 12.3.

8.1.5 Visit 23 – end of main phase

Visit 23 should take place at either ED 50, ED 51 or ED 52.

Assessments for V23 are listed in Table 2–1.

Reminders

- An appointment for the next visit should be made
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing/home treatment must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- The Investigator must prior to the visit instruct the patient's parent(s)/LAR(s) in returning any trial medication, solvent or injection kits that would expire during the following home treatment period
- Home treatment training, if the trial site suspects that the patient's parent(s)/LAR(s) is not fully confident with administration and how to deal with safety related signs and symptoms, see Sections 8.5 and 8.6
- eDiary training, see Section 8.8.3 and 12.3
- eDiary compliance review, see Section 12.3.

8.1.6 Visit 24-27 – extension phase

The patient will continue prophylaxis throughout the extension phase, with 40 IU/kg N9-GP once weekly. See Table 2–1.

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

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

The duration of the extension phase is approximately 1 year for a patient to achieve a total of 100 EDs.

Assessments for V24-V27 are listed in Table 2–1.

Reminders

- An appointment for the next visit should be made
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing/home treatment must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10

- The Investigator must prior to the visit instruct the patient's parent(s)/LAR(s) in returning any trial medication, solvent or injection kits that would expire during the following home treatment period
- Home treatment training,see Section 8.1.12 and 8.8.2.
- eDiary training, see Section 8.8.3 and 12.3
- eDiary compliance review, see Section 12.3

8.1.7 Visit 28 - end of extension phase

V28 should take place at either ED 100, ED 101 or ED 102.

Assessments for V28 are listed in Table 2–1.

Reminders
- An appointment for the next visit should be made
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing/home treatment must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- The Investigator must prior to the visit instruct the patient's parent(s)/LAR(s) in returning any trial medication, solvent or injection kits that would expire during the following home treatment period
- eDiary compliance review, see Section 12.3

8.1.8 Visit 29-X until end of trial

After visit 29 visits are scheduled 24 weeks ± 4 weeks apart. This schedule will last until End of Trial.

At every dosing visit from V29-VX, drug will be dispensed to cover up to 3 months of treatment. If the visit is a N9-GP dispensing visit only, the patient is not required to attend the clinic only for this purpose. Assessments for V29-X are listed in Table 2–1**.**

Reminders
- An appointment for the next visit should be made
- Recording of body weight, see Section 8.3.1, and dispensing of N9-GP for trial site dosing/home treatment must be performed via IWRS, see Section 10
- Drug accountability of trial product must be recorded in the IWRS, see Section 10
- The Investigator must prior to the visit instruct the patient's parent(s)/LAR(s) in returning any trial medication, solvent or injection kits that would expire during the following home treatment period

- eDiary compliance review, see Section 12.3

8.1.9 End-of-trial visit

The EOT visit is the last visit in the trial.
The EOT will take place after completion of at least 100 EDs or if the patient is withdrawn from the trial. For a patient with high titre inhibitor the EOT visit should be performed in connection with the third inhibitor follow-up visit, for scheduled visits other than inhibitor follow-up visits, the EOT visit may replace a scheduled visit if this scheduled visit is scheduled within two weeks of the planned EOT visit.
Assessments for the EOT are listed in Table 2–1.

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

8.1.10 Unscheduled visit

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

The following forms can be found in the unscheduled visit in the eCRF:
- Central lab
- Dosing of N9-GP
- Surgery (Record on 'unscheduled visit' form in eCRF even if performed on a regular visit)
- PK session (Record on 'unscheduled visit' form in eCRF even if performed on a regular visit)

8.1.11 Inhibitor Follow-Up visit

The inhibitor follow-up visit (IFU) should be performed when a patient has a confirmed high titre inhibitor (≥5BU) according to section 8.4.2.2. The patient must be withdrawn from N9-GP treatment upon confirmation of the second test of high titre inhibitor. Three inhibitor follow-up visits must be scheduled with 4 weeks ±7 days interval after confirmation of the inhibitor.

The end of trial visit and EOT assessments should take place in connection with the third IFU visit. The IWRS withdrawal session should not be performed before EOT visit.

In case the patient has been treated with FIX coagulation factors including plasma-derived activated prothrombin complex concentrates (pd-aPCC) within 4 days or FVIIa within 1 day prior to the first

inhibitor follow up visit, the visit must be postponed, please refer to Section 8.4.2.2 for further details.

In the rare case where a patient develops N9-GP binding antibodies and where it at the same time is evaluated by the Investigator that the patient should not continue in the trial based on e.g. decreased drug efficacy, the patient should attend inhibitor follow up visits similar to those described for patients with inhibitors.

Assessments to be performed
- Adverse Events
- Concomitant medication
- Sampling for inhibitor test
- Sampling for FIX activity test
- Sampling for N9-GP binding antibodies
- Sampling for Lupus anticoagulant

Reminder
- Follow up on any AEs according to Section 11.2

8.1.12 Home treatment

Home treatment with N9-GP can commence any time after the first 20 EDs and the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process. See Section 5.3.5

8.1.12.1 Prophylactic home treatment

During main and extension phase, the dose for prophylaxis is 40 IU/kg once weekly ±1 day, See Table 5-1 and Section 8.5

Bleeding episodes must be treated as described in Section 8.6.

The following procedures must be performed during home treatment between visits:
- N9-GP administrations once weekly ±1 day (preferable same week day)
- Prior to each N9-GP administration the patient's parent(s)/LAR(s) must check that neither N9-GP, solvent nor injection kit have expired
- Contact to the investigator/medically qualified person in case of severe bleeding episodes or if bleeding episodes has not responded sufficiently to treatment within 24 hours
- Completion of the patient eDiary, including details of all bleeding episodes and N9-GP administrations

8.1.12.2 Home treatment of bleeding episodes

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

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

The following procedures must be performed

- N9-GP administration for treatment of any bleeding episodes, see Section 8.6
- Completion of the patient eDiary, including details of all bleeding episodes and N9-GP administrations.

8.2 Patient related information

8.2.1 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial at the first visit, (V0) or found as a result of a screening procedure. All concomitant illnesses should be reported including the disease under investigation.

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

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

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

8.2.1.1 Details on haemophilia and haemophilia treatment history

All available information on haemophilia, prior to screening should be recorded including diagnostic FIX activity level, if known. If possible, information about relatives with haemophilia B and inhibitors should be obtained.
Any previous exposures to FIX concentrates and/or blood product components prior to visit 0 must be recorded incl. type or brand, dose/kg bodyweight and date of administration

8.2.1.2 Allergies

Any allergies, including any drug sensitivities should be recorded.

8.2.2 Concomitant medication

A **concomitant medication** is any medication including vaccination, other than the investigational medicinal product (N9-GP), which is taken during the trial until EOT.

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

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

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

8.2.3 Treatment of bleeding episodes in low titre inhibitor patients < 5 BU

Bleeding episodes in low titre inhibitor patients that do not respond sufficiently to N9-GP treatment may in addition be treated with bypassing agents according to local label for a period of up to 2 years. It is recommended to avoid FIX containing bypassing agents. Patients will stay in the trial and continue the 40 IU/kg N9-GP treatment. The time of administration of other haemostatic medication (including bypassing agents) should be entered in the eCRF/eDiary.

8.2.4 Prohibited medication

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

8.2.5 Demography

Demographic data will be collected as allowed per local law:

- Date of birth, year or age (year:months)
- Ethnicity
- Race

8.3 Clinical assessments

Clinical assessments should preferably be performed prior to blood sampling and prior to administration of N9-GP unless it is stated otherwise.

8.3.1 Body measurements

- Height will be collected at visits according to Table 2–1. For patients who have already attended visit 23 and/or visit 28 height at these visits ± 1 month will be collected retrospectively if available in medical records upon parent(s)/LAR(s) consent
- Body weight, wearing light clothing only

Body weight should be measured in connection with regularly visits where trial drug is dispensed. For practical purposes when dispensing trial drug the body weight from an earlier measurement (or visit) can be used if the measurement was performed within the previous 12 weeks (in children < 3 years of age, within 6 weeks). After visit 29, a body weight measured within the previous 12 weeks for all age groups can be used. If new body weight is not needed to be measured at a visit, the body weight from last weighing should be used.

