Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT01467427
Sponsor trial ID:	NN7999-3774
Official title of study:	An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and pharmacokinetics of NNC-0156-0000-0009 (N9-GP) in prophylaxis and treatment of breakthrough bleeding episodes in previously treated children with haemophilia B (12 years of age and younger at inclusion), with extension phase
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*Document date refers to the date on which the document was most recently updated.

Trial ID: NN7999-3774

Safety, Efficacy and Pharmacokinetics of NNC-0156-0000-0009 in Previously Treated Children with Haemophilia B

An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and pharmacokinetics of NNC-0156-0000-0009 (N9-GP) in prophylaxis and treatment of breakthrough bleeding episodes in previously treated children with haemophilia B (12 years of age and younger at inclusion), with extension phase

Trial Phase: 3

Includes:
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List of abbreviations and definition of terms

ABAS-3	Adaptive Behavior Assessment System- Third Edition
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under the curve
BASC3	Behavior Assessment System for Children – Third Edition
BMI	body mass index
BP	blood pressure
BRIEF-2	Behavior Rating Inventory of Executive Function – Second Edition
BRIEF-A	Behavior Rating Inventory of Executive Function – Adult Edition
BU	Bethesda units
BW	body weight
C_{30min}	plasma FIX activity 30 minutes after end of injection
Caregiver	a close person who helps the patient in his daily life. It is not the investigator or the site staff
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CL	total clearance
CNS	central nervous system
CRF	case report form
CRO	contract research organisation
CRP	C-reactive protein
CV	curriculum vitae
DCF	data clarification form
DISP	dispensing
DUN	dispensing unit number
eCOA	electronic Clinial Outcome Assessment
eCRF	electronic case report form
ED	exposure day. One exposure day is defined as each day when a patient is administered coagulation factor IX for prophylaxis, prevention or on-demand treatment
EDC	electronic data capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePRO	electronic patient reported outcomes
EOT	end of trial
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FVII	coagulation factor VII
FVIII	coagulation factor VIII
FIX	coagulation factor IX
FIXa	activated coagulation factor IX
FX	coagulation factor X
FU	follow-up

GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HAEMO-QOL	haemophilia-quality of life
HCP	host cell protein
HCV	hepatitis C virus
HEMO-SAT	hemophilia satisfaction
HIV	human immunodeficiency virus
HRQOL	health related quality of life
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	The International Committee of Medical Journal Editors
IEC	independent ethics committee
IFU	inhibitor follow-up
IgE	immunoglobulin E
IMP	investigational medicinal product
INR	international normalised ratio
Investigator	the individual overall responsible for the conduct of the clinical trial at a trial site
IR_{30}	incremental recovery at 30 min calculated by dividing the baseline adjusted FIX activity (U/mL) measured in plasma 30 min after dosing by the dose injected at time 0 expressed as U/kg body weight
IRB	institutional review board
IU	international unit
i.v.	intravenous
IV/WRS	interactive voice web response system
λ_z	terminal elimination rate constant
LAR	legally authorised representative
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPLV	last patient last visit
m	months
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MESI	medical event of special interest
MIDF	monitor-initiated discrepancy form
MRT	mean residence time
N9-GP	glycopegylated recombinant coagulation factor IX (NNC-0156-0000-0009)
NIMP	non-investigational medicinal product
PCV	packed cell volume
PDCO	Paediatric Committee (EMA)
pd-aPCC	plasma-derived activated prothrombin complex concentrates
pdFIX	plasma derived FIX
pd-PCC	plasma-derived prothrombin complex concentrates
PEF	peak expiratory flow
PEG	polyethylene glycol
PK	pharmacokinetics
PIP	paediatric investigation plan
PRO	patient reported outcomes
PT	prothrombin time
PTP	previously treated patients

Recovery	maximum FIX activity after dosing (% or IU/mL)
rFVIIa	activated recombinant factor VII
rFIX	recombinant coagulation factor IX
SAE	serious adverse event
SAS	safety analysis set
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
TAPQOL	TNO-AZL preschool quality of life
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TMM	trial materials manual
TNO-AZL	The Dutch institute of Prevention and Health and the Leiden University Hospital
TVP	trial validation plan
UTN	Universal Trial Number
Vss	volume of distribution at steady state
w	weeks
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence Fourth Edition
WFH	World Federation of Hemophilia

1 Summary

Primary objective:

- To evaluate immunogenicity of glycopegylated recombinant coagulation factor IX (NNC-0156-0000-0009; hereafter referred to as N9-GP)

Primary endpoint:

- Incidence of inhibitory antibodies against coagulation factor IX (FIX) defined as titre ≥0.6 BU

Key secondary objectives:

- To evaluate safety other than immunogenicity of N9-GP
- To evaluate the efficacy of N9-GP in long-term prophylaxis and in the treatment of breakthrough bleeding episodes
- To evaluate the efficacy of N9-GP through the surrogate marker for efficacy, FIX activity
- To evaluate the pharmacokinetic (PK) properties of N9-GP

Key secondary endpoints:

- Number of bleeding episodes during prophylaxis
- Haemostatic effect of N9-GP in treatment of bleeding episodes by 4-point categorical scale for haemostatic response (excellent, good, moderate and poor)
- Incremental recovery at 30 minutes (IR_{30min})
- Trough level (single-dose and steady state)
- Terminal half-life ($t_{1/2}$)

Timeframes for evaluation of the endpoints:

All key PK endpoints, except trough steady state, will be evaluated at week 0. Trough steady state will be evaluated from week 4 to 44.

The main evaluation of all key endpoints will be done after 52 weeks of treatment. The evaluation of the extension phase will be done after the last patient has completed the trial.

Trial design:

This is an open label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and PK of N9-GP in prophylaxis and treatment of breakthrough bleeding episodes in previously treated paediatric male patients with haemophilia B.

The trial consists of a main phase and an extension phase. The duration of the main phase for each patient will be minimum 52 weeks and the extension phase will continue until LPLV.

The patients will be stratified into two age groups; 0-6 years and 7-12 years, both inclusive. A minimum of 10 patients in each age group must complete the main phase of the trial. The trial has one treatment arm where all patients receive N9-GP once weekly for prophylaxis. In the extension phase, a single dose of 40 IU/kg once weekly will be administered intravenously. Treatment with N9-GP will in addition be administered in case of breakthrough bleeding episodes.

Trial population:

Around 40 patients will be screened in order to start approximately 24 patients on trial product out of which 10 patients in each of the two age groups are expected to complete the main phase of the trial.

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

Key inclusion criteria:

- Male patients with moderately severe or severe congenital haemophilia B with a FIX activity level ≤2% according to medical records
- Age ≤12 years (until patient turns 13 years, at time of inclusion)
- Body weight ≥10 kg
- History of at least 50 exposure days (EDs) to other FIX products
- The patient and/or parent(s)/caregiver are capable of assessing a bleeding episode, keeping an electronic diary (eDiary), capable of conducting home treatment and otherwise able to follow trial procedures

Key exclusion criteria:

- Known history of FIX inhibitors
- Current FIX inhibitors ≥0.6 Bethesda Units (BU)
- Congenital or acquired coagulation disorder other than haemophilia B
- Platelet count <50,000/µL at screening
- Alanine aminotransferase (ALT) >3 times the upper limit of normal reference ranges at screening
- Creatinine level ≥1.5 times above the upper normal limit of normal reference ranges at screening
- Human immunodeficiency virus (HIV) positive, defined by medical records, and with a CD4+ lymphocyte count ≤200/µL
- Immune modulating or chemotherapeutic medication (except single pulse treatment, inhaled and topical steroids)
- Previous arterial thrombotic events (myocardial infarction and intracranial thrombosis, as defined by medical records)

Safety assessments:

Adverse events (AEs) and inhibitory antibodies against FIX will be assessed at each visit throughout the trial.

Efficacy assessments:

The number of bleeding episodes and FIX consumption, for prophylaxis and in treatment of bleeding episodes, will be monitored throughout the trial. Furthermore, the haemostatic effect of N9-GP in treatment of bleeding episodes will be assessed. FIX activity, a surrogate marker for efficacy, will be measured pre- and post-dose at visits in the main phase of the trial.

Pharmacokinetic assessments:

Patient's previous FIX product: If no recovery data are available in medical records, a recovery sample will be collected 30 minutes after dosing with the patient's current product at Visit 1.

N9-GP: All patients must undergo a PK evaluation at Visit 2. The patients will have one PK sample taken prior to dosing with N9-GP and one sample taken 30 minutes post-dose. Four additional PK samples will be collected at 4 different days during the following 7 days.

Trial products:

The following trial products will be used in the trial:

- N9-GP Drug Product
- Histidine solvent

N9-GP Drug Product is supplied as freeze-dried powder in single-use vials to be reconstituted with Histidine solvent. The trial product will be administered as an intravenous (i.v.) bolus injection with a maximum injection rate of 4 mL/min.

A single dose of 40 IU/kg N9-GP will be administered intravenously once weekly during the main phase of the trial. In the extension phase, the same dosing regimen is administered. Patients who experience a bleeding episode should treat the bleeding episode with a single dose of 40 IU/kg N9-GP, unless the bleeding episode is severe, in this case they should be treated with 80 IU/kg N9-GP.

2 Flow charts

Table 2-1 Flow chart for the main phase of the trial

Visit number	**1**[1]	**2**[5, 8]	**3**[11]	**4-6**[11]	**7-10**[11]	**11**[5, 11]	**FU**[5,12]	**IFU1-3**[7]
Visit purpose	**Screening**	**N9-GP first dose**	**N9-GP second dose**	**N9-GP dosing (visits every fourth week)**	**N9-GP dosing (visits every eight week)**	**End of main phase**	**Follow-up visit**	**Inhibitor follow-up visits**
Time of visit (weeks)	**6 w prior to Visit 2**	**0**	**1 w**	**4-12 w**	**20-44 w**	**52 w**	**3 w after Visit 11**	**Every 4 wks after Visit 11**
Visit window (days or weeks)	**±2 w**	**-**	**+1 d**	**±1 w**	**±1 w**	**+2 w**	**±1 w**	**±1 w**
PATIENT RELATED INFORMATION								
Informed consent	X							
Consent to genotyping (if applicable)	X							
Inclusion/exclusion criteria	X	X						
Withdrawal criteria		X	X	X	X	X		
Patient Reported Outcome questionnaires	X					X		
Demography	X							
Concomitant illness	X							
Medical history including haemophilia treatment history, details on haemophilia, inhibitors and joints	X							

Visit number	**1**[1]	**2**[5, 8]	**3**[11]	**4-6**[11]	**7-10**[11]	**11**[5, 11]	**FU**[5,12]	**IFU1-3**[7]
Visit purpose	**Screening**	**N9-GP first dose**	**N9-GP second dose**	**N9-GP dosing (visits every fourth week)**	**N9-GP dosing (visits every eight week)**	**End of main phase**	**Follow-up visit**	**Inhibitor follow-up visits**
Time of visit (weeks)	**6 w prior to Visit 2**	**0**	**1 w**	**4-12 w**	**20-44 w**	**52 w**	**3 w after Visit 11**	**Every 4 wks after Visit 11**
Visit window (days or weeks)	**±2 w**	**-**	**+1 d**	**±1 w**	**±1 w**	**+2 w**	**±1 w**	**±1 w**
Medical record of HIV status	X							
Medical record of HCV status	X							
F9 genotype documentation (if applicable)	X							
Concomitant medication	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration	X	X					X	X
Assessments of bleeding episodes	X	X	X	X	X	X	X	
Compliance review of drug administration and eDiary completion				X	X	X		
ADVERSE EVENTS								
Adverse events	X	X	X	X	X	X	X	X
CLINICAL ASSESSMENTS								
Body measurements	X	X[6]			X[6]	X[6]		
Physical examination	X				X[14]	X		

Visit number	**1**[1]	**2**[5, 8]	**3**[11]	**4-6**[11]	**7-10**[11]	**11**[5, 11]	**FU**[5,12]	**IFU1-3**[7]
Visit purpose	**Screening**	**N9-GP first dose**	**N9-GP second dose**	**N9-GP dosing (visits every fourth week)**	**N9-GP dosing (visits every eight week)**	**End of main phase**	**Follow-up visit**	**Inhibitor follow-up visits**
Time of visit (weeks)	**6 w prior to Visit 2**	**0**	**1 w**	**4-12 w**	**20-44 w**	**52 w**	**3 w after Visit 11**	**Every 4 wks after Visit 11**
Visit window (days or weeks)	**±2 w**	**-**	**+1 d**	**±1 w**	**±1 w**	**+2 w**	**±1 w**	**±1 w**
Vital signs	X	X	X[16]			X		
LOCAL LABORATORY ASSESSMENTS								
Haematology	X	X[4]				X		
CENTRAL LABORATORY ASSESSMENTS								
Biochemistry	X					X		
Coagulation-related parameters		X[4]				X		
FIX recovery (for previous FIX product)	X[3]							
FIX activity[19]	X					X	X	X
-pre-dose		X		X	X			
-post-dose (30 min)		X[2]		X a)	X b)	X b		
N9-GP/FIX antibodies		X[4]		X	X	X	X	X
FIX inhibitors	X	X[4]		X	X	X	X	X
HCP antibodies		X				X		X

Visit number	**1**[1]	**2**[5, 8]	**3**[11]	**4-6**[11]	**7-10**[11]	**11**[5, 11]	**FU**[5,12]	**IFU1-3**[7]
Visit purpose	**Screening**	**N9-GP first dose**	**N9-GP second dose**	**N9-GP dosing (visits every fourth week)**	**N9-GP dosing (visits every eight week)**	**End of main phase**	**Follow-up visit**	**Inhibitor follow-up visits**
Time of visit (weeks)	**6 w prior to Visit 2**	**0**	**1 w**	**4-12 w**	**20-44 w**	**52 w**	**3 w after Visit 11**	**Every 4 wks after Visit 11**
Visit window (days or weeks)	**±2 w**	**-**	**+1 d**	**±1 w**	**±1 w**	**+2 w**	**±1 w**	**±1 w**
Plasma PEG levels[20]	X	X	X	X	X	X		
Allergic reaction testing[13]		X				X		X
Viral antibody test (if HIV and/or HCV status is unknown)	X							
CD4+ lymphocyte count (if HIV positive)	X							
HCV RNA (if HCV positive)	X[18]							
F9 genotype testing (if applicable)	X[10]							
Lupus anticoagulant	X							
TRIAL PRODUCT ADMINISTRATION								
Administration of N9-GP		X[17]	X[17]	X	X	X[9]		
N9-GP dispensing for home treatment			X	X	X	X[9]		
Drug accountability		X	X	X	X	X		
Administration of previous FIX product (if applicable)	X[3]							

Visit number	**1**[1]	**2**[5, 8]	**3**[11]	**4-6**[11]	**7-10**[11]	**11**[5, 11]	**FU**[5,12]	**IFU1-3**[7]
Visit purpose	**Screening**	**N9-GP first dose**	**N9-GP second dose**	**N9-GP dosing (visits every fourth week)**	**N9-GP dosing (visits every eight week)**	**End of main phase**	**Follow-up visit**	**Inhibitor follow-up visits**
Time of visit (weeks)	**6 w prior to Visit 2**	**0**	**1 w**	**4-12 w**	**20-44 w**	**52 w**	**3 w after Visit 11**	**Every 4 wks after Visit 11**
Visit window (days or weeks)	**±2 w**	**-**	**+1 d**	**±1 w**	**±1 w**	**+2 w**	**±1 w**	**±1 w**
TRAINING AND REMINDERS								
Trial card dispensing	X							
Home treatment and eDiary training		X	X	X	X	X[9]		
eDiary dispensing			X					
eDiary collection						X[15]		
Telephone contact with patient/parent(s)/LAR (halfway through the home-treatment period)			X	X	X	X[9]		
IV/WRS	X	X	X	X	X	X		
End of trial form							X	X

Footer	Description
1	Visit 1 can be performed on separate days. The patients should not use coagulation factors within 4 days prior to the laboratory assessments of Visit 1.
2	Additional PK samples will be collected at 24, 48, 96 and 168 hours post-dose. In total, six PK samples will be collected at 4 different days, see Table 2-2.
3	If recovery results for the patient's previous FIX product are not available in medical records or are older than 1 year or are collected more than 1 hour after dosing, the patient will be dosed with his current product at Visit 1 and a FIX recovery sample will be collected 30 minutes after dosing (±10 minutes). This can be done anytime in the period from informed consent and until 4 days prior to the laboratory assessments of Visit 1 or directly after all laboratory assessments of Visit 1 have been completed and until 4 days prior to Visit 2.
4	Will be collected pre-dose and 168 hours post-dose.