8.3.2 Physical examinations

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

- General appearance
- Head, ears, eyes, nose, throat and neck
- Lymph node palpation
- Abdomen
- Skin
- Respiratory system
- Musculoskeletal system
- Central and peripheral nervous systems (general evaluation)
  - Elaborated neurological examination, see Section 8.3.2.1
- Cardiovascular system

8.3.2.1 Neurological Examination

Following aspects of the neurological examination will be assessed:

- General appearance including language, social and developmental aspects, handedness, head circumference, fontanelle assessment (<18 months), and level of consciousness
- Cranial nerves in relation to sight including reaction to light, visual fields and acuity, and eye movements, facial sensation and movement, hearing, palate sound and tongue movement, and trapezius muscle function
- Tone of truncal, upper and lower extremity right and left, and general tone (<18 months)
- Strength of upper and lower extremity right and left
- Reflexes of biceps, triceps, knee and ankle jerk, all right and left, Babinski as well as infantile reflexes (<6 months)

- Sensory aspect of cold, pin prick, light touch and proprioception (toe up/down)
- Gait with regards to walking, running, on heels and toes, tandem (toe/heel walk), stand/hop on one leg/foot right and left, and Romberg sign
- Coordination and Fine Motor including finger-to-nose, rapid index finger tab and rapid finger movement right and left

The timing of the neurological assessments should be planned to allow as much flexibility for the patients as possible and can be made within ±1 month of the visits, except for the visit 1 and EOT visit where the neurological assessments can be made at the visit date or up to 1 month ahead of the visit. In addition to this after trying to obtain the various assessments within acceptable limits without success the individual assessments can be omitted. Moreover, some aspects of the neurological examination may not be applicable for children in particular age groups as evaluated by the Investigator. Each aspect of the neurological examination will be categorised into normal, abnormal (pre-existing or new) or not examined.

8.3.3 Neurocognitive assessments

Neurocognitive assessments should be performed according to Table 2–1, Table 2–2, Table 8-1 and Table 8-2
The following domains will be assessed in all countries:

- Executive function
- Attention/processing speed/working memory

Further, the following domains will be assessed in English speaking countries (e.g. Australia, Canada, United Kingdom, and the United States):

- Neurodevelopment or cognitive function and intelligence
- Emotional behaviour
- Adaptive behaviour

The timing of the neurocognitive assessments should be planned to allow as much flexibility for the patients as possible and can be made within ±1 month of the assessment visits, except for the visit 1 and EOT visit where the neurocognitive assessments can be made at the visit date or up to 1 month ahead of the visit. The first assessment should be planned for the visit immediately after the patient turns either 1 or 2 years of age depending on country. Hereafter the visit schedule as found in Table 8-1 and Table 8-2 should be followed except if the next planned assessment visit is within three months of the initial assessment. All assessments should be performed using generally accepted standardised testing parameters to ensure optimal conditions for performance. A description of

neurocognitive assessments, training, equipment and related procedures will be provided in the Manual for neurocognitive assessments.

An independent External Expert Review Panel will evaluate the results of the neurocognitive assessments in context of the Structured Developmental History and Haemophilia History for each patient. Information regarding responsibilities, procedures, meeting frequency and workflow to be used by the External Expert Review Panel are specified in the External Expert Review Panel charter.

A CRO will provide the results from the External Expert Review Panel to Investigator as narrative reports including normalised domain scores and categorical assessment. It is the responsibility of the Investigator to report any findings if considered qualifying for an AE. If any findings are present at V0 it should be recorded as medical history.

The following Structured Developmental History and Haemophilia History data will be collected in connection with the neurocognitive assessments:

- Demographics
- Parents/caregivers
- Brothers/sisters/other children
- Child´s residence
- Pregnancy
- Birth
- Development
- Medical history
- Family health
- Educational history
- Haemophilia history

Table 8-1 Neurocognitive assessments by age for all countries

Domain	Structured Developmental History and Haemophilia History	Executive Function	Attention / Processing Speed
Assessment visits **Patient age (year:months)**	**The first assessment should be planned for the visit immediately after the patient turns 2 years of age. Hereafter the following visit schedule should be followed except if the visit is within 3 months from the initial assessment: Visit 1, visit 20, visit 23, visit 26, visit 28, visit 29, and all subsequent visits until and including EOT**		
1:0 to 1:11			
2:0 to 3:6	Structured Developmental History and Haemophilia History	BRIEF-P (BRIEF-P 2:0-5:11y Parent)	
3:7 to 3:11	Structured Developmental History and Haemophilia History	BRIEF-P (BRIEF-P 2:0-5:11y Parent)	
4:0 to 5:11	Structured Developmental History and Haemophilia History	BRIEF-P (BRIEF-P 2:0-5:11y Parent)	[redacted] (Custom Battery - Peds (4-9)
6:0 to 6:11	Structured Developmental History and Haemophilia History	BRIEF-2 (BRIEF2 5-18y Parent)	[redacted] (Custom Battery - Peds (4-9)
7:0 to 7:11	Structured Developmental History and Haemophilia History	BRIEF-2 (BRIEF2 5-18y Parent)	[redacted] (Custom Battery - Peds (4-9)
8:0 to 9:11	Structured Developmental History and Haemophilia History	BRIEF-2 (BRIEF2 5-18y Parent)	[redacted] (Custom Battery - Peds (4-9)
10:0 to 10:11	Structured Developmental History and Haemophilia History	BRIEF-2 (BRIEF2 5-18y Parent)	[redacted] (Custom Battery - Adult (10-21)

Table 8-2 Additional neurocognitive assessments by age for English speaking countries (e.g. Australia, Canada, United Kingdom, and the United States)

Domain	Developmental History and Haemophilia History	Neurodevelopment / General Intelligence	Behavioural / Emotional	Adaptive behaviour
Assessment visits **Patient age (year:months)**	**The first assessment should be planned for the visit immediately after the patient turns 1 year of age. Hereafter the following visit schedule should be followed except if the visit is within 3 months from the initial assessment: Visit 1, visit 23, visit 28, visit 30, visit 32, visit 34, …, until and including EOT**			
1:0 to 1:11	Structured Developmental History and Haemophilia History	Bayley-III		ABAS-3 (0-5y Parent)
2:0 to 3:6	Structured Developmental History and Haemophilia History	Bayley-III	BASC3 (PRS-P Parent 2-5)	ABAS-3 (0-5y Parent)
3:7 to 3:11	Structured Developmental History and Haemophilia History		BASC3 (PRS-P Parent 2-5)	ABAS-3 (0-5y Parent)
4:0 to 5:11	Structured Developmental History and Haemophilia History	WPPSI-IV	BASC3 (PRS-P Parent 2-5)	ABAS-3 (0-5y Parent)
6:0 to 6:11	Structured Developmental History and Haemophilia History	WPPSI-IV	BASC3 (PRS-C Parent 6-11)	ABAS-3 (5-21y Parent)
7:0 to 7:11	Structured Developmental History and Haemophilia History	WASI-II	BASC3 (PRS-C Parent 6-11 form)	ABAS-3 (5-21y Parent form)
8:0 to 9:11	Structured Developmental History and Haemophilia History	WASI-II	BASC3 (PRS-C Parent 6-11form and SRP-C 8-11 patient form)	ABAS-3 (5-21y Parent form)

10:0 to 10:11	Structured Developmental History and Haemophilia History	WASI-II	BASC3 (PRS-C Parent 6-11 form and SRP-C 8-11 patient form)	ABAS-3 (5-21y Parent form)

8.3.4 Vital signs

When dosing the first time (V1), vital signs should be recorded pre-dose and post-dosing of N9-GP. Hereafter vital signs will only be measured pre-dose and according to Table 2–1.

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

Vitals signs include assessment of:

- Body temperature (C/F)
- Blood pressure (BP) (mm Hg)
- Pulse (beats/min)

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

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

8.4 Laboratory assessments

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

The sample taken 30 minutes (±10 minutes) post-dose can be taken from the same vein as used for administration of N9-GP if more than 30 minutes have passed after the injection. The same device used for trial drug injection cannot be used for blood draw post-dose.

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

The central laboratories provide results to the trial site in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

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

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

8.4.1 Local laboratory assessments

The trial site must be able to analyse for FIX activity and inhibitors locally if needed to decide on the appropriate medical care. Results of any analyses performed locally will not be recorded in the eCRF except for results at Visit 0.
Local laboratory results are considered as source data and must be signed, dated and categorised by the investigator.

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

8.4.1.1 FIX activity

- FIX activity (% or IU/mL)

If V0 and V1 are combined, as one combined screening visit, and if FIX activity ≤ 2% has not been documented in the patient medical records, it should be analysed locally and documented in the patient medical records.

FIX activity can be measured using a one-stage clotting or a chromogenic assay. If an aPTT based one-stage clotting assay is used it should be calibrated with a N9-GP reference standard.

The reference standard will be provided by Novo Nordisk together with a description of how to handle, store and use. The site must ensure that the reference standard has not expired and order new when relevant.

Dependent on the type of aPTT reagent used by the local laboratory an exemption from this requirement of using the N9-GP reference standard can be made, in such cases Novo Nordisk will need to approve the suggested assay set-up on an individual basis. For approval of aPTT reagents in the one-stage clotting assay the investigator must contact Novo Nordisk.

FIX activity may also be measured with a chromogenic assay if available at the local laboratory. In such cases the N9-GP reference standard is not needed.

8.4.2 Central laboratory assessments

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

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

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

8.4.2.1 FIX activity

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

FIX activity samples should be taken according to Table 2–1.

FIX activity will be measured by the use of the FIX one-stage clotting assay.

Until the implementation of Amendment 6 to the protocol any surplus samples were analysed for FIX activity using the chromogenic assay if deemed relevant.

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

8.4.2.2 Antibody assessments

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

Plasma samples will be collected for assessment of:

- N9-GP binding antibodies
- FIX inhibitors
- HCP antibodies

Antibody samples should be taken according to Table 2–1.

N9-GP binding antibodies

Screening for antibodies is based on assays that are validated according to international recognised guidelines.[14-16] Samples measured above the assay cut-point will be subject to a confirmation test. Samples positive in the confirmatory test will be characterised for specificity to N9-GP, rFIX, and PEG. Isotyping of the anti-drug antibodies will possibly also be performed.

Samples will be analysed regularly for N9-GP binding antibodies and will be reported to the investigators at the end of the trial, or when considered relevant. A positive binding antibody sample will not by itself call for any action, but will be part of the continuous evaluation by sponsor of patient safety and treatment efficacy. In case of clinical suspicion of reduced treatment efficacy, an unscheduled visit must be scheduled by the investigator for measurement of FIX inhibitors, N9-GP binding antibodies and peak/trough FIX activity respectively.

FIX inhibitors

A FIX inhibitor test is defined as positive if the titre is ≥0.6 BU.

A patient has inhibitory antibodies (inhibitor) if tested positive for inhibitors (≥0.6 BU) at two consecutive tests performed at the central laboratory and also tested positive for N9-GP binding antibodies.

If the result of an inhibitor test is positive, a second confirmatory inhibitor test should be performed by the central laboratory (except for the visit 1 sample that will not need to be confirmed). The confirmatory samples should be collected between 1 and 4 weeks after the first positive inhibitor test, but no sooner than 7 days after the last dose of N9-GP. Sampling for assessments of FIX activity (trough and recovery), N9-GP binding antibodies and lupus anticoagulant must also be performed at the same time.

If the result from the lupus anticoagulant test is positive and N9-GP binding antibody test is negative the patient is considered inhibitor negative and can continue in the trial. If the result from the lupus anticoagulant test is positive and N9-GP binding antibody test is positive the patient is considered inhibitor positive.

The confirmatory test will define the level of inhibitors. Inhibitors will be considered as low titre between 0.6 BU and <5 BU and high titre ≥ 5 BU.

If a patient has a confirmed high titre inhibitor N9-GP treatment must be stopped and inhibitor follow-up visits must be planned, see Section 8.1.11.

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

If an investigator decides to perform inhibitor testing locally, he/she must send a duplicate sample for inhibitor testing at a central laboratory. The results from the central laboratory will be used in the analysis of trial data. A positive inhibitor test must always be reported as a MESI irrespective of the test being performed locally or at the central laboratory (refer to Section 11.2, 11.1).

Assessment for FIX inhibitors will be carried out using a heat modified Nijmegen FIX Bethesda assay analysed at a central laboratory. The assay is validated according to international recognised guidelines.[14, 17] The assay is based on measurement of the ability of a plasma sample to inhibit FIX in normal plasma.

PK session (conditional)

In the event of a concern about reduced treatment efficacy it is strongly recommended to perform an unscheduled visit where pre-dose and 30 min post-dose FIX activity (through and peak) and binding antibodies will be assessed. In case of development of binding antibodies a PK session is recommended to be performed with a dose of 40 IU/kg. The PK session will help to address the impact on the efficacy of the N9-GP treatment.

Novo Nordisk can decide based on bleedings, N9-GP usage and the PK profile to call for a safety committee meeting regarding recommendation on the trial continuation of the patient and how the patient should be followed if recommended to continue in the trial. The investigator will be informed of the recommendation from the safety committee.

The suggested time-points for blood sampling for a PK profile session are: pre-dose (within 1 hour prior to dosing), 30 min (± 10 min), 24 h (± 8 h), 48 h (± 8 h). Optional time-points are 72 h (± 8 h) and 96 h (± 8 h).

HCP antibodies

All patients will be assessed for the development of antibodies against Chinese hamster ovary host cell proteins (HCP). Screening for Chinese hamster ovary HCP antibodies is based on assays that are validated according to international recognised guidelines.[14-16] Samples measured above the assay cut-point will be subject to a confirmation test, where the signal will be sought inhibited with excess HCP antigen. The samples will be analysed at a laboratory selected by Novo Nordisk A/S or at a Novo Nordisk laboratory.

HCP antibodies will be taken according to Table 2–1. Samples will be analysed at the end of the trial, or when confirmed relevant by Novo Nordisk.

8.4.2.3 HIV testing and CD4+ lymphocyte count

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

Tests for CD4+ lymphocyte count and HIV viral load are only required for HIV positive patients. HIV positive patients should have CD4+ lymphocytes >200/µL and the HIV viral load <400,000

copies/mL. If the patient is not immunocompetent according to the above mentioned criteria relevant anti-HIV treatment should be initiated.

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

- HIV antibodies (positive/negative)
- CD4+ lymphocyte count
- HIV viral load

HIV and CD4+ samples should be taken according to Table 2–1.

8.4.2.4 Haematology

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

Haematology samples should be taken according to Table 2–1 however

- If test results for the above mentioned haematology parameters are available from within one month prior to V0 they can be used for the V0 haematology assessment
- If test results are more than one month old at visit 0 a new sample must be drawn and shipped for analysis at the central laboratory
- If V1 is more than a month after V0 a new haematology sample for central laboratory must be drawn at visit 1 prior to administration the first dose of N9-GP.
- Results from haematology samples taken within ±1 month of visits 23 and 28, or within 1 month before EOT, can be used for the respective visits if analysed at the central laboratory.

8.4.2.5 Biochemistry

The following analyses will be performed by the central lab

- Creatinine
- Alanine aminotransferase (ALT)
- C-reactive protein (CRP)
- Urea / BUN
- Total bilirubin

And to the extent the blood volume collected allows:

- Sodium
- Potassium
- Albumin
- Aspartate aminotransferase (AST)

- Gamma glutamyl transferase (GGT)
- Alkaline phosphatase

Biochemistry samples should be taken according to Table 2–1; however

- If test results for creatinine, alanine aminotransferase, and C-reactive protein are available from within one month prior to V0 they can be used for the V0 biochemistry assessment
- If V1 is more than a month after V0 a new biochemistry sample for central laboratory must be drawn at visit 1 prior to administrating the first dose of N9-GP
- If biochemistry assessments at V0 were local assessments a new biochemistry sample for central laboratory must be drawn at V1 prior to administrating the first dose of N9-GP if the blood volume allows
- Results from biochemistry samples taken within ± 1 month of visits 23, visit 26, and at all visits from visit 28 to EOT visit can be used for the respective visits if analysed at the central laboratory.

8.4.2.6 *F9* and *HLA* genotype testing

At Visit 0, all patient's parent(s)/LAR(s) will be asked about documentation of previous *F*9 and Human Leucocyte Antigen (*HLA*) genotype tests and results should be recorded in the eCRF, if available. If not available or if it needs to be re-tested, based on the investigators discretion, *F*9 and *HLA* genotype sample should be taken prior to administrating the first dose of N9-GP or as soon as possible taking the limitation of the allowed blood sampling volume into account. The *F*9 and *HLA* genotype analysis will be performed at a laboratory selected by Novo Nordisk A/S. No analysis will be performed concerning other genes than *F*9 and *HLA*. Samples will be disposed appropriately after the test and all test results are kept confidential.