5	The patients should not use coagulation factors within 4 days prior to Visit 2 and FU visit, and within 6 days prior to Visit 11.
6	Body weight only.(Height at Visit 11 will be collected retrospective if available in medical records and consent obtained)
7	For patients developing FIX inhibitors ≥5 BU, please refer to Section 8.1.9. If treated with FIX within 4 days prior to the first inhibitor follow up visit (IFU1), the visit must be postponed. The end of trial form should be signed at the last IFU visit.
8	Please refer to Table 2-2 for a detailed flow chart for the PK sampling visit (Visit 2).
9	Only applicable for patients continuing in the extension phase.
10	*F9* genotype testing is optional and will only be performed if there is no existing records on the *F9* genotype and if the parent(s)/LAR consents. Can be performed at Visit 1 or at any later visit.
11	Between each visit to the trial site there are home treatment periods with dosing once weekly, see Section 8.2.
12	For patients who do not proceed into the extension phase or are withdrawn.
13	Will only be measured in patient developing severe allergic reactions against N9-GP. If a severe allergic reaction develops, additional blood samples should be collected within 15 minutes (if possible), 1-4 hours and ~1 week after onset of the reaction at unscheduled visits.
14	At Visit 8 only.
15	The eDiary should be collected at Visit 11 for patients who are withdrawn or not continuing in the extension phase.
16	Vital signs will be assessed pre-dose and 60 minutes post-dose.
17	At Visit 2 and 3, the patient has to be observed in a hospital setting for 60 minutes after N9-GP has been administered.
18	Can be performed at Visit 1 or at any later visit.
19	In case a patient has a positive antibody detected at the N9-GP Antibody assay analysis the patient will be asked to have a PK session performed after the next dosing. Blood sampling for FIX activity will be performed at the following time points: pre-dose, 30 min, 24h, 48h, 96h and 168h.
20	PEG will be measured if enough plasma is available from leftover samples and if consent obtained.
a)	Only at visit 5
b)	Only at visit 7, 9 and 11

Table 2-2 Detailed flow chart for PK sampling visit (Visit 2)

Day	**0**				**1**	**2**	**4**	**7**
Nominal time	**Pre-dose**	**0**[2]	**30 min**[3]	**60 min**[3]	**24h**[3]	**48 h**[3]	**96 h**[3]	**168h**[3]
Visit window	**-1h**[1]	**-**	**±10 min**	**±10 min**	**+8h**	**±8 h**	**±8 h**	**±24 h**
PATIENT RELATED INFORMATION								
Inclusion/exclusion criteria	X							
Withdrawal criteria	X							
Concomitant medication	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration	X							
Assessments of bleeding episodes[4]	X				X	X	X	X
ADVERSE EVENTS								
Adverse events	X	X	X	X	X	X	X	X
CLINICAL ASSESSMENTS								
Body measurements (body weight)	X							
Vital signs	X			X				
LOCAL LABORATORY ASSESSMENTS								
Haematology	X							X
CENTRAL LABORATORY ASSESSMENTS								
Coagulation-related parameters	X							X

Day	**0**				**1**	**2**	**4**	**7**
Nominal time	**Pre-dose**	**0[2]**	**30 min[3]**	**60 min[3]**	**24h[3]**	**48 h[3]**	**96 h[3]**	**168h[3]**
Visit window	**-1h[1]**	**-**	**±10 min**	**±10 min**	**+8h**	**±8 h**	**±8 h**	**±24 h**
FIX activity	X		X[6]		X	X	X	X
N9-GP/FIX antibodies	X							X
FIX inhibitors	X							X
HCP antibodies	X							
Plasma PEG levels[7]	X							
Allergic reaction testing[5]	X							
N9-GP ADMINISTRATION								
Administration of N9-GP		X						
Drug accountability		X						
TRAINING AND REMINDERS								
Home treatment and eDiary training	X							
IV/WRS	X							

Footer	Description
1	The 1 hour pre-dose time window is only applicable for laboratory assessments. Any other assessments (eg, body measurements, vital signs etc) have to be performed prior to dosing at the day of dosing.
2	The actual time of completed N9-GP injection corresponds to time point = 0.
3	Refers to time elapsed after completed N9-GP injection.
4	Any bleeding episodes during Visit 2 must be recorded in the eCRF. If a bleeding episode, requiring treatment, occurs within 96 hours after N9-GP administration, the patient can be rescheduled for a new PK evaluation at any later visit during the main phase.
5	Will only be measured in patient developing severe allergic reactions against N9-GP. If a severe allergic reaction develops, additional blood samples should be collected within 15 minutes (if possible), 1-4 hours and ~1 week after onset of the reaction at unscheduled visits.
6	The blood sample taken 30 minutes post-dose must not be taken from the same vein as used for N9-GP administration.
7	PEG will be measured if enough plasma is available from leftover samples from already collected samples and if consent obtained

Table 2-3 Detailed flow chart for the extension phase of the trial

Visit number	12[5]	13[5, 9]	14[5, 9]	15[5, 9]	16[5, 9]	17[5, 9]	X[1, 5, 9]	EOT[5]	IFU1-3[2]	Additional visit
Months after Visit 11	**3 m^3**	**6 m^3**	**12 m^3**	**18 m^3**	**24 m^3**	**30 m^3**	**Every 6 m^3**	**Minimum 6 days after last N9-GP dose**	**Every 4 wks after EOT visit**	**See footnote[10]**
Visit window	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**-**	**±1 w**	**±2 w**
PATIENT RELATED INFORMATION										
Withdrawal criteria	X	X	X	X	X	X	X	X		X
Patient Reported Outcome questionnaires						X		X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Date and time of last coagulation factor administration									X	
Assessments of bleeding episodes	X	X	X	X	X	X	X	X		X
Compliance review of drug administration and eDiary completion	X	X	X	X	X	X	X	X		X
ADVERSE EVENTS										
Adverse events	X	X	X	X	X	X	X	X	X	X
CLINICAL ASSESSMENTS										
Body measurements	X	X	X	X	X	X	X	X		X
Physical examination							X	X		

Visit number	12[5]	13[5, 9]	14[5, 9]	15[5, 9]	16[5, 9]	17[5, 9]	X[1, 5, 9]	EOT[5]	IFU1-3[2]	Additional visit
Months after Visit 11	**3 m^3**	**6 m^3**	**12 m^3**	**18 m^3**	**24 m^3**	**30 m^3**	**Every 6 m^3**	**Minimum 6 days after last N9-GP dose**	**Every 4 wks after EOT visit**	**See footnote[10]**
Visit window	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**-**	**±1 w**	**±2 w**
Neurological examination							X	X		
Neurocognitive assessments[12]							X	X		
Vital signs	X							X		
LOCAL LABORATORY ASSESSMENTS										
Haematology								X		
CENTRAL LABORATORY ASSESSMENTS										
Biochemistry							X	X	X	
FIX activity -pre-dose	X	X	X	X	X	X	X	X	X	X
N9-GP/FIX antibody and FIX inhibitor test	X	X	X	X	X	X	X	X	X	X
HCP antibodies	X	X	X	X	X	X	X	X	X	X
Allergic reaction testing[6]								X	X	
Biospecimen for storage: Serum and Plasma (if applicable)		X		X		X	X[7]	X		X
Biospecimen for storage: Genotype	(X)[8]	(X)[8]	(X)[8]	(X)[8]	(X)[8]	(X)[8]	(X)[8]			(X)[8]

Visit number	12[5]	13[5, 9]	14[5, 9]	15[5, 9]	16[5, 9]	17[5, 9]	X[1, 5, 9]	EOT[5]	IFU1-3[2]	Additional visit
Months after Visit 11	**3 m^3**	**6 m^3**	**12 m^3**	**18 m^3**	**24 m^3**	**30 m^3**	**Every 6 m^3**	**Minimum 6 days after last N9-GP dose**	**Every 4 wks after EOT visit**	**See footnote[10]**
Visit window	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**±2 w**	**-**	**±1 w**	**±2 w**
(if applicable)[8]										
Plasma PEG levels[11]	X	X	X	X	X	X	X	X	X	
Urinalysis							X	X	X	
N9-GP ADMINISTRATION										
Administration of N9-GP	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]			X[4]
N9-GP dispensing for home treatment[9]	X	X	X	X	X	X	X			X
Drug accountability	X	X	X	X	X	X	X	X		X
TRAINING AND REMINDERS										
Home treatment and eDiary training	X	X	X	X	X	X	X			X
eDiary collection								X		
Contact with patient/parent(s)/LAR (halfway through the home treatment period)	X	X	X	X	X	X	X			X
IV/WRS	X	X	X	X	X	X	X	X		X
End of trial form								X	X	

Footer	Description
1	The visit can be repeated until LPLV. X can therefore be any sequential number from 18 – 32+.
2	For patients developing FIX inhibitors ≥5 BU, please refer to Section 8.1.9. If treated with FIX within 4 days prior to the first inhibitor follow up visit (IFU1), the visit must be postponed,
3	One month is defined as four weeks.
4	Patients can either be dosed with N9-GP at the trial site or at home after the visit (if no lab samples are required).
5	Between each visit to the trial site there are home treatment periods with dosing once weekly or less frequently, see Section 8.2.
6	Will only be measured in patient developing severe allergic reactions against N9-GP. If a severe allergic reaction develops, additional blood samples should be collected within 15 minutes (if possible), 1-4 hours and ~1 week after onset of the reaction at unscheduled visits.
7	Every second visit, (17, 19 etc)
8	Biospecimen for storage: genotype sample to be collected once during extension phase
9	The amount of N9-GP dispensed at each visit corresponds to approximately 3 months of home treatment. Halfway in-between two visits from visit 13 additional N9-GP should be dispensed for further 3 months home treatment. The patient is not required to attend the clinic only for N9-GP interim dispensing.
10	Between V15 and V17 a subset of patients will be requested to attend an additional visit. If applicable the visit may be planned by the investigator to coincide with the interim dispensing of N9-GP. Investigators to affected patients will be informed by Novo Nordisk
11	PEG will be measured if enough plasma samples is available from leftover samples and if consent obtained, from BioSpecimen for storage plasma samples or from designated PEG plasma samples.
12	Assessments will be performed at every assessment visit in all countries. For selected countries additional assessments will be performed yearly.

3 Introduction

3.1 Basic information

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

3.1.1 Background

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. It is caused by mutations in the *F9* gene, located in the distal part on the long arm of the X-chromosome. The gene-defects are transferred from a heterozygotic mother (carrier), or are ascribable to new, spontaneous mutations. The incidence of haemophilia B is approximately 1 per 25,000 male births.

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[1]. Haemophilia B is classified according to the plasma activity of FIX as severe (<1%), moderate (1-5%) or mild (>5-40%).

The main treatment for patients with haemophilia B is 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 (on-demand treatment) or - during recent years - haemostatic agents are administered for longer periods to prevent bleeding (bleeding prophylaxis).

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 the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis. In repeated cases this is followed by synovitis in the affected joint. Recurrent bleeding episodes in the same location, most commonly a weight-bearing joint, may lead to chronic arthropathy, muscular atrophy and deformities. Bleeding episodes may occur in all parts of the body including rare, but life-threatening events such as: bleeding in the central nervous system (CNS), throat, neck or retroperitoneum.

Today, the most serious complication of replacement therapy is inhibitor development. FIX inhibitors are allogenic antibodies to FIX that reduce or eliminate the activity of FIX. For clinical purposes, the magnitude of the inhibitor response can be quantified through the performance of a functional inhibitor assay from which a BU inhibitor titre can be reported[2]. The definitions for thresholds are 0.6-<5 BU for a "low titre" and ≥5 BU for a "high titre" inhibitor[3]. Approximately 1-3% of patients with haemophilia B develop inhibitors following exposure to FIX[4-7]. Among patients with severe haemophilia B the percentage is however as high as 9%[7].

3.1.2 N9-GP

Novo Nordisk A/S is developing a recombinant FIX (rFIX) molecule - N9-GP - with a prolonged half-life for the treatment of patients with haemophilia B. 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. 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)[8] and any updates hereof.

3.1.3 Risks and benefits

Children are among those who might benefit significantly from prophylaxis with N9-GP. Current products available for the treatment of haemophilia B have short half-life of 18-19 hours demanding frequent dosing for prophylaxis of bleeding, with 2-3 injections a week[9]. The prolonged half-life of N9-GP offers an expected advantage of once weekly or potentially even less frequent injections.

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 to the currently marketed rFIX product and is produced from the Chinese hamster ovary (CHO) cell-line, a mammalian cell line shown to be free of known infectious agents.

Hypersensitivity reactions may occur with the administration of N9-GP, as with any protein injected intravenously. Even if N9-GP is not anticipated to be more immunogenic than any other FIX products, patients with known or suspected hypersensitivity to N9-GP or related products will be excluded from participation in this trial.

There is a potential risk for development of antibodies against N9-GP and/or FIX that could decrease the effectiveness of future treatments with FIX products. However, this risk is not expected to be greater than with other FIX products.

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 (refer to IB). The potential clinical implications of these animal findings are unknown. No adverse neurologic 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.

To minimise switching between FIX products, the trial includes an extension phase in which the patients can continue with N9-GP treatment until LPLV.

3.2 Rationale for the trial

The rationale for performing this trial is to investigate safety, efficacy and PK of N9-GP in the treatment of haemophilia B patients ≤12 years. Based on clinical and non-clinical studies conducted, N9-GP is a promising drug candidate for prevention/prophylaxis and on-demand treatment of bleeding episodes in haemophilia B patients.

The completed phase 1 PK trial (NN7999-3639) showed a mean half-life of N9-GP of 93 hours which is approximately 5 times longer than commercially available FIX products. In addition, the recovery of N9-GP was 94% higher when compared to rFIX and 20% higher when compared to plasma-derived FIX (pdFIX)[10].