Only applicable for Israel: *The parent(s)/LAR(s)/caregiver of withdrawn trial patients enrolled under protocol version 1, dated 4 November 2013, will be approached for consent to obtaining the F9 genotype, if already available.*

8.4.2.7 Investigation of allergic reactions

Allergic reaction testing will only be performed in patients developing a severe allergic reaction which by the investigator is assessed to be related to the N9-GP treatment. The baseline sample taken at Visit 0 or Visit 1 pre-dose will only be analysed in this case and further blood samples should be taken at an unscheduled visit as soon as convenient, but no later than 2 months after the event. The allergic reaction assessments will be performed at a laboratory selected by Novo Nordisk A/S or at a Novo Nordisk laboratory.

Tests to be performed:

- N9-GP IgE antibodies
- FIX IgE antibodies

- FIX inhibitors
- Tryptase
- N9-GP/rFIX binding antibodies

Other supportive allergic tests related to an allergic reaction may be performed by Novo Nordisk:

- HCP IgE antibodies
- HCP IgG antibodies
- Histamine (Only relevant if sample is drawn within 15 min of the allergic reaction)
- Complement activation test (C3, C4) (Only relevant if sample is drawn within 15 min of the allergic reaction)

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

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

8.4.2.8 Urinalysis

Urine samples should be taken according to Table 2–1. Urine samples should be obtained if possible, but to increase flexibility for patient, it can be made at home same day of visit and brought to site if transported in a cooling bag. The following parameters will be evaluated based on a urine sample:

- Albumin/Creatinine ratio
- Blood
- Leucocytes
- Protein
- Glucose
- pH

Albumin/Creatinine ratio will be measured at the central laboratory the rest will be analysed with dip-stick at site.

8.4.2.9 Exploratory analysis of PEG in plasma

The plasma concentration of PEG will be analysed for exploratory purposes according to Table 2–1. Blood samples for PEG analysis should be taken at visit 0 taking the limitation of the allowed blood sampling volume into account. If not taken at visit 0 the blood sample should be taken at visit 1 pre-dose, if the blood volume allows.

8.4.3 Blood sampling in infants and children

The blood sampling volume for the patient must not exceed 1% of the total blood volume at one occasion or 3% within in 28 days. This is in accordance with European regulatory guidelines (Directive 2001/20/EC).[18]

If all samples are taken the total volume of blood to be collected for each patient per visit will not exceed 18 mL.

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

It is recommended not to attempt venepuncture more than 3 times for the purpose of obtaining sufficient blood sampling. Documentation must be available in medical records. The vein used for trial drug injection cannot be used for blood sampling until more than 30 minutes have passed after the injection. The same device used for trial drug injection cannot be used for blood draw post-dose.

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

Only applicable for Portugal: For venous punctures, pain control measures are allowed according to local practice.

8.4.4 Storage of samples

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

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

Antibody samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA). The retained antibody samples may be used for further characterisation for antibody responses towards trial drug if required by health authorities or for safety reasons, see Section 23.2.

8.5 N9-GP administration

N9-GP will be administered while the patient is in a comfortable position and according to Table 5-1.

The first 20 EDs with N9-GP should be administered at the trial site. It is however possible to administer EDs 11-20 outside trial site if this is according with local procedures and must be under supervision of a health care professional qualified of handling anaphylactic reactions.

Precautions to take when injecting the first dose of N9-GP (V1)

- The patient has to be observed for 60 minutes in a hospital setting after N9-GP has been fully administered, with the line used left in place, if possible
- The first 0.5 mL of N9-GP should be administered slowly (for the duration of 1 minute), while the remaining N9-GP volume should be administered over a period of at least 2 minutes. The patient is to be observed closely during this administration, and the injection should be stopped immediately if any signs of allergic or anaphylactic reactions appear
- The date and the actual time of completion of the injection must be recorded in the eCRF

Precautions to take when injecting the second dose of N9-GP (V2)

- The patient has to be observed for 60 minutes in a hospital setting after N9-GP has been fully administered, with the line used left in place, if possible
- The dose of N9-GP should be administered as an i.v. bolus injection (maximum 4 mL/min). The patient is to be observed closely during this administration, and the injection should be stopped immediately if any signs of allergic or anaphylactic reactions appear
- The date and the actual time of completion of the injection must be recorded in the eCRF

Precautions to take when injecting ED 3-20 of N9-GP (V3-V20) at trial site

- The injection should be performed as an i.v. bolus injection (maximum 4 mL/min).
- The date and the actual time of completion of the injection must be recorded in the eCRF

Precautions to take when injecting ED 11-20 of N9-GP (V11-V20) outside the trial site

- Presence of a relevant health care professional qualified of handling anaphylactic reactions
- The injection should be performed as an i.v. bolus injection (maximum 4 mL/min).
- The date and the actual time of completion of the injection must be recorded in the eCRF

Trial injection kits (butterflies etc) will be provided by Novo Nordisk. Choice of butterfly or cannula for N9-GP injections is at the discretion of the investigator.

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

Home treatment from ED 21 and until EOT

Home treatment with administration of N9-GP can start after 20 EDs if the patient or the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process.

- Home treatment may be given by the patient's parent(s)/LAR(s) or a home nurse, as applicable
- The injection should be performed as an i.v. bolus injection (maximum 4 mL/min). The date and the actual time of completion of the injection must be recorded in the patient's eDiary
- All treatment requiring bleeding episodes should be treated and registered independently of the on-going prophylaxis treatment regime
- If a bleeding episode occurs earlier at the same day as the planned prophylaxis, the dose should be registered for the bleeding episode and not as prophylaxis and the planned prophylaxis dose later same day should be omitted
- When a prophylaxis dose has been taken and a bleeding episode occurs later the same day, the bleeding episode should be treated and registered independent of the prophylaxis dose.

8.6 Bleeding episodes

All bleeding episodes and treatments with N9-GP must be recorded in the eCRF by the investigator or in the eDiary by the patient's parent(s)/LAR(s). Bleeding episodes and other symptoms (eg synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. In case of life-threatening bleeding episode, it should always be reported as a SAE.

8.6.1 Assessments of bleeding episodes and treatment response

The severity of bleeding episodes is defined as

- Mild/moderate: Bleeding episodes that are uncomplicated joint bleeding episodes, muscular bleeding episodes without compartment syndrome, mucosal- or subcutaneous bleeding episodes. These bleeding episodes can be treated at home after visit 20 and details of the bleeding episodes should be entered in the eDiary by the patient's parent(s)/LAR(s).
- Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeding episodes must be categorised as severe. Muscle bleeding episodes with compartment syndrome and/or bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe (it is the investigators decision if haemoglobin measurements should be performed). The investigator must be contacted if a severe bleeding episode occurs.

In case of treatment requiring bleeding episode occurs outside the trial site's opening hours and prior to home treatment or treatment outside trial site (Section 5.3.5) has been initiated, the patient must be treated according to local procedure.

Bleeding Episode - information to be collected

Information about bleeding episodes prior to the 20 ED (V20) should always be recorded in eCRF. In case the patient is treated outside the trial site the trial site should be informed in case of a bleeding episode and the details hereof. After 20 EDs bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see Section 12.3.

Classification and recording of severe bleeding episodes is the responsibility of the investigator and should always be registered in the eCRF.

- Date and time the bleeding episode started
- Date and time the bleeding episode stopped
- Cause of the bleeding episode
  - i.e. spontaneous, traumatic or due to surgery
- Anatomical location of bleeding episodes
- Treatment of bleeding episodes
  - amount, date and time of each dose of N9-GP
- Severity of treatment requiring bleeding
    - mild/moderate, severe
- Haemostatic response assessed by the 4-point scale defined in the below Table 8-3

Table 8-3 4-point scale

Classification	N9-GP dosing	Description
Excellent	• One dose within 8 hours	Abrupt pain relief and/or clear improvement in objective signs of bleeding
Good	• One dose within 8 hours	Noticeable pain relief and/or improvement in signs of bleeding
Moderate	• More than one dose within 8 hours	Probable or slight beneficial effect after the first injection
Poor	• More than one dose within 8 hours	No improvement or worsening of symptoms

Re-bleed

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

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

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

8.7 Surgery

Before any surgery is performed blood samples for assessment of FIX inhibitors must be taken and send to central lab unless samples has already been sent to central lab within the last 30 days. The results do not have to be available before the surgery.

Emergency surgeries are allowed in this trial if adequate supply of N9-GP is available at site to ensure haemostasis and wound healing.

Patients undergoing surgery will continue the regular visit schedule, but additional visits may be performed in the peri-operative period as decided by the investigator. Surgery will be documented as unscheduled visits. It is up to the investigator to decide how long the post-surgery period should be and when the patient should resume regular prophylaxis or pre-prophylaxis treatment. All N9-GP doses administered in relation to a surgery must be registered on the surgery form in the eCRF or eDiary.

8.7.1 Minor surgery

Preventive N9-GP treatment before minor surgery including placement or removal of central venous access port can be performed within this trial at the investigator's discretion according to local guidelines. A dose of 40 IU/kg N9-GP prior to minor surgery is recommended to prevent perioperative bleeding episodes, see Table 5-1. Definition of minor surgery, see Section 5.3.8. For minor surgery the following should be recorded in the eCRF:

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

8.7.2 Major surgery

Major surgery can be performed while participating in the present trial. For definition of major surgery, see Section 5.3.8. Novo Nordisk must be contacted in due time prior to surgery, to ensure sufficient supply of N9-GP.

N9-GP dosing prior to, during and after surgery should aim at FIX activity levels as defined and recommended in the WFH Guidelines for the management of haemophilia.[8] The preoperative N9-GP dose should aim at FIX activity level of approximately 100% which is expected to be achieved with dose of 40 or 80 IU/kg of N9-GP. Trough and peak levels, and incremental recovery of the particular patient must be taken into consideration by the Investigator when deciding the dose.

During the post-operative phase, clinical haemostatic response combined with close FIX activity monitoring is recommended to determine appropriate intervals for postoperative dosing of 40 IU/kg N9-GP. The dose interval should be adjusted in order to reach postoperative FIX activity levels as recommended by the WFH Guidelines for the management of haemophilia.[8]

It is the responsibility of the Investigator to determine when the patient must stop the weekly prophylaxis administrations of N9-GP prior to the surgery and when these should be resumed after the surgery. If the patient has not resumed weekly prophylaxis within 6 days from the day of surgery the reason must be documented. The first weekly prophylaxis dose after surgery should be omitted if it falls on the same day (± 1day) as the last postoperative dose. The following must be documented:

- Date and time the patient stops the weekly prophylaxis with 40 IU/kg N9-GP prior to the surgery
- Date and time the patient resumes the weekly prophylaxis with 40 IU/kg N9-GP after the post-surgery period

During this period, all bleeding episodes and any haemostatic treatment administered must be recorded in the eCRF when the patient is at the site and in the eDiary when the patient is at home, refer to Section 12.3.

Perioperative procedures, assessments and blood sampling will be performed at the Investigators discretion and documented in the patients' medical records.

- Type of surgery (e.g. arthroscopy), indication (e.g. prosthetic knee replacement) and location
- Elective or emergency surgery
- Duration of surgical procedure: The date and time of first incision (knife-to-skin) and skin closure (last stitch)
- Concomitant medication, including anaesthetics and haemostatic medication
- Clinical narrative incl. description of any complication, estimated blood loss, if any re-operations etc.
- Blood product transfusions, if any: Type, volume (mLs), Start date and time
- Other i.v. infusions, if any: Type (ex. saline, crystalloids/colloids), concentration and volume (mLs), Start date and time
- Haemoglobin measurements, if any
- Clinical evaluation of haemostatic response to be evaluated upon completion of the surgical procedure by the Surgeon, Anaesthesiologist and/or Investigator, based on experience as follows:
    - Excellent: Better than expected/predicted in this type of procedure
    - Good: As expected in this type of procedure
    - Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen
    - Poor: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required

8.8 Training and reminders

8.8.1 Trial card dispensing

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

8.8.2 Home treatment training

Home treatment training with administration of N9-GP can start after administrations of the first 3 EDs at trial site until V20 (see Section 8.1.12), but may be postponed until the patient's parent(s)/LAR(s) are comfortable with the reconstitution and administration process.

A home treatment guide for the reconstitution will be available as handouts for the patient's parent(s)/LAR(s).

Training in reconstitution and administration must be performed until parent(s)/LAR(s) feel comfortable in handling the treatment. The training must be documented in the medical records.

All patient's parent(s)/LAR(s) must be carefully instructed in recognising and dealing with signs and symptoms of an anaphylactic reaction. If the patient does not follow the planned dosing schedule, the investigator must retrain the patient's parent(s)/LAR(s).

8.8.3 Electronic diary (eDiary)

Pre-prophylaxis treatment, prophylaxis treatment and bleeding episodes should be recorded in eCRF for the first 20 EDs. When the first 20 EDs have been administered, the data will be captured either in eCRF and/or eDiary according to Section 12.3.

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

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

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

8.8.3.1 eDiary dispensing and collection

The eDiary will be dispensed to the patient's parent(s)/LAR(s) latest at the visit when home treatment is started.

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

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

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

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

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

The communication will focus on the well-being of the patient, including enquiry of all AEs, and any medical treatment (including treatment of bleeding episodes) since the last contact. The

investigator/medically qualified person should not suggest specific AEs to patient's parent(s)/LAR(s), but should inquire e.g. "how is your child doing?", "has your child had any problems since the last contact?" and "have you remembered to enter all treatments in the eDiary?"

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

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

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

- Assessment of bleeding episodes
- Adverse events
- Concomitant Medication
- eDiary compliance
- N9-GP administration compliance

8.8.5 Interactive web response system

Please refer to Section 10 regarding the IWRS.

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

8.9 Patient compliance

Throughout the trial the investigator will remind the patient's parent(s)/LAR(s) to follow the trial procedures and requirements to ensure patient compliance. If a patient is found to be non-compliant, the investigator will remind the patient's parent(s)/LAR(s) of the importance of following the instructions given including taking the trial product as described.

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

Failure to comply with scheduled visits and N9-GP administration may result in withdrawal in accordance with the protocol withdrawal criteria, see Section 6.4.

Treatment with FIX concentrate, other than N9-GP, during the trial is not allowed and violation of this may lead to withdrawal due to non-compliance (please refer to Section 8.2.4). Regarding by-passing agent, see Section 8.2.3.

Compliance with N9-GP treatment must be addressed at each visit. Compliance check includes a cross check between number of injections recorded in eDiary, expected number of injections and the used/returned vials.

9 Trial supplies

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

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

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

9.1 Trial product

The following trial product will be provided by Novo Nordisk A/S, Denmark.

Table 9-1 Trial Product

Trial Product	Strength	Dosage form	Route of administration
N9-GP (nonacog beta pegol)	• 500 IU/vial • 2000 IU/vial	Freeze-dried Powder for solution for injection	i.v. injection

N9-GP is supplied as a sterile freeze-dried powder for solution for injection in single use vials with a nominal content of 2000 IU/vial or 500 IU/vial to be reconstituted with 4.2 mL Histidine solvent. After reconstitution each vial contains 500 IU/mL or 125 IU/mL N9-GP, respectively. The reconstituted solution is a clear and colourless solution free from clearly visible particles. The reconstituted solution must not be diluted further. The trial product must not be used if it does not appear clear and colourless free from clearly visible particles.

After reconstitution the appropriate volume of the vials will be drawn into a syringe. Maximum 4 mL should be withdrawn from each vial of reconstituted N9-GP. The content of several vials may be combined in one syringe. N9-GP may not be added to or mixed with any other material than Histidine.

Administration of the appropriate volume of N9-GP will be given as i.v. bolus injection. Maximum injection rate is 4 mL/min (please refer to Section 8.5).

The investigator must explain to the patient's parent(s)/LAR(s) how much this corresponds to in terms of injection time when administering N9-GP at home.

The maximum dose to be administered to a patient within 24 hours is 200 IU/kg, with a maximum individual dose of 80 IU/kg to be administered no more than every hour. These doses are only relevant in case of trauma, severe bleedings or surgery.

Histidine for reconstitution of the N9-GP trial product will be supplied by Novo Nordisk. Novo Nordisk will not supply any further Non Investigational Medical Products (NIMPs).

9.2 Packing, labelling and dispensing

Labelling of the trial product will be in accordance with Annex 13[19], local regulations and trial requirements. Novo Nordisk A/S will label and pack the trial product.

N9-GP and Histidine will be provided in boxes. The boxes will be provided with labels containing the following information: product name, expiry date and storage conditions. Each trial product box will have a unique Dispensing Unit Number (DUN) for identification and traceability.

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

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

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

9.3 Storage

Storage must be done according to the table below.