In compliance with paediatric regulations and to adequately study the safety and efficacy of N9-GP in children, the present trial is being carried out in accordance with the paediatric investigation plan (PIP) that was approved by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) on 12-Nov-2010. For Europe, EMA requires separate investigation in the paediatric population as part of the development programme, and paediatric trial results are now compulsory in any new market authorisation application, or at a minimum accepted for full or partial waiver/deferral in the PIP, when accepted by the PDCO. In some countries outside the EU, paediatric investigation is necessary to achieve labelled indication for children. 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

Type of trial	Trial description	Trial ID	Status
Phase 1 PK trial	A multi-centre, multinational, open-label, dose escalation trial evaluating safety and PK of ascending intravenous doses of N9-GP in patients with haemophilia B	NN7999-3639 (paradigm™1)	Completed
Phase 3a pivotal safety and efficacy trial	A multi-centre, single-blind trial evaluating safety and efficacy, including PK, of N9-GP when used for treatment and prophylaxis of bleeding episodes in patients with haemophilia B	NN7999-3747 (paradigm™2)	Completed
Phase 3a surgery	An open-label, multi-centre, non-controlled trial evaluating efficacy and	NN7999-3773	Completed

Type of trial	Trial description	Trial ID	Status
trial	safety of N9-GP treatment during surgical procedures in patients with haemophilia B	(paradigm™3)	
Phase 3b extension trial	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	NN7999-3775 (paradigm™4)	Completed
Phase 3 paediatric, safety and efficacy trial	An open-label, single-arm, multinational, non-controlled, confirmatory trial investigating safety, efficacy and PK of N9-GP in prophylaxis and treatment of bleeding episodes in children with haemophilia B with extension phase	NN7999-3774 (paradigm™5)	Current trial
Phase 3b safety trial	An open-label, multi-centre, non-controlled, safety and efficacy trial in previously untreated patients with haemophilia B	NN7999-3895 (paradigm™6)	Ongoing

4 Objectives and endpoints

4.1 Objectives

4.1.1 Primary objective

- To evaluate immunogenicity of N9-GP

4.1.2 Secondary objectives

- To evaluate safety other than immunogenicity of N9-GP
- To evaluate the efficacy of N9-GP in long-term prophylaxis and in the treatment of breakthrough bleeding episodes
- To evaluate the efficacy of N9-GP through the surrogate marker for efficacy, FIX activity
- To evaluate the PK properties of N9-GP
- To evaluate patient reported outcomes (PROs) and assess health economic impact of treatment with N9-GP

4.2 Endpoints

4.2.1 Primary endpoint

- Incidence of inhibitory antibodies against FIX defined as titre ≥0.6 BU

4.2.2 Secondary endpoints

4.2.2.1 Safety endpoints

- Adverse events including serious adverse events (SAEs) and medical events of special interest (MESI), and development of host cell protein (HCP) antibodies

4.2.2.2 Efficacy endpoints

- Number of bleeding episodes during prophylaxis
- Haemostatic effect of N9-GP in treatment of bleeding episodes by 4-point categorical scale for haemostatic response (excellent, good, moderate and poor)
- FIX consumption described as frequency of dose/kg for prophylaxis use and number of doses and amount consumed for the treatment of bleeding episodes

4.2.2.3 Pharmacokinetic endpoints

Pharmacokinetic endpoints, except trough steady state and FIX activity at 30 minutes (C_{30min}) steady state, are assessed after a single dose (Visit 2). Steady state trough and C_{30min} will be assessed at Visit 4 - Visit 10 during the main phase of the trial.

- Incremental recovery at 30 minutes (IR_{30min}) ([IU/mL] / [IU/kg])
- Trough level (IU/mL) (single-dose and steady state)
- Area under the curve (AUC) (Uxh/mL)
- Terminal half-life ($t_{1/2}$) (h)
- Clearance (CL) (mL/h/kg)
- Mean residence time (MRT) (h)
- Volume of distribution at steady state (V_{ss}) (mL/kg)
- FIX activity at 30 minutes (C_{30min}) (IU/mL) (single-dose and steady state)

4.2.2.4 Patient reported outcomes and health economic endpoints

- Changes in health related quality of life (HRQOL) from Visit 1,Visit 11, Visit 17and to Visit 22/23/24 (the relevant visit where neurocognitive assessments are performed for the first time for each patient) , assessed using age and disease specific patient reported outcomes (PRO) questionnaires: Haemophilia-quality of life (HAEMO-QOL), Hemophilia treatment satisfaction (HEMO-SAT), and TNO-AZL preschool quality of life (TAPQOL)
- Health economic impact of N9-GP treatment through characterisation of hospitalisations, emergency room visits, missed work and/or school days, and mobility aid requirements

5 Trial design

5.1 Type of trial

This is an open label, single-arm, multinational non-controlled trial investigating safety, efficacy and PK of N9-GP in prophylaxis and treatment of breakthrough bleeding episodes in paediatric male patients with haemophilia B.

The trial consists of a main phase and an extension phase. The duration of the main phase for each patient will be minimum 52 weeks. After completion of the main phase, the patients can continue in an extension phase.

For Japan only: The NN7999-3774 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.

The patients will be stratified into two age groups; 0-6 years and 7-12 years. A minimum of 10 patients in each age group must complete the main phase of the trial with at least 50 EDs. The trial has one treatment arm where all patients receive N9-GP once weekly for prophylaxis. In the extension phase, the same dosing regimen is administered. In addition, N9-GP will be administered in case of breakthrough bleeding episodes during the main phase and extension phase.

5.2 Rationale for trial design

The trial design will provide information on safety, efficacy and PK of N9-GP in paediatric previously treated patients (PTP) with haemophilia B, aged ≤12 years and a FIX activity level of ≤2%.

The purpose of the present trial is to provide sufficient exposure to N9-GP to evaluate immunogenicity of N9-GP and to provide efficacy and safety data for N9-GP in long-term prophylaxis. Prophylaxis of bleeding episodes is cited as the primary goal of therapy in the literature and treatment guidelines and must be the goal of all haemophilia care programmes until a cure is available[9,11,12]. Due to a 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 examinations and neurocognitive assessments as well as laboratory analyses of plasma PEG levels, liver and kidney parameters.

The main phase of the trial will generate safety data from at least 50 EDs on each patient collected during minimum 52 weeks continuous treatment with measurable FIX activity levels. This number

of EDs is as required both by the Food and Drug Administration (FDA) and in the EMA guideline[3] for evaluation of immunogenicity of new FIX products and taking potential seasonal differences in bleeding patterns into account. One ED is defined as each day a patient is administered FIX for prophylaxis, prevention and/or on-demand treatment.

The trial is not controlled by a placebo group. It is unethical to administer an ineffective treatment to patients with haemophilia and the EMA guideline does not require a comparison to placebo[3].

There will be no randomisation due to the single-arm nature of the trial. However, the patients will be stratified into two age groups at the time of signed informed consent; 0-6 years and 7-12 years, both inclusive. Patients belonging to the youngest age group will not be included in the trial before PK data from Visit 2 for 5 patients in the 7-12 year age group are evaluated.

The trial design follows current standards for similar trials, and the recently published guideline[3] from Committee for Medicinal Products for Human Use (CHMP) of EMA. The EMA guideline describes the mandatory components of paediatric trials in patients with haemophilia B.

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

5.3 Treatment of patients

Around 40 patients will be screened in order to start approximately 24 patients on trial product out of which 10 patients in each of the two age groups must complete the main phase of the trial. The duration of treatment in the main phase of each patient, from first N9-GP administration to the last N9-GP administration, is minimum 52 weeks and at least 50 EDs. The duration of treatment in the extension phase is until LPLV.

The two initial doses of N9-GP will be administered in a hospital setting enabling the patient to be observed for potential hypersensitivity reactions. Therefore, all trial sites must be prepared in handling hypersensitivity reactions. After the two initial doses of N9-GP have been administered, home treatment can be initiated. All patients have previously received at least 50 doses of FIX and are by themselves, or helped by parent(s)/caregivers, familiar with or instructed in home treatment of both prophylaxis and treatment of bleeding episodes.

5.3.1 Prophylaxis

All patients will be administered a fixed dose of 40 IU/kg N9-GP once weekly as i.v. injections during at least 52 weeks in the main phase of the trial. The dose level chosen is based on modelling of data from the phase 1 PK trial (NN7999-3639) and the recommended FIX activity levels according to the World Federation of Hemophilia (WFH)[9]. The regimen is planned to give

measurable FIX activity of ≥1% during the entire prophylaxis period as the aim is to convert severe haemophilia to a milder phenotype of haemophilia.

Fewer administrations than with currently marketed FIX products will be given due to the longer plasma half-life of N9-GP. In the main phase, N9-GP must be administered every 7th day ±1 day.

Additional prophylactic treatment is not allowed during the main phase of the trial, eg, before planned physical activity.

5.3.2 Treatment of bleeding episodes

The dose for treatment of a mild or moderate bleeding episode, for example a joint bleed, is a single dose of 40 IU/kg since this dose is expected to give a recovery of at least 60-70% FIX activity and the FIX activity level 5 days after dosing is still expected to be above 20%. If there is no apparent effect of 40 IU/kg, the patient or parent(s)/legally authorised representative (LAR) should contact the investigator prior to administration of the second dose of 40 IU/kg. A severe bleed should be treated immediately at home or at a local emergency room with 80 IU/kg and the trial site must be contacted immediately thereafter for further instructions or transport to the trial site. For definition of the severity of a bleeding episode, please refer to Section 8.3.4.1.

5.3.3 Surgery

Minor surgery

Minor surgeries and placement of central venous access ports can be performed while participating in this trial by administering an additional dose of 40 IU/kg N9-GP, or aligned to local practice after confirmation from sponsor's medical expert (see Attachment I). The dose level is based on the WFH guideline[9].

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. Examples of minor surgery include implanting pumps in subcutaneous tissue, skin excisions, drainage of abscess or simple dental procedures.

Major surgery

Major surgery may be performed during participation in the current trial.

In a separate completed N9-GP surgery trial (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 drug 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[9]. Determination of

dose and dose intervals to achieve adequate haemostasis should include close monitoring of FIX activity through and peak levels, consideration of t½ of N9-GP and ongoing 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 is provided in section 8.3.6.2

Definition of major surgery

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

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

5.3.4 Patients continuing into the extension phase

After completion of the main phase, the patient can continue with prophylaxis in the extension phase until LPLV.

After 10 patients in each of the two age groups (0-6 and 7-12 years of age) have completed the main phase, any remaining patients will be offered continued treatment in the extension phase. Data collected up to the point where the patient is transferred to the extension phase will be used in the analyses of data from the main phase of the trial.

In the extension phase, a single dose of 40 IU/kg once weekly will be administered intravenously.

5.4 Rationale for treatment

Lack of compliance with a frequent injection schedule is one of the most commonly cited reasons for failure of prophylaxis with coagulation factor treatment[13]. The longer half-life of N9-GP will allow for prophylaxis with fewer injections and will presumably result in better compliance.

All patients will be administered a fixed dose of 40 IU/kg N9-GP once weekly as i.v. injections in both the main phase and the extension phase of the trial. The dose level is based on modelling of data from the phase 1 PK trial (NN7999-3639), from which the two doses levels 10 IU/kg and 40 IU/kg were chosen for the pivotal trial (NN7999-3747). Although not shown yet in patients with

haemophilia B, there is an anticipated higher CL of coagulation factors in children as compared with adults, and therefore the higher of the two dose levels has been chosen. This is based on published observations in patients with haemophilia A where body weight adjusted CL of coagulation factor VIII (FVIII) has been found to decrease with age and/or body weight during growth from infancy to adulthood, with a corresponding increase in terminal half-life[14].

The maximum dose of N9-GP, based on non-clinical safety data, 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 frequently than every hour. These doses are only relevant in case of trauma or severe bleeding.

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

6 Trial population

6.1 Number of patients to be studied

Countries planned to participate: Canada, Germany, Italy, Japan, Malaysia, Taiwan, United Kingdom and United States

Planned number of patients to be screened (ie, documented informed consent): 40

Planned number of patients to be started on trial product: 24

Planned number of patients to complete the main phase of the trial: 20

- Minimum 10 patients must be 7-12 years old at screening
- Minimum 10 patients must be 0-6 years old at screening

Planned number of trial sites: 20-30

6.2 Inclusion criteria

1. Informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the patient)
2. Male patients with moderately severe or severe congenital haemophilia B with a FIX activity level ≤2% according to medical records
3. Age ≤12 years (until patient turns 13 years, at time of inclusion)
4. Body weight ≥10 kg
5. History of at least 50 EDs to other FIX products
6. The patient and/or parent(s)/caregiver are capable of assessing a bleeding episode, keeping an eDiary, capable of conducting home treatment and otherwise able to follow trial procedures

6.3 Exclusion criteria

1. Known or suspected hypersensitivity to FIX, hamster protein or related products
2. Previous participation in this trial defined as withdrawal after administration of N9-GP
3. The receipt of any investigational medicinal product (IMP) within 30 days prior to enrolment into this trial
4. Documented diagnosis of obesity defined as body mass index (BMI) equal to or greater than the 95th percentile for age for children ≥2 years (refer to Appendix D)
5. Known history of FIX inhibitors based on existing medical records, laboratory report reviews and patient/caregiver interviews
6. Current FIX inhibitors ≥0.6 BU (central laboratory)
7. Congenital or acquired coagulation disorder other than haemophilia B

8. Platelet count <50,000/µL at screening (local laboratory)
9. Alanine aminotransferase (ALT) >3 times the upper limit of normal reference ranges at screening (central laboratory)
10. Creatinine level ≥1.5 times above the upper normal limit of normal reference ranges at screening (central laboratory)
11. HIV positive, defined by medical records, and with a CD4+ lymphocyte count ≤200/µL. If the patient's HIV status is unknown or if negative HIV test results in medical records are older than one year, it should be tested at the screening visit. If the patient is HIV positive, the CD4+ lymphocyte count must be tested
12. Immune modulating or chemotherapeutic medication (except single pulse treatment, inhaled and topical steroids)
13. Previous arterial thrombotic events (myocardial infarction and intracranial thrombosis, as defined by medical records)
14. Any disease or condition which, according to the investigator's judgment, could imply a potential hazard to the patient, interfere with trial participation or trial outcome
15. Unwillingness, language or other barriers precluding adequate understanding and/or cooperation from patients and parent(s)

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

6.4 Withdrawal criteria

The patient may withdraw at will at any time. The patient's parent(s) or LAR may withdraw the patient from the trial at any time.

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

The patient must be withdrawn if the following applies:

1. Development of FIX inhibitors ≥5 BU confirmed by two consecutive samples at the central laboratory
2. Anaphylactic reaction to the trial product (Section 12.1.2)
3. Significant thromboembolic event
4. Incapacity or unwillingness to follow trial procedures

If a patient experiences treatment failure described as more than two bleeding episodes where haemostatic response is rated as poor according to Section 8.3.4.1, the investigator should consider if it is in the patient's best interest to continue in the trial.

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

6.5 Patient replacement

Withdrawn patients may be replaced to ensure that 10 patients in each of the two age groups complete the main phase of the trial (52 weeks) with at least 50 EDs. It is assumed that minimum 24 patients must be started on N9-GP to achieve this. However, this may be adjusted during the trial based on the actual drop-out rate.

Re-screening is allowed and patients re-screened in the trial must be provided with a new patient number. Patients should be re-screened if the maximum visit window of 8 weeks between Visit 1 and 2 is exceeded.

6.6 Rationale for trial population

The current trial will enrol patients with haemophilia B as they are the target population for N9-GP treatment. The age range is 0-12 years of age, stratified with minimum 10 patients in the age range of 0-6 years and minimum 10 patients in the age range of 7-12 years at the time of signing informed consent. The patients will count in the age group which they were initially assigned to, even when they become older. Since the N9-GP pivotal trial (NN7999-3747) will be conducted in male patients 13-70 years of age, N9-GP will be investigated in all age groups, as required by regulatory authorities.