Table 9-2 Storage

Products	Storage conditions (not-in-use)	In-use conditions
N9-GP (nonacog beta pegol)	• 2-8°C • Protect from light	• 4 hours below 30°C • Do not freeze • Avoid direct sunlight
Histidine	• 2-25°C • Protect from light	N/A

The trial product N9-GP powder and Histidine solvent must be stored in a secure place at trial site. For N9-GP under refrigeration at 2-8°C, and for Histidine solvent at 2-25°C, both protected from light and are hereby stable until the expiry date given. It is recommended to use the reconstituted N9-GP immediately following reconstitution. If not used immediately, the reconstituted product can be stored in the vial for up to 4 hours below 30°C. Exposure to direct sunlight as well as freezing must be avoided after reconstitution. As for other parenteral preparations, the product should be inspected visually for particulate matter and discoloration prior to administration and discarded if either is present. 'In use time' starts from completion of the reconstitution, see the Handling instruction for further details. The trial site must carefully instruct the patients' parent(s)/LAR(s) in how to store the trial product. No temperature monitoring is required after the trial product is taken home by the patient.

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

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

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

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator. The investigator or delegated person, e.g., a trial nurse will perform drug accountability in the IWRS Drug Accountability Module.

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

Drug accountability is not required for Histidine solvent used for reconstitutions, but it is the responsibility of the investigator or delegate to follow Histidine expiry and prevent patient use after expiry.

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

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

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

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

9.5 Auxiliary supply

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

9.6 Shipment of trial product to patient's home

For selected countries and if permitted by local regulations, the investigator may offer to send trial product and auxiliaries from the trial site or pharmacy to the patient's home by courier service.

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

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

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

10 Interactive /web response system (IWRS)

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

IWRS is used for:

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

* For inhibitor patients attending inhibitor follow-up the IWRS withdrawal session should not be performed prior to EOT on the third inhibitor follow-up visit.

IWRS call can be done the day before the actual visit.

IWRS user manuals will be provided to each trial site.

11 Adverse events and technical complaints

11.1 Definitions

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

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

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

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

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

- **Causality assessment**
  The following terms are used when assessing the relationship between an AE and the relevant trial product:
  - **Probable** - Good reason and sufficient documentation to assume a causal relationship.
  - **Possible** - A causal relationship is conceivable and cannot be dismissed.

- **Unlikely** - The event is most likely related to aetiology other than the trial product.

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

Serious adverse event:

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

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

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

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

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

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

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

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

Non-serious adverse event

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

Medical event of special interest

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

1. Medication errors concerning trial product:
   - Administration of wrong drug
   - Wrong route of administration
   - Accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although not necessarily did happen.
2. Inhibitor formation against FIX. Blood samples for measurement of FIX inhibitors will be analysed at a central laboratory selected by Novo Nordisk A/S. If an investigator obtains information of a positive central laboratory result or any indication of inhibitor formation by clinical signs or local laboratory results, this should be reported as a MESI prior to confirmation by two central laboratory results.
3. Thromboembolic events (clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral

infarction/thrombosis, deep vein thrombosis, other clinically significant thormboembolic events and peripheral artery occlusion, see definitions below).
4. Anaphylactic reaction as defined by Sampson et al 2006[20] (see below).
5. Allergic reaction including, but not limited to, any acute immunoglobulin E (IgE) mediated reaction of delayed type hypersensitivity (clinical signs may include various types of skin rashes) that does not meet the definition of anaphylaxis as described by Sampson en al[20].
6. CNS-related adverse events, including but not limited to any learning and behavioural deficits. Examples include but are not limited to:
    - Headache
    - Seizures
    - Vision problems
    - Acute changes in mental status
    - Developmental, cognitive or behavioural issues
7. Renal adverse events including new onset of renal disorder or renal impairment or acute and chronic renal failure

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

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

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

Definition of pulmonary embolism:

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

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

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

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

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

Definition of other clinically significant thromboembolic events:
Sign or suspicion of clinically significant thromboembolic event, e.g.:

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

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

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

Clinical criteria for diagnosing anaphylaxis (infants and children only) (Sampson et al. 2006[20]):

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2x age]) from 1 to 10 years.

Technical complaint

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

Examples of technical complaints:

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

11.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient's parent(s)/LAR(s) has signed the informed consent until the end of the trial. The events must be recorded in the applicable CRF forms in a timely manner. See timelines below.

AEs experienced after signing of informed consent and before first dosing should only be reported if associated with trial related activities.

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

All AEs, either observed by the investigator or reported by the patient, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents: Investigator's Brochure[7], N9-GP, current version and any updates thereto.

For Japan only: If obtaining marketing approval in Japan, sponsor's assessment of expectedness is done according to the package insert of the commercial products in Japan.

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

For each SAE and MESI an electronic Safety Information Form (eSIF) should be completed in addition to the AE form in the eCRF. If several symptoms or diagnoses occur as part of the same clinical picture, one SIF may be used to describe all the SAEs. All concerned AE numbers must be included in the AE number field on the SIF.
MESIs, regardless of seriousness, must be reported using both the AE form and the safety information form. For MESIs of allergic aetiology, the hypersensitivity questionnaire must be completed.

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

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

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

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

- **MESIs of allergic aetiology:** The hypersensitivity questionnaire must be completed within 14 days

If the eCRF is unavailable, the concerned AE and SIF (if applicable) information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as

stated above. When the eCRF becomes available again, the investigator must re-enter the information on the appropriate forms in the eCRF.

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

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

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and GCP[1], unless locally this is an obligation of the investigator.

11.3 Follow-up of adverse events

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

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

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

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

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

calendar days of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria.

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

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

11.4 Technical complaints and technical complaint samples

11.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- N9-GP 500 IU/vial
- N9-GP 2000 IU/vial
- Histidine vial
- Novo Nordisk trial injection kit

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

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

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

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

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

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

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

11.4.2 Collection, storage and shipment of technical complaint samples

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

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

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

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

11.5 Precautions and/or overdose

As with any protein injected i.v. hypersensitivity reactions may occur. The possible events include rash, pruritus, fever, nausea, headache, vomiting and changes in blood pressure. If any of these events are suspected, further N9-GP administration should be stopped and the patient should receive treatment as appropriate according to the hospital practice and guidelines prior to further treatment with N9-GP.

If an overdose is suspected further N9-GP administration should be stopped and the patient should receive treatment as appropriate according to hospital practice and guidelines prior to further treatment with N9-GP.

11.6 Committees related to safety

11.6.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal N9-GP safety committee to perform ongoing safety surveillance.

The safety committee works according to a written guideline and will meet regularly to discuss and evaluate the overall safety of N9-GP for this trial and all other N9-GP trials.

Any event occurring after administration of N9-GP fulfilling the SAE/MESI criteria must be reported to Novo Nordisk. If one of the below mentioned criteria is fulfilled, all investigators will be informed in writing, and an extraordinary safety committee meeting will be called for to decide whether or not the trial can continue with or without modifications.

- Anaphylaxis in two patients after trial product administration
- Occurrence of two significant thromboembolic events in two different patients (e.g. myocardial infarction, pulmonary embolism, cerebral thrombosis/infarction or other significant thromboembolic events)
- Death related to trial product assessed by Novo Nordisk or by the Investigator

Dosing of patients on treatment may continue while further evaluation of the SAE/MESI is made, but recruitment of additional patients will be put on hold unless otherwise decided by the safety committee. The evaluation of fulfilment of the above criteria by the safety committee will take into consideration whether or not the patient was dosed according to protocol.

Furthermore, the safety committee will meet following every inhibitor (neutralising antibody, Bethesda unit of ≥ 0.6) confirmed by two consecutive tests at the central laboratory. Recruitment of new patients may continue during safety committee assessment of inhibitor formation.

Finally, the safety committee might meet in case of development of binding antibodies and suspicion of decreased drug efficacy.

12 Case report forms

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

The investigator or delegated person should ensure that all relevant questions are answered, and that no empty data field exists.

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

The following will be provided as paper CRF:

1. Hypersensitivity questionnaire

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

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

If a test or an assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

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

12.1 Corrections to case report forms

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

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

Corrections to the data in paper CRFs may only be made by drawing a straight line through the incorrect data and then writing the correct entry next to the data that were crossed out. Each

correction must be initialled, dated and explained (if necessary) by the investigator or the investigator's authorised staff.