The trial population selection criteria is in line with the guideline developed by CHMP of EMA[3].

Children are amongst those who might benefit significantly from prophylaxis. Less frequent injections 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).
- Criteria nos. 2, 3 and 5 are included to select the patient group recommended in the EMA guideline[3].
- Criterion no. 4 is included to protect the patients and is in line with requirements on blood draw limits (see Appendix C).

- 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.

6.6.2 Rationale for exclusion criteria

- Criteria nos. 1, 4, 11, and 14 are included to prevent unnecessary exposure of potentially fragile patients to a new compound.
- Criterion no. 2 is to ensure that a patient only counts once in the data analyses.
- Criteria nos. 3 and 12 are included to minimise any effect of external compounds on the patient's coagulation and immune system.
- Criteria nos. 5, and 6 are to prevent exposure of FIX to patients with FIX inhibitors.
- Criteria nos. 7, 8, 9 and 10 are chosen to exclude patients with endogenous abnormalities of the coagulation system, other than haemophilia B, and to exclude patients with severely impaired liver or kidney function.
- Criterion no. 13 is chosen to minimise the risks of thrombotic manifestations.
- Criterion no. 15 is included to ensure compliance with protocol requirements and to protect the patient’s safety.

6.6.3 Rationale for withdrawal criteria

- Criteria nos. 1-5 are included to protect the patient's safety.

7 Trial schedule

Planned duration of recruitment period (first patient first visit – last patient first visit): 11 months

All investigators will be notified immediately when the recruitment period comes to an end, after which no patients may be screened unless required due to patient withdrawals.

- Planned first trial site ready: 01-Mar-2012
- Planned date for first patient first visit: 01-Apr-2012
- Planned date for last patient last visit of main phase: 01-Apr-2014
- Planned completion of clinical trial report of main phase: 01-Oct-2014
- Planned date for last patient last visit of extension phase: 30-Nov-2023
- Planned completion of clinical trial report of extension phase: 22-May-2024

The trial will end when the last patient has turned 12 years old and has attended a scheduled or EOT visit hereafter. The end of the clinical trial is defined as last patient last visit of the extension phase.

Protocol information for this trial will be subject to public disclosure at external web sites (www.clinicaltrials.gov, www.clinicaltrialsregister.eu and www.novonordisk-trials.com) according to international regulations eg the International Committee of Medical Journal Editors (ICMJE)[15], the Food and Drug Administration Amendments Act (FDAAA)[16] as reflected in Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

8 Methods and assessments

8.1 Visit procedures

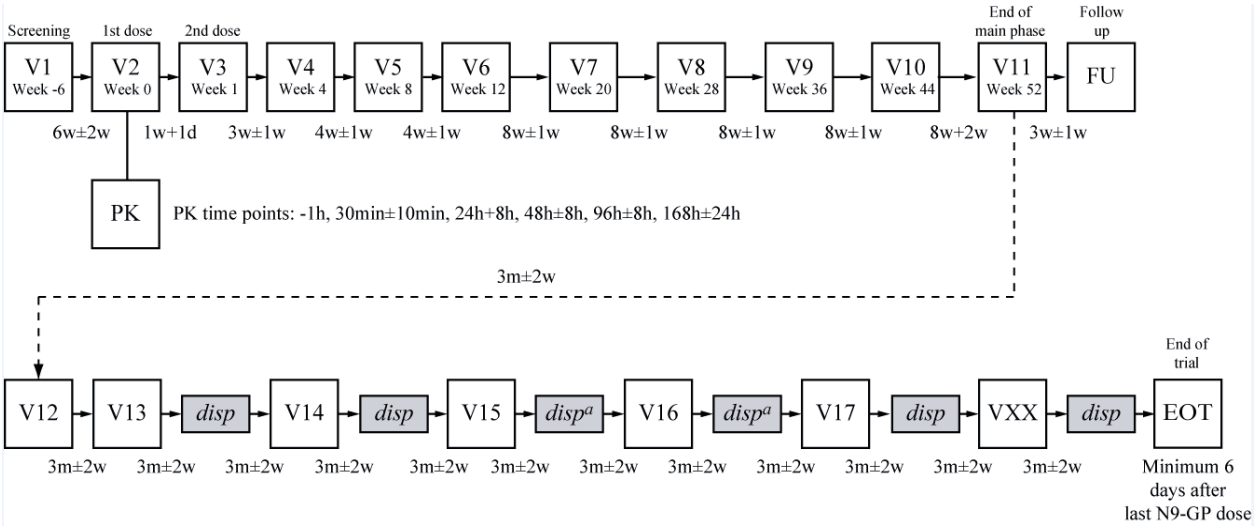

Figure 8-1 Overview of visits

The trial consists of a main phase (Visit 1 – Visit 11) and an extension phase (Visit 12 – EOT visit). Around 40 patients will be screened to start approximately 24 patients on trial product out of which at least 10 patients in each of the two age groups must complete the main phase of the trial. A PK profile must be obtained for all patients at Visit 2. After Visit 3, there will be home treatment periods with dosing once weekly between the visits to the trial site. Patients withdrawn during the main phase, or patients not continuing in the extension phase, will be scheduled for a follow-up visit (FU). This will be the end of trial visit for these patients.

disp: Interim dispensing of N9-GP trial drug for home treatment

a: Between V15 and V17, a subset of patients will be requested to attend an additional visit with procedures and assessments identical to visit 16. If applicable the visit may be planned by the investigator to coincide with the interim dispensing of N9-GP (see Table 2-3 and section 8.1.7).

The main phase of the trial consists of the following visits:

Visit 1: Screening visit.
Patients in the youngest age group (0-6 years) will not be included before PK data from Visit 2 for 5 patients in the 7-12 years age group are evaluated.

Visit 2: Dosing and PK visit at the trial site.
The patients will have an initial dose of N9-GP at the trial site and will undergo a PK session. The patients will have to return to the trial site 4 times during the following 7 days.

Visit 3: Dosing visit at the trial site.
The second dose of N9-GP will be administered at the trial site after the last PK sample of Visit 2 has been collected. If a bleeding episode occurs between the first and second dose, the patient should come to the clinic for treatment with N9-GP.

Visit 4-10: Dosing visits at the trial site.

Visit 11: End of main phase.
Patients, not continuing in the extension phase, will be scheduled for a follow-up visit. Patients continuing in the extension phase will be dosed with N9-GP when assessments of Visit 11 are completed.

Follow-up visit (FU): Inhibitor testing for patients who are withdrawn or not continuing in the extension phase of the trial.

Inhibitor follow-up visit 1-3 (IFU1-3): Conditional inhibitor follow-up visits, which must be conducted if FIX inhibitors are developed or suspected.

The extension phase of the trial consists of the following visits:

Visit 12-17 + Visit X (X = 18 and onwards): Dosing visits at the trial site.

End of trial (EOT) visit: Inhibitor testing for patients who are withdrawn from, or completing the extension phase of the trial.

Inhibitor follow-up visit 1-3 (IFU1-3): Conditional inhibitor follow-up visits, which must be conducted if high titre FIX inhibitors (≥5 BU) are identified.

For a detailed schematic overview of the trial visits and assessments, please refer to the flow charts in Section 2 and the trial diagram (Figure 8-1). Procedures of the trial visits are described in detail in Sections 8.1.1 to 8.1.10.

It must be stated in the medical records that the patient is participating in the trial. Patients enrolled will be provided with a card stating that they are participating in the trial, with contact addresses and telephone numbers. The patient and parent(s)/LAR should be instructed to return the card to the investigator or destroy the card after the last trial visit.

Screening and enrolment log

The investigator must keep a subject identification list as well as a subject screening and subject enrolment log (these may be combined in one document).

Informed consent procedure

The patient's parent(s) and/or caregiver(s) (ie, LAR for the patient) 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. The information will include, eg, descriptions of N9-GP, the procedures involved, the practical implications of participating, responsibilities and rights while participating in the trial including the possible advantages and disadvantages. Patients and parent(s)/LAR will have the opportunity to ask questions and have ample time to consider participation. If the patient wishes to participate, the parent(s)/LAR will be requested to sign and date the informed consent form. This must be done prior to any trial-related activities, ie, procedures that would not have been performed during normal management of the patient. The patient should sign a child assent form if capable, and if required by local requirements.

It must be emphasised that any change in a patient's normal treatment routine is a trial-related activity which is not allowed before informed consent has been given. For example; if a patient is taken off prophylaxis to allow for 4 days without FIX treatment before screening and the interval between the patient's normal prophylactic doses is less than 4 days, it is a trial related activity. In such case, it is essential that the informed consent procedure is completed prior to the trial-related activities.

Screening failures

Screening failures are defined as patients for whom the parent(s)/LAR have signed the Informed Consent Form, but fail to comply with the inclusion and exclusion criteria or if the consent is withdrawn prior to dosing. Data in respect to the screening visit (Visit 1) will be entered in the screening failure form in the electronic case report form (eCRF). A screening failure call must be made in the interactive voice/web response system (IV/WRS). Serious and non-serious AEs from screening failures will be entered by the investigator in the eCRF, and consequently transferred to the clinical database. When the trial related procedures have been finalised for screening failures, no more AEs should be entered in the eCRF. Follow-up of AEs should be made according to Section 12.

For withdrawn patients

Withdrawn patients are defined as patients who meet the withdrawal criteria after dosing, see Section 6.4. In case a patient is being prematurely withdrawn from the trial the investigator must aim to undertake the procedures for the last visit as soon as possible, if possible. If the patient is withdrawn prior to Visit 11, an end of main phase visit (Visit 11) and a follow-up (FU visit) should be scheduled, and if the patient is withdrawn after Visit 11, an EOT visit should be scheduled. The primary reason (AE, non-compliance with protocol or other) for discontinuation must be specified in the eCRF. The end of trial form must be completed, final drug accountability must be performed and the case book must be signed, even if the patient is not able to attend. All data collected in the period the patient participated in the trial will be entered into the eCRF. A withdrawal session must

be performed in IV/WRS. If a patient is withdrawn due to inhibitor development, the patient must be followed according to Section 8.1.9.

End of trial (EOT) visit

The end of trial form should be signed at the EOT visit or the last visit of the patient. If a patient continues in FU or IFU the end of trial form will be signed at the FU visit or the last IFU visit. If a patient is withdrawn prior to completion of the trial, all attempts must be made to schedule an end of trial visit for the patient. For patients not proceeding into the extension phase, the FU visit will be the end of trial.

8.1.1 Visit 1 - screening visit

Before enrolment in the trial and prior to conduct of any trial-related procedures/activities, the parent(s) and/or LAR of the patient must have signed the informed consent form after having received written and verbal information about the trial. The patient should sign a child assent form if capable, and if required by local requirements. This can be performed on a separate day.

The laboratory assessments of Visit 1 should be scheduled at least 4 days after the last administration of coagulation factor products. If the interval between the patient's normal prophylactic doses is less than 4 days, this is considered as a trial-related activity. The visit must be rescheduled, if the patient has been administered coagulation factor products within 4 days prior to the planned laboratory assessments of Visit 1.

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

If at all possible, planned vaccinations should be postponed beyond the first three months of N9-GP treatment.

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

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

At Visit 1 the following assessments will be performed and/or recorded in the eCRF:

- Informed consent form, signed, dated including time, see Section 19.1
- Consent to genotyping (if applicable), see Section 8.8.9 and 19.1
- Inclusion and exclusion criteria, see Section 6.2 and 6.3
- PRO questionnaires, see Section 8.3.1
- Demography, see Section 8.3.2
- Concomitant illness, see Section 8.3.3
- Medical history including haemophilia treatment history and details on haemophilia and inhibitors and joints, see Section 8.3.3.1

- Medical records of HIV and hepatitis C virus (HCV) status. If HIV and/or HCV positive, or if negative test results are older than one year, or if status is unknown, see Section 8.8.8
- CD4+ lymphocyte count, if HIV positive, see Section 8.8.8
- *F9* genotype documentation (if applicable), see Section 8.8.9 and 19.1
- Concomitant medication, see Section 11
- Date and time of last coagulation factor administration
- Assessments of bleeding episodes (date, severity and location), if any, within the 4 days without FIX treatment, see Section 8.3.4
- Adverse events, see Section 12.1
- Body measurements, see Section 8.5.1
- Physical examination, see Section 8.5.2
- Vital signs, see Section 8.5.4

Blood sampling for local laboratory assessments:

- Haematology, see Section 8.7.1

Blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.8.1
- FIX activity, see Section 8.8.4
- FIX inhibitors, see Section 8.8.5.2
- Viral assessments:
    - HIV, see Section 8.8.8. If the patient's HIV status is unknown or if negative HIV test results in medical records are older than one year, please await the central laboratory HIV test. If the patient's HIV status, in medical records, is positive or the central laboratory HIV test is positive, await the CD4+ lymphocyte count before determining whether or not the patient is eligible for the trial
    - HCV, see Section 8.8.8. If the patient's HCV status is unknown or if negative HCV test results in medical records are older than one year, anti-HCV antibodies should be tested by the central laboratory. If the patient's HCV status, in medical records, is positive or the central laboratory anti-HCV antibodies test is positive, HCV RNA should be tested
- *F9* genotype, if consent is given and documentation is not available in medical records, as allowed per local regulations, see Section 8.8.9
- Lupus anticoagulant, see Section 8.8.10

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

Dosing with the patient's previous FIX product (only for patients without recovery data in medical records):

If no recovery data for the patient's previous FIX product exist in medical records, or if the data is older than one year or the recovery sample is collected more than one hour after completed dosing, the patient should be dosed with his product at Visit 1 and a recovery sample should be collected. This can be done anytime in the period from informed consent and until 4 days prior to the laboratory assessments of Visit 1 or directly after all laboratory assessments of Visit 1 have been completed and until 4 days prior to the planned Visit 2.

Post-dose blood sampling for central laboratory assessments after dosing with patient's current product (only for patients without recovery data in medical records):

- FIX recovery: 30 minutes (±10 minutes), see Section 8.8.3

The blood sample taken 30 minutes (±10 minutes) post-dose must not be taken from the same vein as used for administration of the patient's current product.

Training and reminders:

- Dispense trial card, see Section 8.10.1
- An appointment for Visit 2 should be made within four to eight weeks of Visit 1
- A confirmation call in the IV/WRS as soon as the patient is deemed eligible for the trial but no later than two weeks prior to the planned Visit 2, see Section 10
- Patient should withhold treatment with coagulation factor products 4 days prior to Visit 2. Otherwise, Visit 2 should be rescheduled
- Patients should be reminded that Visit 2 will consist of 5 visit-days to the site during a period of 8 days
- If possible, planned vaccinations should be postponed beyond the first three months of N9-GP treatment

8.1.2 Visit 2

Visit 2 should preferably take place four to eight weeks after the screening visit (Visit 1).

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

- Major surgery within one month prior to the first planned injection of N9-GP
- Use of coagulation factors within 4days prior to the first injection of N9-GP
- Subjective signs of illness or fever within 48 hours prior to the first injection of N9-GP

The patients will be administered their first dose of N9-GP and a 30 minutes post-dose sample will be collected. Four PK samples will be collected at 4 different days during the following 7 days. The blood samples and assessments to be performed are outlined in Table 2-2.

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

Pre-dose assessments to be made before the first dose of N9-GP at the day of dosing:

- Confirmation of inclusion and exclusion criteria, see Section 6.2 and 6.3
- Withdrawal criteria, see Section 6.4
- Concomitant medication, see Section 11
- Date and time of last coagulation factor administration
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4
- Adverse events, see Section 12.1
- Body measurements (**body weight only**), see Section 8.5.1
- Vital signs, see Section 8.5.4

Pre-dose sampling for local laboratory assessments to be taken within 1 hour prior to dosing:

- Haematology, see Section 8.7.1

Pre-dose blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- Coagulation-related parameters, see Section 8.8.2
- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2
- HCP antibodies, see Section 8.8.6
- Allergic reaction testing, see Section 8.8.7

First N9-GP administration:

- Administration of 40 IU/kg N9-GP
- Stop time of injection must be recorded, this corresponds to time point = 0
- Precautions to take when injecting the initial doses of N9-GP, see Section 8.9

Post-dose assessments after the first dose of N9-GP:

- Concomitant medication, see Section 11
- Assessments of bleeding episodes including date, see Section 8.3.4
- Adverse events, see Section 12.1
- Vital signs: 60 minutes (± 10 minutes), see Section 8.5.4

Post-dose blood sampling for local laboratory assessments after the first dose of N9-GP:

- Haematology: 168 hours (±24 hours), see Section 8.7.1

Post-dose blood sampling for central laboratory assessments after the first dose of N9-GP:

- Coagulation-related parameters: 168 hours (±24 hours), see Section 8.8.2
- FIX activity: 30 minutes (±10 minutes), 24 hours (+8 hours), 48 hours (±8 hours), 96 hours (±8 hours) and 168 hours (±24 hours), see Section 8.8.4
- N9-GP/FIX antibodies: 168 hours (±24 hours), see Section 8.8.5.1
- FIX inhibitors: 168 hours (±24 hours), see Section 8.8.5.2

The blood sample taken 30 minutes (±10 minutes) post-dose must not be taken from the same vein as used for administration of N9-GP.

Training:

- Home treatment/eDiary training, see Sections 8.3.7, 8.9 and 8.10.2

IV/WRS:

- Drug accountability of trial product at Visit 2 must be recorded in the IV/WRS, see Section 10
- Recording of body weight and dispensing of N9-GP for site dosing via IV/WRS, see Section 10

Reminders:

- An appointment for Visit 3 should be made. The second dose of N9-GP (Visit 3) should be administered directly after the last assessments of Visit 2 are completed
- If a bleeding episode occurs during Visit 2 or in the period between Visit 2 and 3, the patient should come to the trial site for treatment with N9-GP. If a bleeding episode, requiring treatment, occurs within 96 hours after N9-GP administration, the patient can be rescheduled for a new PK evaluation at any later visit during the main phase of the trial if deemed appropriate by the investigator
- If possible, planned vaccinations should be postponed beyond the first three months of N9-GP treatment

8.1.3 Visit 3

Visit 3 should take place directly after Visit 2, preferably on the same day as the 168 hour post-dose assessments of Visit 2 are completed.

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

Pre-dose assessments to be made before the second dose of N9-GP at the day of dosing:

- Withdrawal criteria, see Section 6.4
- Concomitant medication, see Section 11
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4
- Adverse events, see Section 12.1
- Vital signs, see Section 8.5.4

Second N9-GP administration (6-8 days after first N9-GP dose):

- The second dose should be administered after all 168 hours post-dose assessments of Visit 2 are completed
- Administration of 40 IU/kg N9-GP
- Stop time of injection must be recorded
- Precautions to take when injecting the initial doses of N9-GP, see Section 8.9

Post-dose assessments after the second dose of N9-GP:

- Adverse events, see Section 12.1
- Vital signs: 60 minutes (± 10 minutes), see Section 8.5.4

Training:

- Home treatment/eDiary training, see Sections 8.3.7, 8.9 and 8.10.2

IV/WRS:

- Drug accountability of trial product at Visit 3 must be recorded in the IV/WRS, see Section 10
- Recording of body weight and dispensing of N9-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10

Reminders:

- N9-GP dispensing for home treatment
- eDiary dispensing, see Section 8.10.3
- An appointment for Visit 4 (3 weeks±1week) should be made
- Remember telephone contact with the patient halfway through the home treatment period between visits (±1 week), see Section 8.10.4
- If possible, planned vaccinations should be postponed beyond the first three months of N9-GP treatment

8.1.4 Visit 4 to Visit 10

The home treatment periods are:

- 3 weeks±1 week between Visit 3 and 4
- 4 weeks±1 week between Visit 4, 5 and 6
- 8 weeks±1 week between Visit 6, 7, 8, 9 and 10
- 8 weeks+2 weeks between Visit 10 and 11

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

Pre-dose assessments at the day of dosing:

- Withdrawal criteria, see Section 6.4.

- Concomitant medication, see Section 11
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4. Any new bleeding episodes detected or bleeding episodes recorded in the eDiary, considered as severe, should be entered in the eCRF
- Compliance review of drug administration and eDiary completion, see Sections 8.3.7
- Adverse events since previous visit, see Section 12.1
- Body measurements (**body weight, Visit 7, 8, 9 and 10 only**), see Section 8.5.1
- Physical examination (**Visit 8 only**), see Section 8.5.2

Pre-dose blood sampling for central laboratory assessments to be taken within 1 hour prior to dosing:

- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2

N9-GP administration:

- Administration of 40 IU/kg N9-GP, see Section 8.9
- Stop time of injection must be recorded, this corresponds to time point = 0

Post-dose assessments:

- Adverse events, see Section 12.1

Post-dose blood sampling for central laboratory assessments to be taken 30 minutes (±10 minutes) after dosing:

- FIX activity, see Section 8.8.4

The blood sample taken 30 minutes (±10 minutes) post-dose must not be taken from the same vein as used for administration of N9-GP.

IV/WRS:

- Drug accountability for all the products dispensed, or any product returned from the previous visits, must be recorded in IV/WRS, see Section 10
- Recording of body weight and dispensing of N9-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10

Training:

- Home treatment/eDiary training, if the site suspects that the patient is not fully confident with self administration and how to deal with safety related signs and symptoms, see Sections 8.3.7, 8.9 and 8.10.2

Reminders for each visit:

- An appointment for the next visit should be made
- N9-GP dispensing for home treatment
- Remember telephone contact with the patient halfway through each home treatment period between visits (±1 week), see Section 8.10.4

8.1.5 Visit 11 - end of main phase

Visit 11 can be scheduled as soon as the patient has been in 52 weeks of prophylactic treatment with N9-GP. In case the patient has been treated with N9-GP within 6 days prior to the planned Visit 11, the visit should be postponed.

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

- Withdrawal criteria, see Section 6.4
- PRO questionnaires, see Section 8.3.1
- Concomitant medication, see Section 11
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4. Any new bleeding episodes detected or bleeding episodes recorded in the eDiary, considered as severe, should be entered in the eCRF
- Compliance review of drug administration and eDiary completion, see Section 8.3.7
- Adverse events since previous visit, see Section 12.1
- Body measurements (retrospective height at visit 11 will be collected if available in medical records ± 3 months from visit and consent obtained), see Section 8.5.1
- Physical examination, see Section 8.5.2
- Vital signs, see Section 8.5.4

Pre-dose blood sampling for local laboratory assessments:

- Haematology, see Section 8.7.1

Pre-dose blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.8.1
- Coagulation-related parameters, see Section 8.8.2
- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2
- HCP antibodies, see Section 8.8.6
- Allergic reaction testing, see Section 8.8.7

N9-GP administration (only for patients continuing in the extension phase):

- Administration of 40 IU/kg N9-GP, see Section 8.9

Post-dose assessments (only for patients continuing in the extension phase):

- Adverse events, see Section 12.1

IV/WRS (only for patients continuing in the extension phase):

- Drug accountability for all the products dispensed, or any product returned from the previous visits, must be recorded in IV/WRS, see Section 10
- Recording of body weight and dispensing of N9-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10

IV/WRS (only for patients not continuing in the extension phase):

- Drug accountability for any product returned from the previous visits, must be recorded in IV/WRS, see Section 10
- Perform a completion session in IV/WRS, see Section 10

Training (only for patients continuing in the extension phase):

- Home treatment/eDiary training; if the site suspects that the patient is not fully confident with self-administration and how to deal with safety related signs and symptoms, see Sections 8.3.7, 8.9 and 8.10.2

Reminders (only for patients not continuing in the extension phase):

- eDiary collection, see Section 8.10.3
- An appointment for a follow-up visit should be made within 3 weeks±1 week
- Treatment with N9-GP is ended
- After this visit, the patient can be treated with other coagulation factors than N9-GP according to standard practice
- The patient should not be treated with any coagulation factors within 4 days before the FU visit

Reminders (only for patients continuing in the extension phase):

- An appointment for Visit 12 (3 months±2 weeks) should be made
- N9-GP dispensing for home treatment.
- Remember telephone contact with the patient halfway through the home treatment period (±1 week), see Section 8.10.4

8.1.6 Follow-up visit

This follow-up visit is for patients who are withdrawn during the main phase or not continuing in the extension phase. The visit should take place 3 weeks±1 week after Visit 11.

If FIX inhibitors are identified at this visit the patient should attend inhibitor follow-up visits, please refer to Section 8.1.9.

If a bleeding episode occurs within 4 days prior to the planned FU visit, and the patient has been treated with coagulation factors, the visit should be postponed.

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

- Concomitant medication, see Section 11
- Date and time of last coagulation factor administration
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4
- Adverse events since previous visit, see Section 12.1
- End of trial form

Blood sampling for central laboratory assessments:

- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2

Reminder:

- Follow up on any AEs according to Section 12.2.1

8.1.7 Visit 12 to Visit 32+

Visit 12 to Visit 32+ are scheduled 6 months ±2 weeks apart, with the reference to when visit 11 took place.

Between V15 and V17, a subset of patients will be requested to attend an additional visit. Procedures and assessments will be identical to visit 16. If applicable the visit may be planned by the investigator to coincide with the interim dispensing of N9-GP halfway in-between two visits. Novo Nordisk will inform relevant investigators who in turn should schedule the visit date with the affected patients.

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The home treatment periods are:

- 3 months±2 weeks between Visit 11, 12 and 13.
- 6 months±2 weeks between Visit 13, 14, 15, 16, 17 and up to 32+. The amount of N9-GP dispensed at each visit corresponds to approximately 3 months of home treatment. Halfway in-between two visits additional N9-GP should be dispensed for further 3 months home treatment. The patient is not required to attend the clinic only for N9-GP interim dispensing.

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

Pre-dose assessments:

- Withdrawal criteria, see Section 6.4

- PRO questionnaires (visit 17 only), see Section 8.3.1
- Concomitant medication, see Section 11
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4. Any new bleeding episodes detected or bleeding episodes recorded in the eDiary, considered as severe, should be entered in the eCRF
- Compliance review of drug administration and eDiary completion, see Section 8.3.7
- Adverse events since previous visit, see Section 12.1
- Body measurements, see Section 8.5.1
- Physical examination, see Section 8.5.1
- Neurological examination, see Section 8.5.2.1
- Neurocognitive assessments, see Section 8.5.3
- Vital signs (Visit 12 and EOT), see Section 8.5.4

Pre-dose blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.8.1
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2
- FIX activity, see section 8.8.4
- HCP antibodies, see Section 8.8.6
- PEG, see Section 8.8.12
- Biospecimens for storage, if applicable **(visit 13, 15, 17, etc),** see section 8.8.13 and 25.1
- Urinalyses, see Section 8.8.11

N9-GP administration (either at the trial site or at home after the visit):

- Administration of 40 IU/kg of N9-GP, see Section 8.9
- The date and the actual time of completion of the injection must be recorded in the eCRF or patient eDiary

Post-dose assessments (only if the patient is dosed at the trial site):

Adverse events, see Section 12.1

IV/WRS:

- Drug accountability for all the products dispensed or any product returned from the previous visit must be recorded in IV/WRS, see Section 10
- Recording of body weight and dispensing of N9-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10

Training and reminders:

- An appointment for the next visit should be made

- N9-GP dispensing for home treatment
- Remember contact with the patient halfway through each home treatment period (±1 week), see Section 8.10.4
- Home treatment/eDiary training (if applicable), see Section 8.10.2
- The EOT visit should be scheduled minimum 6 days after the last N9-GP administration

8.1.8 End of trial visit

End of Trial visit should take place within the 2 months prior to the End of Trial date listed in section 7. The End of Trial visit may replace a scheduled visit if last scheduled visit took place 6 months ago.

If a bleeding episode occurs prior to the EOT visit, and the patient is treated with N9-GP, the visit should be postponed with at least 6 days.

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

- Withdrawal criteria, see Section 6.4
- Concomitant medication, see Section 11
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4. Any new bleeding episodes detected or bleeding episodes recorded in the eDiary, considered as severe, should be entered in the eCRF
- Compliance review of drug administration and eDiary completion, see Section 8.3.7
- Adverse events since previous visit, see Section 12.1
- Body measurements, see Section 8.5.1
- Physical examination, see Section 8.5.2
- Neurological examination, see section 8.5.2.1
- Neurocognitive assessments, see section 8.5.3
- Vital signs, see Section 8.5.4
- End of trial form

Blood sampling for local laboratory assessments:

- Haematology, see Section 8.7.1

Blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.8.1
- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2
- HCP antibodies, see Section 8.8.6
- PEG, see Section 8.8.12

- Allergic reaction testing, see Section 8.8.7
- Biospecimens for storage, if applicable, see section 8.8.13 and 25.1
- Urinalyses, see Section 8.8.11

IV/WRS:

- Drug accountability for any product returned from the previous visit must be recorded in IV/WRS, see Section 10
- Perform a completion session in IV/WRS, see Section 10

Reminder:

- eDiary collection, see Section 8.10.3

8.1.9 Inhibitor follow-up visit 1-3

The inhibitor follow-up visits should only be conducted if a new high titre FIX inhibitor (≥5 BU) is identified and confirmed at an assessment visit or unscheduled visit by the central laboratory. As soon as possible after this has been confirmed, the N9-GP treatment should be stopped and the patient scheduled for an end of trial visit (Visit 11, if during the main phase, or EOT visit, for the extension phase). The end of trial visit should preferably be performed prior to initiation of treatment with another FIX product. The first IFU visit must be scheduled 4 weeks±1 week after the end of trial visit and the patient must, as a minimum, attend three inhibitor follow-up visits (IFU1-3) with 4 week±1 week intervals. Additional follow-up visits may be arranged at intervals as long as clinically warranted.

In case the patient has been treated with coagulation factors within 4 days prior to the first inhibitor follow up visit (IFU1), the visit must be postponed, please also refer to Section 8.8.5.2 for further details.

If low titre inhibitors *(<5 BU)* are identified and confirmed by the central laboratory during the main phase, the patient is allowed to continue with N9-GP treatment. In this case, the patient should be scheduled for Visit 11, and thereafter proceed into the extension phase. If low titre inhibitors are detected during the extension phase, the patient can continue as planned.