Corrections necessary after the paper CRFs have been removed from the investigator's trial site must be documented on a Data Clarification Form (DCF) or a Monitor-Initiated Discrepancy Form (MIDF).

12.2 Case report form flow

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

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

When the final Clinical Trial Report (CTR) is available, the data will be archived by Novo Nordisk.

12.3 Electronic diary

Novo Nordisk will provide the patient's parent(s)/LAR(s) with an eDiary for electronic recording of details of their child's prophylaxis administration, bleeding episodes and treatment hereof, see Sections 8.1.1 and 8.6. The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

When initiating home treatment, the patient's parent(s)/LAR(s) will receive the eDiary and they will be trained in the use thereof by the investigator or delegated person. Data will be entered by the patient's parent(s)/LAR(s) in the eDiary device during home treatment.

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

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

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

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

It is the responsibility of the investigator or delegated staff to review and thereby ensure the eDiary data quality. Following must be checked as minimum: that the eDiary data is complete, consistent and according to the requirements defined in this protocol. Upon review the investigator or delegated staff must document that the review has taken place and any actions required e.g. retraining of patients.

It must be confirmed by the patient's parent(s)/LAR(s) if missing eDiary data need to be entered and/or if the transferred eDiary data needs to be corrected. This is done by filling in and forwarding a Data Clarification Form (DCF) to the eDiary vendor. An audit trail will be maintained.

12.4 Tablets for neurocognitive assessments

The CRO will provide the sites with tablets for neurocognitive assessments including Structured Developmental History and Haemophilia History. In some occurrences the collection of these assessments will be done on paper forms.

Data will be entered on the tablet at site by the patient, patient's parent(s)/LAR(s) and in some cases by trained staff. All data entered will be transferred from the tablet to a database.

The results of the assessments will be viewable on a web based portal when transmitted from the tablet. The web based portal is password protected.

13 Monitoring procedures

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

After site initiation visit, site should be contacted every quarter, and visited at least every 6 months. The contacts (calls or visits) can be part of a monitoring visit in another trial. These contacts should be documented.

A monitoring visit must be performed as soon as possible after FPFV and no longer than 4 weeks after. The monitoring intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The intervals between monitoring visits must not exceed 12 weeks whilst patients are in the trial between visit 0 and visit 28. In the period after visit 28, intervals between monitoring visits must not exceed 24 weeks ± 4 weeks (whilst patients are on the trial), provided site contact at least every 12 weeks. The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

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

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

- Ethnicity
- Race

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

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

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

For screening failures: Data for the screening visit must be entered in the eCRF within preferably 5 days after data are available and the Screening Failure Form must be completed. Source data verification is not required except for informed consent, reason for screening failure and for data relating to any AEs if applicable. All data entered in the eCRF will be transferred into the trial database.

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

All information captured during visits to the trial site will be collected either in the eCRF, via tablet or on paper questionnaires. When home treatment is initiated all bleeding episodes and injections with N9-GP occurring outside the trial site should be entered in the eDiary by the patient's parents/LAR (see Section 8.8.3). The completed eDiary is considered source data.

14 Data management

Data management is always the responsibility of Novo Nordisk.

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

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

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

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

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

The system and paper based questionnaires for neurocognitive assessments and support services for the systems will be supplied by a CRO. The CRO will collect, query, and process data from Structured Developmental and Haemophilia History, as well as Neurocognitive assessments. The CRO will transfer assessment results and outcomes from the External Expert Review Panel to Novo Nordisk.

15 Computerised systems

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

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

Novo Nordisk will use CONNECT as investigator portal to distribute and share trial-related documents and information with the participating sites.

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

16 Statistical considerations

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

The main statistical reporting of the trial will be performed when at least 20 patients have completed main phase (minimum 50 weeks) with at least 50 EDs and completed visit 23. Data from patients not yet having completed main phase and data from patients that have entered extension phase at this point will be included up to latest visit prior to this cut-off date. The data will be presented for the main phase and extension phase separately as well as combined. Except for the confidence interval for inhibitor rate and for annualised bleeding rate, the evaluation of data will be based on descriptive statistics, i.e. summary tables, listings and figures.

An updated statistical reporting of the trial with supportive data will be performed when at least 40 patients have had at least 100 EDs. Data from all patients will be included up to latest visit prior this cut-off date. The data will be presented for the main + extension phase and the extended prophylaxis period (beyond 100 EDs) separately as well as combined.

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

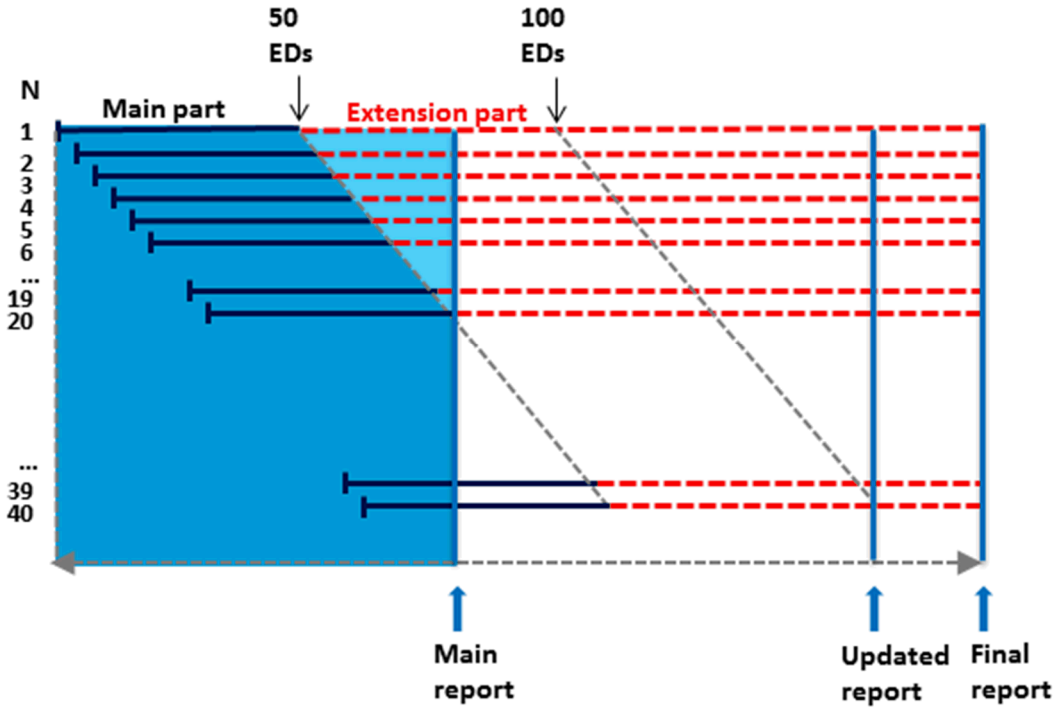

Figure 16–1 Individual patient flow and time period for main trial report

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

All bleeding endpoints will be evaluated based on bleeding episodes treated with N9-GP unless the bleeding was considered clinically insignificant (non-treatment requiring bleeding episode) and the associated treatment given was part of prophylaxis.

Neurocognitive assessments will be evaluated primarily based upon reference ranges gained from children and young adults of a parallel observational haemophilia normative study (HAEM-4436, eTHINK) and secondarily upon normative reference ranges from the general population to the extent possible. Individual case review by an External Expert Review Panel, considering also analysis of factors influencing outcome in haemophilia and reported in the structured developmental history, will be reflected in narrative and categorical assessments (see Section 8.3.3).

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

16.1 Sample size calculation

No formal sample size calculations have been performed. The sample size of 40 completers is based on EMA guideline[5].

16.2 Definition of analysis sets

Descriptions and analysis of efficacy will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines.[22] The FAS includes all patients exposed to N9-GP. The safety analysis and descriptions will be based on the Safety Analysis Set (SAS). The SAS will consist of all patients exposed to N9-GP.

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

16.3 Primary endpoint

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

The rate of inhibitory antibodies will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the rate the numerator will include the patients with inhibitors, while the denominator will include all

patients with a minimum of 10 exposure days plus any patient with less than 10 exposure days but with inhibitors.

16.4 Secondary endpoints

16.4.1 Confirmatory secondary endpoints

There are no confirmatory secondary endpoints.