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

- Concomitant medication, see Section 11
- Date and time of last coagulation factor administration
- Adverse events, see Section 12.1
- End of trial form (at the last visit)

Blood sampling for central laboratory assessments:

- Biochemistry, see Section 8.8.1

- FIX activity, see Section 8.8.4
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2
- HCP antibodies, see Section 8.8.6
- PEG, see Section 8.8.12
- Allergic reaction testing, see Section 8.8.7
- Urinalyses, see Section 8.8.11

Reminder:

- Follow up on any AEs according to Section 12.2.1

8.1.10 Unscheduled visits

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

Visits/contacts with the site regarding non-trial related activities do not need to be reported as an unscheduled visit.

The following can be performed at an unscheduled visit, if deemed relevant:

- Withdrawal criteria, see Section 6.4
- Concomitant medication, see Section 11
- Date and time of last dose of coagulation factor prior to an unscheduled visit
- Assessments of bleeding episodes (date, severity and location), see Section 8.3.4
- Health economic resource use: where treatment for a severe bleed occurred, how the patient arrived at the treatment facility (eg, ambulance), and general and intensive care ward hospitalisation days
- Compliance review of drug administration and eDiary completion, see Section 8.3.7
- Adverse events since previous visit, see Section 12.1
- Body measurements, see Section 8.5.1
- Physical examination, see Section 8.5.2
- Vital signs, see Section 8.5.4
- Haematology, see Section 8.7.1
- Biochemistry, see Section 8.8.1
- Coagulation-related parameters, see Section 8.8.2
- FIX activity, see Sections 8.7.2 (local laboratory) and 8.8.4 (central laboratory)
- N9-GP/FIX antibodies, see Section 8.8.5.1
- FIX inhibitors, see Section 8.8.5.2

- HCP antibodies, see Section 8.8.6
- PEG, see Section 8.8.12
- Allergic reaction testing, see Section 8.8.7
- Viral antibody test (HIV and/or HCV), see Section 8.8.8
- CD4+ lymphocyte count, see Section 8.8.8
- HCV RNA, see Section 8.8.8
- *F9* genotype testing, see Section 8.8.9
- Lupus anticoagulant, see Section 8.8.10
- Urinalyses, see Section 8.8.11
- Administration of N9-GP, see Section 8.9
- Dispensing of N9-GP for site dosing/home treatment must be performed via IV/WRS, see Section 10
- Home treatment/eDiary training, see Sections 8.9, 8.10.2 and 8.3.7
- Drug accountability of N9-GP, see Section 10
- eDiary dispensing, see Section 8.10.3
- eDiary collection, see Section 8.10.3
- Surgery, see Section 8.3.6.1 and 8.3.6.2
- Biospecimens for storage (if applicable) see section 8.8.13

8.2 Home treatment

Home treatment with administration of N9-GP can start after N9-GP administrations have been performed in the trial site at Visit 2 and Visit 3, but may be postponed until the patient and/or the patient's parent(s)/caregiver are comfortable with the reconstitution and administration process. A caregiver is a close person who helps the patient in his daily life. It is not the investigator or the site staff.

8.2.1 Prophylactic home treatment

The dose for prophylaxis during the main phase is 40 IU/kg once weekly (± 1 day). In the extension phase of the trial the same dosing regimen is administered.

In case a patient has treated a bleeding episode on a day not planned for prophylaxis dosing, the next prophylactic dose should still be taken on the planned day. If a bleeding episode occurs earlier on 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 if a bleeding episode occurs later the same day, the bleeding episode should be treated and registered independent of the prophylaxis dose.

Bleeding episodes must be treated as described in Section 8.2.2.

The following procedures and assessments must be performed:

- N9-GP administrations once weekly (every 7th day ±1 day), during the extension phase
- Adverse events calls by the investigator/medically qualified person halfway through the home treatment period (±1 week)
- Completion of the patient eDiary, including details of all bleeding episodes and N9-GP administrations (see Section 8.3.7)

If an individual patient has not reached 50 EDs after 52 weeks continuous treatment, the trial participation should be prolonged further until at least 50 EDs are reached. This will be done by extending the home treatment period between Visit 10 and Visit 11.

8.2.2 Home treatment of bleeding episodes

Bleeding episodes must be treated as soon as identified. The dose for treatment of an uncomplicated mild/moderate bleeding episode, for example a joint bleed, is a single dose of 40 IU/kg. At steady state, this dose is expected to give a recovery of at least 60-70% FIX activity and the activity level 5 days after dosing is still expected to be above 20%. If there is no observed effect of 40 IU/kg, the patient or parents(s)/LAR should contact the investigator prior to administration of the second dose of 40 IU/kg.

A severe bleeding episode should be treated immediately at home, at the trial site or at a local emergency room with 80 IU/kg. If treated at home, the trial site must be contacted immediately for further instructions or transport.

Patients and parents(s)/caregiver are instructed by the investigator how to treat themselves for a bleeding episode at home and how to record this in the eDiary.

The following procedures and clinical assessments must be performed:

- N9-GP administration for treatment of any bleeding episodes
- Completion of the patient eDiary, including details of all bleeding episodes and N9-GP administrations (see Section 8.3.7)

8.3 Patient related information

8.3.1 Patient reported outcomes and health economic assessments

Patient reported outcomes will be assessed at Visit 1, Visit 11, Visit 17 and Visit 22/23/24 (the relevant visit where neurocognitive assessments are performed for the first time for each patient) . The questionnaires should preferably be completed before any other trial-related activities during these visits.

Several questionnaires will be used to assess disease and age-group specific quality of life and treatment satisfaction.

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

For patients below the age of 4:

- TAPQOL children; Questionnaire for parents (6 months–6 years)

For patients aged 4-7:

- HAEMO-QOL; Questionnaire for children I (4-7 years, to be read to the child)
- HAEMO-QOL parents; Questionnaire for parents I (4-7 years)
- HEMO-SAT parents; Questionnaire for parents

For patients aged 8-12:

- HAEMO-QOL; Questionnaire for children II (8-12 years)
- HAEMO-QOL parents; Questionnaire for parents II (8-12 years)
- HEMO-SAT parents; Questionnaire for parents

The PRO questionnaires are disease and age-group specific and are designed to minimise patient burden. The patients and parent(s)/LAR will continue at Visit 11 and Visit 17 with the same questionnaires as completed at Visit 1 regardless of changes in age. For those patients that grow out of their initial age group during the trial, patients and parent(s)/LAR should – in addition to the questionnaires applicable to the patient's initial age group – at Visit 17 complete the questionnaires applicable to the age group, in which the patient has grown into at the time of Visit 17. For patients having grown out of the upper age group (8 – 12 years) at Visit 17, patients and parents(s)/LAR should continue with only the same questionnaires as completed at Visit 1. At the end of trial visit only the questionnaire completed at Visit 17 representing the patient actual age group at the time of Visit 17 or the upper age group (8-12 years) should be completed.

The HAEMO-QOL questionnaires were originally developed and validated in UK English. They have been translated and linguistically validated into other languages. The HEMO-SAT questionnaire was developed in UK English and has been translated and linguistically validated into other languages. The TAPQOL questionnaire was developed and validated in Dutch (Netherlands) and has been translated into other languages.

The PRO data will be entered in the database and analysed by Novo Nordisk. Analyses will be made after all data are collected.

To characterise the impact of prophylactic treatment on health economic resource use, the following data should be recorded by the trial staff in the eCRF:

- Bleed related treatment: where treatment occurred, how the patient arrived at the treatment facility, and, if relevant, the number of general and intensive care hospitalisation days

The following will be recorded on an ongoing basis in the patient's eDiary for health economic purposes:

- Number of bleed related days the patient was unable to attend preschool or school
- Number of bleed related days the patient used mobility aids (wheelchair and/or crutches)
- Number of bleed related days the patient's parent(s)/caregiver was unable to work
- Number of bleed related days the patient's parent(s)/caregiver was unable to attend school/studies

8.3.2 Demographic data

Demographic data will be collected as allowed per local law:

- Date of birth or age
- Ethnicity
- Race

8.3.3 Medical history/concomitant illness

Complete medical history will be obtained during the screening procedure. In the event a diagnosis is unknown, the description of symptoms will be recorded. Onset date for all significant illnesses within the last 5 years should be recorded. All chronic illnesses should be recorded.

The following organ systems should be assessed:

- Central and peripheral nervous systems
- Eyes-ears-nose-throat
- Cardiovascular
- Respiratory
- Gastrointestinal
- Renal-genitourinary
- Endocrine-metabolic
- Musculoskeletal
- Dermatologic
- Haematopoietical-lymphatic
- Immunological

Conditions related to the following items should be assessed:

- Allergies, including any drug sensitivities

- Abuse of drug or any substance

Details on haemophilia and inhibitors:

- Diagnosis of haemophilia B (date)
- Other coagulation-related diseases
- Classification of haemophilia B and FIX activity level (%) from medical history
- Underlying gene defect (if known)
- Clinical suspicion of inhibitors data from medical history
- Number of inhibitor tests and/or FIX recovery tests within the last 5 years
- Relatives with haemophilia B and inhibitors

Details on joints:

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

8.3.3.1 Haemophilia treatment history

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

- Number of months on prophylaxis
- Dose and frequency of dosing
- rFIX or pdFIX product
- Recovery results for previous FIX product (% or IU/mL)
- Dose and number of doses most commonly used to treat a bleeding episode
- Number of bleeding episodes within the last 12 months prior to initiation of prophylactic therapy (number of treatment requiring bleeding episodes/number of non-treatment requiring bleeding episodes)
- Number of bleeding episodes within the last 12 months (number of treatment requiring bleeding episodes/number of non-treatment requiring bleeding episodes).
- History of switching FIX products (type of products and age at switching)

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

- Number of months on on-demand treatment
- Dose and number of doses most commonly used to treat a bleeding episode

- Number of bleeding episodes within the last 12 months (number of treatment requiring bleeding episodes/number of non-treatment requiring bleeding episodes).
- rFIX or pdFIX product
- Recovery results for previous FIX product (% or IU/mL)
- History of switching FIX products (type of products and age at switching)

For all patients, the following should be recorded:

- Surgeries within the last 5 years, if applicable
  - Date of surgery
  - Indication
  - rFIX or pdFIX product
- Number of EDs prior to trial entry, must be >50 days
  - If it is not possible to count the actual number of exposures in the patient's medical records, the investigator should make a written statement with an estimate based on, eg, patient age, treatment frequency, medical history, discussion with previous doctor/transfer note, and other relevant information
- Vaccinations in the last 12 months
- Planned vaccinations in the next 12 months from time of screening visit (should be recorded as concomitant medication at the time of vaccination)

8.3.4 Bleeding episodes

8.3.4.1 Assessments of bleeding episodes and treatment response

All bleeding episodes and treatment of bleeding episodes will be recorded in the medical records and/or the eCRF by the investigator/trial staff or in the eDiary by the patient or parent(s)/caregiver. For details regarding treatment and reporting in connection with a bleeding episode, please refer to Section 8.2.2 and 8.3.7.

If a patient experience a bleeding episode at home, treatment with N9-GP should be initiated irrespectively of severity of the bleeding episode, please refer to Section 8.2.2 for details. The bleeding episode will per default be considered as mild/moderate when it is uncomplicated and can be treated at home. If the patient is in contact with the investigator, it is the responsibility of the investigator to assess the severity of the bleeding episode.

The severity of bleeding episodes is defined as:

- Mild/Moderate: Bleeding episodes that are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds. If the patient is discharged, these bleeding episodes can be treated at home and details of the bleeding episodes entered in the eDiary by the patient or parent(s)/LAR.

- Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe. These bleeding episodes must be treated immediately at home or at the local emergency room, and the trial staff must be contacted. The details of severe bleeding episodes must be entered in the eCRF by the investigator or trial staff. Traumatic bleeding episodes at other locations than described above can always be considered severe at the investigators discretion.

For bleeding episodes the following should be recorded in either the eCRF or the eDiary (refer to Section 8.2.2 and 8.3.7):

- Date and time of onset of bleeding episode
  - Date and time of stop of bleeding episode
- Cause of the bleeding episode
  - Spontaneous, traumatic or other origin
- Anatomical location of bleeding episodes
  - Location (including left or right side) and description of tissue, eg, CNS, joint, gastrointestinal, subcutaneous, muscle, mucosal or other
  - If assessed by the patient any pain, swelling and restriction of motion should be indicated
  - If assessed by a medically qualified person, the result of the physical examination of the bleeding episode should be recorded
- Treatment of bleeding episodes
  - Number of doses, amount, vial concentration, and time of each dose of N9-GP
  - Other haemostatic medication (eg, tranexamic acid)
  - Pain relieving medication
  - Other therapy used (ice, compression, etc)
- Haemostatic response

  - The assessment for haemostatic response will be made by the patient or parent(s)/caregiver and discussed with the investigator during visits to the trial site. If there is no observed effect of 40 IU/kg, the investigator should be contacted prior to administration of the second dose of 40 IU/kg. If the investigator re-classifies a mild/moderate bleeding episode to a severe bleeding episode, treatment with a double dose of 40 IU/kg is considered as a single injection of 80 IU/kg.
  - The 4-point scale is defined below and will take into account the improvement in signs of bleeding episodes, mainly by pain relief, but also taking swelling and motion into account. The evaluation should take place during and at 8 hours.

  - **The 4-point scale is defined as follows:**
  - **Excellent** – abrupt pain relief and/or clear improvement in objective signs of bleeding within 8 hours after a single injection

- **Good** – noticeable pain relief and/or improvement in signs of bleeding within 8 hours after a single injection
- **Moderate** – probable or slight beneficial effect within the first 8 hours after the first injection but requiring more than one injection within 8 hours
- **Poor** – no improvement, or worsening of symptoms within 8 hours after two injections

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 worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after stopping the treatment. 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.

Consequences of a bleeding episode

The following will be recorded by the trial staff in the eCRF for health economic purposes:

- Bleed related treatment at unscheduled visits where treatment occurred: how the patient arrived at the treatment facility, and, if relevant, the number of general and intensive care hospitalisation days

The following will be recorded in the patient's eDiary for health economic purposes:

- Number of bleed related days the patient was unable to attend preschool or school
- Number of bleed related days the patient used mobility aids (wheelchair and/or crutches)
- Number of bleed related days the patient's parent(s)/caregiver was unable to work
- Number of bleed related days the patient's parent(s)/caregiver was unable to attend school/studies

8.3.5 Prophylaxis

Prophylactic injections will be recorded in the eDiary unless the dose is given at the trial site, in which case the details will be recorded in the eCRF.

For prophylaxis the following should be recorded in either the eCRF or the eDiary:

- Date and time of N9-GP administration
- Dose administered (mL)
- Vial concentration (2000 IU or 500 IU per vial) – only to be recorded in the eCRF and only when dose is given at the trial site
- Reason for prophylaxis (planned or in connection with surgery)

8.3.6 Surgery

8.3.6.1 Minor surgery

Preventive N9-GP treatment before minor surgery and placement 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. For the definition of minor surgery, refer to section **5.3.3**.

For minor surgery the following should be recorded in either the eCRF or the eDiary:

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

8.3.6.2 Major surgery

Major surgery can be performed while participating in the present trial. For definition of major surgery refer to section **5.3.3**. 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[9]. 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 postoperative 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[9].

The site must have ability to measure FIX activity at a local laboratory. Please refer to section 8.7.2 for requirements to assay calibration with the N9-GP reference standard.

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/kg N9-GP after the post-surgery period

During this period, all bleeding episodes and any haemostatic treatment administered must be recorded in a paper CRF when the patient is at the site and in a paper diary when the patient is at home; the patient is requested to hand in the eDiary to the site to avoid duplicate entries.