16.4.2 Supportive secondary endpoints

16.4.2.1 Number of bleeding episodes during prophylaxis

Annualised bleeding rate will be summarised and a 95% two sided confidence interval will be provided based on a negative binomial regression model with number of bleeding episodes requiring treatment with N9-GP (also referred to as breakthrough bleeding episodes) as the outcome variable, and adjusting for exposure time. For comparison with previous trials, a sensitivity analysis based on a Poisson regression model allowing for over-dispersion will also be performed.

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

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

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

16.4.2.2 Haemostatic effect

Description of the haemostatic effect of N9-GP when used for treatment of bleeding episodes will be summarised and listed according to the four point scale for haemostatic response (poor, moderate, good and excellent).

A success rate will be calculated based on counting good or excellent as successes and poor and moderate as failures and based only on reported outcomes.

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

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

Haemostatic response will also be summarised by type of bleeding.

16.4.2.3 FIX activity

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

FIX trough level is defined as the activity recorded immediately before N9-GP injection is given and reported as IU/mL. IR_{30min} is defined as the rise in FIX activity per IU/kg administered and is recorded 30 minutes after the end of N9-GP injection, and reported as [IU/mL]/[IU/kg]. It is calculated as the pre-dose subtracted FIX activity recorded 30 minutes after ended N9-GP injection and dividing the administered dose (IU/kg body weight (bw)).

16.4.2.4 FIX consumption

Amount of N9-GP used for prophylaxis (IU/Kg/month/year) and amount consumed per bleeding episode (number of doses and IU/kg bw/bleeding episode) will be summarised and listed.

16.4.2.5 Safety endpoints

Adverse events including SAEs, MESI and development of HCP antibodies

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

MESIs will be summarised similarly to AEs.

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

HCP antibodies will be listed.

All additional safety parameters such as laboratory parameters, including calculation of estimated glomerular filtration rate (eGFR), and physical examinations, including neurological assessments, will be summarised and listed.

16.5 Neurocognitive assessments

Age-adjusted domain and composite scores for each neurocognitive instrument will be calculated using available methods.

The individual patient overall/domain/sub-scores for each neurocognitive assessment instrument will be expressed as an individual's Z-score (i.e. an indication of how many standard deviations a domain score is from the mean) and compared to reference ranges from normative data for children and young adults with haemophilia (adjusted for appropriate identified covariates) (HAEM-4436, eTHINK study). All the scores will be provided by a CRO. The individual score versus time of exposure (years) will be presented graphically per patient.

In addition, all data and scores will be summarised and listed.

16.6 Interim reporting

All data from main phase of the trial will be analysed and reported when minimum 20 patients have completed main phase with at least 50 EDs and completed visit 23. This report will cover all endpoints and will form the basis for the paediatric indication. Data from patients that have entered extension phase at this point will be included up to latest visit prior this cut-off date. The data will be presented separately for the main phase and extension as well as combined. The main conclusion from the trial will be drawn based on the main phase data.

Furthermore, interim analyses may be performed in association with marketing authorisation applications or in connection with Health Authorities e.*g.* FDA, EMA and PMDA requirement for/during the regulatory review or to obtain safety data.

An updated report with supportive data will be made when minimum 40 patients have had at least 100 EDs. A final report with supportive data will be made when all patients have completed both parts of the trial.

16.7 Sequential safety analysis and safety monitoring

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

16.8 Reporting of *F*9 and *HLA* genotype

Information about underlying gene defects of *F*9 and *HLA* will be listed in the clinical trial report. No statistical analysis will be performed.

17 Ethics

Participation in this trial could be a possible benefit for the patient in terms of closer monitoring of the patient by the investigator, compared to standard care and possible avoidance of bleeding episodes. As with all investigational drugs, there is an anticipated risk of potential side effect (ref. IB).[7]

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

17.1 Informed consent

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

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

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

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

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

A voluntary, signed and personally dated informed consent form must be obtained from the patient's parent(s)/LAR(s) before any trial-related activity. In this trial where informed consent and exposure to the N9-GP may occur on the same day, informed consent form must include a time field next to the date field.

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

For children, from birth to the age of 3 years old, it is not possible to obtain assent and understanding of research is not expected.[18]

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

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

The informed consent form contains a section explaining that Novo Nordisk is asking permission to store left over blood from blood samples and use it to analyse for further analyses characterising biomarkers within the trial. The accept is voluntary and independent on participation in the trial. If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient and/or the patient's parent(s)/LAR in a timely manner, and a revised written informed consent must be provided and a new informed consent must be obtained.

***F*9 and *HLA* genotype testing/collection of previous genotype documentation:**
If documentation of the patients' genotype already exists, the data can be used for trial purpose. Only the *F*9 and *HLA* genotype will be analysed by the central laboratory selected by Novo Nordisk A/S and no other genomic analyses will be carried out. Samples will be appropriately disposed of, after the test. All test results are kept strictly confidential in sufficient consideration of individual information.

17.2 Data handling

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

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

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

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

The trial site will be offered a communication package to the patient and/or the patient's parent(s)/LAR(s) during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters/booklets intended for distribution to the

patients. The letters/booklets will be translated and adjusted to local requirements and distributed to the patient and/or the patient's parent(s)/LAR(s) by discretion of the investigator. The patient and/or the patient's parent(s)/LAR(s) may receive a "welcome to the trial letter" and a "thank for your participation letter" at the end of the trial. Further the patient and/or the patient's parent(s)/LAR(s) may receive trial letters and/or small toy during the trial period.

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

17.4 Premature termination of the trial and/or trial site

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

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

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

18 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

19 Audits and inspections

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

20 Critical documents

An Investigator Portal (CONNECT) will be used as primary media for exchange and handling of investigator trial file documents between Novo Nordisk and the trial site.

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

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

Only applicable for US trial sites:

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

FDA form 1572:

For US sites:

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

For sites outside the US:

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

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

For local lab parameters the following will be collected:

- Laboratory normal ranges
- Laboratory certification/QA scheme/other documentation
- Laboratory methods (only non-standard assays) and/or analytic methods

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

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

21 Responsibilities

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

The investigator is accountable for the conduct of the trial at his/her trial site. If any tasks are delegated, the investigator must maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients. At least investigator must be trained in the protocol at a Novo Nordisk meeting or by web training in the protocol. It is recommended that all site staff takes the web protocol training. A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions. The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

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

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

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

During any period of unavailability, the investigator should delegate responsibility for medical care of patients to a specific qualified physician who will be readily available to patients during that time.

If the investigator is no longer able to fulfil the role of investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

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

22 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by Novo Nordisk for regulatory purposes and for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studies in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report.

A principal investigator will be designated as the signatory investigator with the responsibility to review and sign the main report based on data from when at least 20 PUP have reached at least 50 EDs.

22.1 Communication of results

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

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure[23].

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

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

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any

disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

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

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

22.1.1 Authorship

Authorship of publications should be determined in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors (sometimes referred to as the Vancouver Criteria[24]).

Authorship credit should be based on:

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

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

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

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

22.2 Investigator access to data and review of results

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

23 Retention of clinical trial documentation and human biospecimens

23.1 Retention of clinical trial documentation

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

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

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

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

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

23.2 Retention of human biospecimens

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

Blood samples apart from antibody and biospecimen samples will be destroyed after the finalisation of the CTR. Antibody samples (samples for binding antibodies and inhibitors) will be stored until drug approval by Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) or until the project terminates, but no longer than 15 years from end of trial. Biospecimens will be destroyed at the latest 15 years from end of trial. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of N9-GP may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial. The samples will be stored at Novo Nordisk A/S or a Novo Nordisk designated referral bio-repository with access to the samples. Samples might be transferred to other countries, if not prohibited by local regulations. The

patient's identity will remain confidential and samples will only be marked and identified by a unique sample ID (patient number and visit number). No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and bio-repository personnel (if applicable) will have access to the stored bio specimens.

24 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

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

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

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC (not applicable for Japan).

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

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

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

25 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with:

Only applicable for Argentina: Novo Nordisk Pharma Argentina S.A. has contracted insurance (policy reference number 87828 and its respective updates) with the company [redacted]. Domiciled in [redacted]. Telephone number: [redacted].

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

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

Only applicable for France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research".

Only applicable for Netherlands: Wetgeving betreffende geneesmiddelen; geneesmiddelenwet 1 juli 2007 (Medicines Law, 1 July 2007). De Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO), 1 maart 2006 (Medical Research Involving Human Subjects Act, 1 March 2006). Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015, 24 november 2014 (Decree compulsory insurance in medical research involving human subjects 2015, 24 November 2014).

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

Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law'.

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16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

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

Content: Global key staff and Country key staff.