Perioperative procedures, assessments and blood sampling will be performed at the Investigators discretion and documented in the patients' medical records. The following must be performed and recorded in a paper CRF:

- 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, see section 11
- 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 (results in local units eg. g/dL or mmol/L)
- Clinical evaluation of haemostatic response will be assessed 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

8.3.7 Entry of patient eDiary data and eDiary compliance review

During the home treatment period the patient or the patient's parent(s)/caregiver must ensure that all prophylactic home treatment, bleeding episodes, treatment of bleeding episodes and assessments thereof are captured in the eDiary. Data should not be recorded in the eDiary until after Visit 3.

As a minimum the following data will be collected in the eDiary:

- Date and time of prophylactic home treatment with N9-GP
- Dose administered (mL)
- Vial concentration (2000 IU or 500 IU per vial)
- Reason for prophylaxis (planned or in connection with minor surgery)
- Date and time of onset of bleeding episode
- Date and time of stop of bleeding episode

- Cause of bleeding episode (eg, spontaneous)
- Location of the bleeding episode
- Symptoms related to the bleeding episode (swelling, reduced mobility or pain)
- Treatment of the bleeding episode (N9-GP dose and time of administration)
- Other therapy used (ice, compression etc)
- Pain relieving medication
- Evaluation of the haemostatic response (excellent, good, moderate or poor)
- Number of bleed related days the patient was unable to attend preschool or school
- Number of bleed related days the patient used mobility aids (wheelchair and/or crutches)
- Number of bleed related days the patient's parent(s)/caregiver was unable to work
- Number of bleed related days the patient's parent(s)/caregiver was unable to attend school/studies

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

The entries made in the patient eDiary will be reviewed by the investigator to ensure consistency and compliance. The information in the patient's eDiary is regarded as source data. If information is missing in the eDiary, but is available in the medical records, then this information can be used.

8.4 Adverse event assessments

Monitoring of AEs will be performed from screening until the post-treatment follow-up period, according to the procedures described in Section 12.

For recording of bleeding episodes, please refer to Sections 8.3.4 and 12.1.3.

For details regarding the contact between the investigator/medically qualified person and patient, please refer to Section 8.10.4.

8.5 Clinical assessments

Clinical assessments should preferably be performed prior to blood sampling and prior to administration of N9-GP unless it is clearly stated otherwise. All assessments should be recorded in the eCRF if nothing else is stated.

8.5.1 Body measurements

- Body weight, wearing light clothing only (kg)
- Height, without shoes (cm) (Visit 1, to be measured at every visits going forward from approval of amendment 9. Height at Visit 11 ± 3 month will furthermore be collected retrospectively if available in medical records upon patient/parent(s)/LAR consent)

- Body mass index calculation (kg/m^2) (**Visit 1 only**)

8.5.2 Physical examinations

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

- General appearance
- Head, ears, eyes, nose, throat and neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system, including mouth
- Musculoskeletal system
- Central and peripheral nervous systems (general evaluation)
  - Elaborated neurological examination, see Section 8.5.2.1
- Skin
- Lymph node palpation
- Signs and symptoms of vascular thrombosis (eg but not limited to swelling, tenderness and leg pain)

8.5.2.1 Neurological Examination

Following aspects of the neurological examination will be assessed:

- General appearance including language, social and developmental aspects
- Parameters including handedness, head circumference 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
- Trapezius muscle function
- Tone of truncal, upper and lower extremity right and left
- Strength of upper and lower extremity right and left
- Reflexes of biceps, triceps, knee and ankle jerk, all right and left as well as Babinski
- Sensory aspect of cold, pin prick, light touch and proprioception (tor up(down)
- Gait with regards to walking, running, on heels and toes, tandem (toe/heel walk), standing or hop 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
-

- Each aspect of the neurological examination will be categorised into normal, abnormal (pre-existing or new) or not examined. Some aspects of the neurological examination may not be applicable for children in particular age groups.
-
- Any preexisting physical or neurological finding that was present at the time of enrolment in the study should be reported as medical history, new abnormal findings or any changes in the findings which fulfil the criteria of an AE must be recorded as such (see Section 12.1).
-

8.5.3 Neurocognitive assessments

Neurocognitive assessments should be performed according to Table 2-3 and Table 8-1. The following neurocognitive domains will be assessed in all countries:

- Executive function
- Attention/processing speed /working memory

Further, the following neurocognitive domains will be assessed in Canada, United Kingdom, and the United States:

- Neurocognitive function and intelligence
- Emotional behaviour
- Adaptive behaviour

At the discretion of the site and to facilitate scheduling the neurocognitive assessments, these may be made up to 1 month before or after the scheduled visits, except for the EOT visit where it may only be up to 1 month before visit. In general, the timing of the neurocognitive assessments should be planned to allow as much flexibility for the patients as possible. 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 which should be followed accordingly.

An 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 considering 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 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 and country

Domain:	Executive Function	Attention / Processing Speed	Structured Developmental History and Haemophilia History	General Intelligence	Behavioural / Emotional	Adaptive behaviour
Countries:	**For all countries**			**Additional testing for Canada, United Kingdom, and the United States**		
Visit number: / **Patient age (years : months)**	**All assessment visits and EOT**			**Yearly testing at assessment visits and EOT**		
6:0 to 6:11	BRIEF-2 (5-18y Parent form)	COGSTATE (Custom Battery - Peds (4-9)	Structured Developmental History and Haemophilia History	WPPSI-IV	BASC-3 (PRS-C Parent 6-11 form)	ABAS-3 (5-21y Parent form)
7:0 to 7:11	BRIEF-2 (5-18y Parent form)	COGSTATE (Custom Battery - Peds (4-9)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-C Parent 6-11 form)	ABAS-3 (5-21y Parent form)
8:0 to 9:11	BRIEF-2 (5-18y Parent form)	COGSTATE (Custom Battery - Peds (4-9)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-C Parent 6-11 form and SRP-C 8-11 patient form)	ABAS-3 (5-21y Parent form)
10:0 to 10:11	BRIEF-2 (5-18y Parent form)	COGSTATE (Custom Battery - Adult (10-21)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-C Parent 6-11 form and SRP-C 8-11 patient form)	ABAS-3 (5-21y Parent form)
11:0 to 11:11	BRIEF-2 (5-18y Parent form) BRIEF-2 (11-18 SR)	COGSTATE (Custom Battery - Adult (10-21)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-C Parent 6-11 form and SRP-C 8-11 patient form)	ABAS-3 (5-21y Parent form)

Domain:	Executive Function	Attention / Processing Speed	Structured Developmental History and Haemophilia History	General Intelligence	Behavioural / Emotional	Adaptive behaviour
	For all countries			Additional testing for Canada, United Kingdom, and the United States		
Patient age (years : months)	All assessment visits and EOT			Yearly testing at assessment visit and EOT		
12 to 15	BRIEF-2 (5-18y Parent form) BRIEF-2 (11-18 SR)	COGSTATE (Custom Battery - Adult (10-21)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-A Parent 12-21 form and SRP-A 12-21 patient form)	ABAS-3 (5-21y Parent form)
16 to 17	BRIEF-2 (5-18y Parent form) BRIEF-2 (11-18 SR)	COGSTATE (Custom Battery - Adult (10-21)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-A Parent 12-21 BASC-3 SRP-A 12-21)	ABAS-3 (5-21y Parent and 16-89 Adult)
18 to 21	BRIEF-A (18-90 Adult)	COGSTATE (Custom Battery - Adult (10-21)	Structured Developmental History and Haemophilia History	WASI-II	BASC-3 (PRS-A Parent 12-21 BASC-3 SRP-College 18-25)	ABAS-3 (5-21y Parent and 16-89 Adult)

8.5.4 Vital signs

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 (eg sitting or lying down) throughout the trial for each individual patient.

Vitals signs include assessment of:

- Body temperature (°C or °F)
- Pulse (beats/min)
- Blood pressure (BP) (mm Hg)
- Respiratory rate (breaths/min)

8.6 Blood sampling volume

Blood samples for laboratory analysis of safety, efficacy and PK parameters will be drawn as outlined in Table 2-1, Table 2-2 and Table 2-3. The blood sampling volume for the patient should not exceed 1% of the total blood volume at one occasion or 3% within in 28 days (see Appendix C). This is in accordance with European regulatory guidelines (Directive 2001/20/EC)[17] and FDA requirements. In total, approximately 90 mL blood will be collected per patient during the main phase of the trial and approximately 9-18 mL blood per visit and patient during the extension phase.

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

8.7 Local laboratory assessments

Local laboratory results are considered as source data and must be signed, dated and categorised by the investigator. The laboratory results must be categorised as “normal”, “out of normal range, not clinically significant” or “out of normal range, clinically significant”. A clinically significant value must be recorded as an AE, or if present at Visit 1 it should be recorded as concomitant illness.

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

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

8.7.1 Haematology

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

8.7.2 FIX activity

- FIX activity (% or IU/mL)

The trial site must have ability to measure FIX activity at a local laboratory and the investigator can at any time during the trial assess FIX activity at his/her discretion. 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 the 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 specific APPT 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.

8.8 Central laboratory assessments

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 by fax or email. Upon review of the results the investigator must sign and date the laboratory reports. A clinically significant value must be recorded as an AE, or if present at Visit 1 it should be recorded as concomitant illness.

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.

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

A detailed description in the central laboratory manual of procedures for sampling, handling, particulars of instrumentation, shipment of laboratory samples and all materials such as test tubes and labels will be provided by the central laboratory. The central laboratory manual and the central laboratory results will include the reference ranges. It will be possible for the central laboratory to report in other predefined units than listed below.

If the patient or parent(s)/LAR agree, residuals from all blood samples will be stored for possible future testing, but for no longer than 15 years from end of trial. If the patient or parent(s)/LAR do not agree upon this, all samples will be destroyed after finalisation of the trial report, except antibody samples which will be stored for possible future testing, at least until evaluation of the clinical trial by regulatory authorities.

8.8.1 Biochemistry

- Sodium (mmol/L)
- Potassium (mmol/L)
- Creatinine (µmol/L)
- Albumin (g/L)
- Total bilirubin (µmol/L)
- Aspartate aminotransferase (AST) (IU/L)
- Alanine aminotransferase (ALT) (IU/L)
- Gamma glutamyl transferase (GGT) (IU/L)
- Alkaline phosphatase (IU/L)
- C-reactive protein (CRP) (mg/L)
- Urea

8.8.2 Coagulation-related parameters

- Prothrombin time (PT) (sec, INR)
- Activated partial thromboplastin time (aPTT) (sec)
- Fibrinogen (g/L)

- Antithrombin (AT) (%)

8.8.3 Recovery for previous FIX product

Recovery results for the patient's previous FIX product should be collected from medical records. Recovery is defined as maximum FIX activity after dosing.

If recovery results are not available or are older than 1 year, or collected more than 1 hour after dosing, a new recovery sample should be collected. In this case, the patient should be dosed with his previous FIX product and a recovery sample should be collected 30 minutes±10 minutes after dosing. This can be done anytime in the period from informed consent and until 4 days prior to the laboratory assessments of Visit 1 or directly after all laboratory assessments of Visit 1 have been completed and until 4 days prior to the planned Visit 2.

- FIX activity (% or IU/mL)

8.8.4 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 should follow the recommendations provided by Novo Nordisk A/S. A description of the method and assay validation will be submitted with the final report of the trial.

The patient is enrolled in the trial based on the FIX activity reported in the medical records. If for some reason the baseline FIX activity level is not reported in the medical records, the patient may be enrolled in the trial based on the central laboratory results from Visit 1.

Visit 1:

- FIX activity (% or IU/mL)

All other visits:

- FIX activity (% or IU/mL)

Blood samples for analysis of FIX activity will be collected from all patients at Visit 2; pre-dose and 30 minutes, 24 hours, 48 hours, 96 hours and 168 hours post-dose. Pre-dose samples and 30 minutes post-dose samples will be collected at visit 5, 7, 9 and 11 during the main phase and pre-dose samples will be collected at the dosing visits during the extension phase. The sampling time points are relative to completion of N9-GP administration, and actual time must be documented.

The analysis of PK will be based on a one-stage clot assay.

8.8.4.1 One-stage clot activity assay

The one-stage bioassay (FIX activity clot assay) measures the activity of the compound in a specific process (clot formation). The FIX activity assay is a modified one-stage clot assay (modified aPTT assay). A primary reference standard of N9-GP is used, which biological activity is determined relative to the Ph. Eur. Human Coagulation Factor IX, batch 2. The biological activity in the reference material is defined so that one unit of N9-GP equals one FIX IU at establishment.

8.8.4.2 Chromogenic activity assay

The chromogenic bioassay (FIX activity chromogenic assay) measures the activity of the compound with a two-stage method. The FIX activity is determined by measuring the FVIIIa/FIXa-mediated FX activation with a chromogenic FXa substrate. It is a validated assay calibrated with an internal N9-GP reference standard or normal human plasma. This assay will be used for exploratory purposes. After the implementation of amendment 10 the chromogenic assay will no longer be used in this trial.

8.8.5 Antibody assessments

The N9-GP/FIX antibody and FIX inhibitor assessments will be performed at a laboratory selected by Novo Nordisk A/S or at a Novo Nordisk laboratory. The procedures for analyses should follow the recommendations provided by Novo Nordisk A/S. A description of the method and assay validation will be submitted with the final report of this trial.

8.8.5.1 N9-GP/FIX antibody assay

Screening for N9-GP antibodies and for FIX antibodies is based on a bridging ELISA and is validated according to international recognised guidelines[18]. Samples measured above the assay cut-point will be subject to a confirmation test where the signal will be inhibited with excess of unlabelled N9-GP. Also an investigation of cross reactivity to rFIX will be performed as a confirmation test by inhibition with excess of unlabelled rFIX. A polyclonal rabbit antibody that neutralises the FIX clot activity is used for the preparation of the positive control samples. Confirmed antibody positive samples will be titrated below two times cut-point and results given as a titre.

FIX activity levels measured at the scheduled visits will be reviewed by Novo Nordisk on an ongoing basis. If any post dose FIX activity level is below 60% of expected level defined as the post dose activity at visit 4 and there is no specific reason, an N9-GP antibody analysis (bridging ELISA assay) will be performed on the corresponding sample as soon as possible for this patient.

In case a patient has a positive antibody detected in the N9-GP antibody assay, the patient will be asked to attend the site for the next planned N9-GP administration followed by a PK session

- FIX activity (% or IU/ml)

Blood sampling during the PK session will be performed at the following time points (identical to Visit 2): pre-dose, 30 minutes (± 10 min), 24h (± 8 hours), 48h (± 8 hours), 96h (± 8 hours) and 168h (± 24 hours).

8.8.5.2 FIX inhibitors

Detection of FIX inhibitors (neutralising antibodies) will be carried out using a Nijmegen modified FIX Bethesda assay following heat pre-treatment of samples. The assay is validated according to international recognised guidelines[19]. The assay is based on measurement of the FIX activity (inhibitory activity) in plasma samples mixed with a fixed amount of normal plasma pool in buffer. Inhibitors will be considered as "low positive" with 0.6-<5 BU and "high positive" with a BU ≥5. Inhibitors will be recognised by comparison to a clinical cut-point of ≥0.6 BU. A polyclonal antibody, that neutralises the FIX clot activity, is used for the preparation of the positive control samples.

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 blood sample must be shipped to the central laboratory for inhibitor analysis. If the result of the Bethesda assay is positive, a second confirmatory Bethesda assay should be performed by the central laboratory. The confirmatory samples should be collected as soon as possible, but no sooner than 6 days after the last dose of N9-GP. If high titre inhibitors are identified and confirmed (≥ 5 BU) or significant clinical impact is seen, the patient should be withdrawn. In case low titre inhibitors (0.6–<5 BU) are identified and confirmed, the patient can continue with N9-GP treatment. If the low titre inhibitors are identified during the main phase, the patient should be scheduled for Visit 11, and can thereafter proceed into the extension phase. If this happens during the extension phase, the patient can continue as planned (see Figure 8-2).

Blood samples for FIX activity (trough and optional 30 minutes post dose), N9-GP/FIX antibodies and lupus anticoagulant must be taken in conjunction with the second confirmatory inhibitor sample (unscheduled visit).

At least three inhibitor follow-up visits should be scheduled for patients with high titre inhibitors and additional follow-up visits may be arranged at intervals as long as judged clinically warranted (see Section 8.1.9).

If an investigator decides to perform inhibitor testing locally, he/she must also send a duplicate sample for inhibitor testing at the central laboratory. The results from the central laboratory will be used in the official analysis of trial data. A positive inhibitor test must always be reported as a MESI no matter if the test is performed locally or centrally (refer to Section 12.1.2).

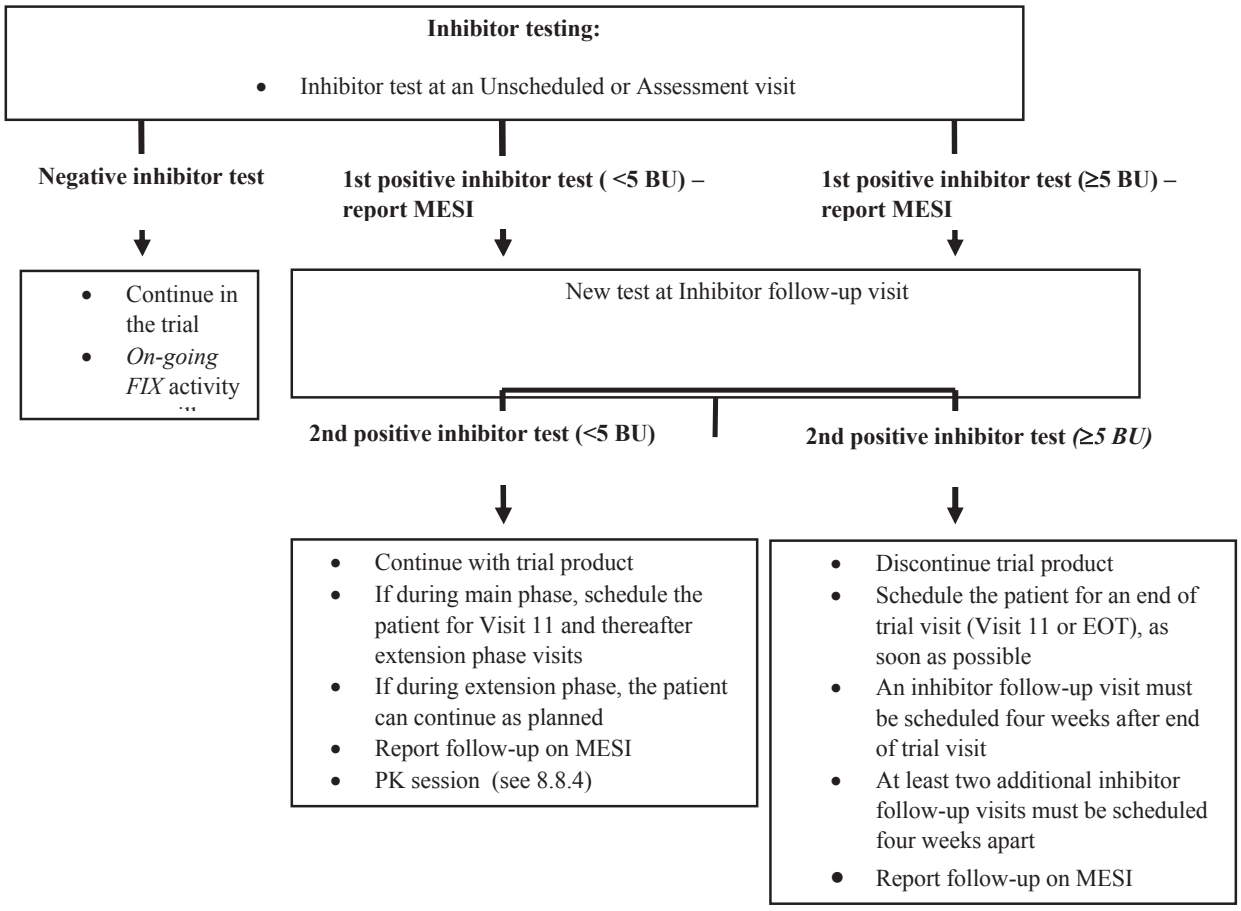

Figure 8-2 Process flow for inhibitor testing

8.8.6 Host cell protein antibodies

All patients will be examined for the development of antibodies against HCP. The samples will be analysed at a laboratory selected by Novo Nordisk A/S or at a Novo Nordisk laboratory.

8.8.7 Allergic reaction testing (conditional)

Allergic reaction testing will only be performed in patients developing severe allergic reactions related to N9-GP treatment.

If a severe allergic reaction related to treatment occurs, blood samples should be taken within 15 minutes (if possible), 1-4 hours and ~1 week after onset of the reaction at unscheduled visits. In this case, mandatory tests and selected optional exploratory tests will be performed, if considered relevant by Novo Nordisk Global Safety: The allergic reaction assessments will be performed at a laboratory selected by Novo Nordisk A/S or at a Novo Nordisk laboratory.

Allergic reaction testing in relation to positive inhibitor reaction, will only be performed once for each IFU visit, hence not 1-4 hours and 1 week after onset of the reaction.

Mandatory tests (30 minutes-3 hours and ~1 week):

- Immunoglobulin E (IgE) antibodies against N9-GP
- IgE antibodies against rFIX
- FIX inhibitors
- N9-GP/FIX binding antibodies
- Tryptase

Optional exploratory tests:

- IgE antibodies against CHO-HCP; all time points
- Anaphylaxins (C3a, C4a, C5a), <15 minutes and ~1 week
- Histamine, <15 minutes and ~1 week
- Complement activation test (C3, C4), 30 minutes - 3 hours and ~1 week

Optional exploratory tests will be performed using scientific sound non-validated tests. If relevant, baseline levels for optional exploratory test can be set using samples from other patients enrolled in the trial.

Detection of IgE antibodies against N9-GP and rFIX will be determined using the ImmunoCAP platform. Visit 2 samples (pre-dosing of N9-GP) and subsequent samples will be measured to follow IgE development over time. Caps will be coated with N9-GP or rFIX, and the specific IgE will be detected with anti-IgE antibody conjugate. Positive control samples will be based on a mouse monoclonal anti-N9-GP antibody humanised with regards to the IgE constant region. Samples read ≥0.35 kUA/L will be subject to a confirmation test where the signal will be inhibited with excess of unlabelled N9-GP or rFIX.

8.8.8 Viral assessments (HIV and HCV) and CD4+ lymphocyte count

- HIV 1 and 2 antibodies
- CD4+ lymphocyte count

If the patient's HIV status is unknown or if negative HIV test results in medical records are older than one year, HIV status should be tested at Visit 1. If the patient is HIV positive, the CD4+ lymphocyte count must be tested.

- Anti-HCV antibodies
- HCV RNA

If the patient's HCV status is unknown or if negative HCV test results in medical records are older than one year, anti-HCV antibodies should be tested at Visit 1. If the patient is HCV positive in medical records or if the anti-HCV antibodies test is positive, HCV RNA should be tested.

8.8.9 *F9* genotype testing

At Visit 1 all patients and parent(s)/LAR will be asked about documentation of previous *F9* genotype tests. If not available, *F9* genotype testing will be offered at Visit 1 or at any later visit where blood draw volume limits are not exceeded, and if allowed according to local law. Investigator, parent(s) or LAR have the right to refuse to provide patients' *F9* genotype documentation or to refuse genotyping. The *F9* genotype is analysed at a laboratory selected by Novo Nordisk A/S. No further analysis will be carried out for any other parameters and samples will be disposed of appropriately after the test. All test results are kept strictly confidential.

8.8.10 Lupus anticoagulant

- Lupus anticoagulant (dilute Russell's viper venom time)

8.8.11 Urinalysis

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.

8.8.12 Plasma PEG levels

The plasma concentration of PEG will be analysed for exploratory purposes. Plasma PEG levels will be measured in residuals, in Biospecimens for storage or in dedicated samples going forward from approval of amendment 9.

8.8.13 Biospecimens for storage

The patient or parent(s)/legally authorised representative (LAR) will be asked to consent to blood sampling for potential future assessments. The samples should only be taken if blood volume limitations allows for this. The samples will be stored at a Novo Nordisk appointed central laboratory (biorepository) and Novo Nordisk will have access for up to 15 years after the end of trial after which all samples will be destroyed according to standard operating procedures at the central laboratory. Refer to section 25.1. for information about long term retention of blood samples for exploratory purposes. It is voluntary for patients to participate in the collection of samples for Biospecimen, and the patient will not be withdrawn if decline to participate.

8.9 N9-GP administration

N9-GP will be administered while the patient is in a comfortable position.

At the trial site

The two first doses must be administered at the trial site by, or under direct supervision of, the investigator or an attending physician.

Precautions to take when injecting the first dose of N9-GP (Visit 2):

- 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.

Precautions to take when injecting the second dose of N9-GP (Visit 3):

- The patient has to be observed for 60 minutes in a hospital setting, 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.

    - Drug 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. If a central venous access port or cannula, sealed with heparin is used, it has to be flushed and sealed with saline the evening before administration of N9-GP.

The actual time of completion of the injection will be recorded and corresponds to trial time point = 0. All following PK sample time points at Visit 2 is relative to t = 0. The sample taken 30 minutes (±10 minutes) post-dose, must not be taken from the same vein as used for administration of N9-GP.

During remaining visits at trial site (Visit 4 to Visit X):

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

At home:

- Home treatment with administration of N9-GP can start after N9-GP administrations have been performed in the trial site at Visit 2 and Visit 3, or when the patient or the patient's parent(s)/caregiver are comfortable with the reconstitution and administration process.
- Home treatment may be given by the patient, parent(s)/caregiver 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.
- In case a patient has treated a bleeding episode on a day not planned for prophylaxis dosing, the next prophylactic dose should still be taken on the planned day. If a bleeding episode occurs earlier on 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 if a bleeding episode occurs later the same day, the bleeding episode should be treated and registered independent of the prophylaxis dose.

In the extension phase, a single dose of 40 IU/kg once weekly (± 1 day) will be administered intravenously. This must be documented in the medical records and the eCRF. In the extension phase, the patient can be administered the planned doses of N9-GP either at the trial site or at home after the visit.

8.10 Training and reminders

8.10.1 Trial card dispensing

At Visit 1 the patient 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.

8.10.2 Home treatment training

Home treatment with administration of N9-GP can start after N9-GP administrations have been performed in the trial site at Visit 2 and Visit 3 (see Section 8.1.2 and 8.1.3), but may be postponed until the patient and/or the patient's parent(s)/caregiver are comfortable with the reconstitution and administration process. All patients and/or parent(s)/caregivers must be carefully instructed in

recognising and dealing with signs and symptoms of an anaphylactic reaction. This includes knowledge of which medical facility to contact in this situation.

If the patient does not follow the planned dosing schedule, the investigator must retrain the patient and/or the patient's parent(s)/caregiver. The training must be documented in the medical records.

8.10.3 eDiary and paper diary dispensing and collection

The eDiary will be dispensed to the patients at Visit 3. For details regarding entry of patient diary data in the eDiary, please refer to Section 8.3.7. No data should be entered in the eDiary until after Visit 3.

For patients withdrawn during the main phase or not continuing in the extension phase, the eDiary will be collected at Visit 11. For patients completing the extension phase, the eDiary will be collected at the EOT visit.

A paper diary will be dispensed to the patient in the period prior to the surgery where the weekly prophylaxis has been stopped and until the post-surgery period has stopped. All haemostatic treatment administered at home during this period will be recorded in a paper diary and the patient must be requested to hand in the eDiary to the site to avoid duplicate entries.

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

The investigator and/or medically qualified person must establish contact with the patient at least once halfway through each home treatment period, either by visits at the trial site or other contacts, e.g. telephone calls.

The communication will focus on the well-being of the patient and will include all AEs. The investigator/medically qualified person should not suggest specific AEs to patients, but should inquire generally about how the patient feels and ask the patient or parent(s)/caregiver questions such as: "How do you feel?"/ "How do you believe your child feels?" and "Have you had any medical problems since the last contact?"/ "Has your child had any medical problems since the last contact?".

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

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

8.10.5 Interactive voice/web response system

Please refer to Section 10 regarding the IV/WRS.

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

8.11 Patient compliance

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

Failure to comply with scheduled visits and N9-GP administration may result in withdrawal in accordance with the protocol withdrawal criteria. Treatment with FIX concentrates, 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 11). Compliance with N9-GP prophylaxis must be addressed at each visit.

9 Trial supplies

9.1 Trial product(s)

The following trial products will be supplied by Novo Nordisk A/S, Denmark:

- N9-GP Drug Product
- Histidine solvent 4.2 mL

N9-GP Drug Product is supplied as freeze-dried powder 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 further diluted.

Detailed instruction regarding reconstitution and dosing will be given in the Trial Materials Manual (TMM). After reconstitution the appropriate volume of the vials will be drawn into a syringe. The content of several vials N9-GP may be combined in one syringe. N9-GP may not be added to or mixed with any other material.

Administration of the appropriate volume of N9-GP will be given as an i.v. bolus injection. Maximum injection rate is 4 mL/min (please refer to Section 8.9). The investigator will explain to the patient/caregiver how much this corresponds to in terms of injection time when administering N9-GP at home. If a central venous access port or cannula is used for N9-GP injection at dosing visits, and is sealed with heparin, it has to be flushed and sealed with saline the evening before the visit. This procedure is not necessary prior to home treatment injections.

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 frequently than every hour. These doses are only relevant in case of trauma, severe bleeding or surgery.

If the patient lacks recovery data for his previous FIX product, he will be dosed with this product at Visit 1. The FIX product is either a Non-Investigational Medicinal Product (NIMP) or IMP (Germany).

For Germany only: In accordance with German GCP-Verordnung, the patient's previous FIX product is also defined as an IMP. The patient's previous FIX product could be any of the products currently authorised in Germany. The Summary of Product Characteristics for the actual IMP will be submitted.

In accordance with GCP-Verordnung §5, for IMPs (8) currently authorised in Germany, and which are intended for use in the clinical trial without any additional manufacturing steps, special labelling on the containers and outer packaging is not necessary. This is allowed by the concept of the

clinical trial. The particulars according to GCP-Verordnung § 5 (1) will be shown in an accompanying document.

9.2 Non-investigational medicinal product(s)

If the patient lacks recovery data for his previous FIX product, he will be dosed with this product at Visit 1. In this case, the patient's FIX product is defined as a NIMP. Traceability of the FIX products will be ensured by recording the brand name and batch number in the eCRF.

Novo Nordisk A/S will not provide the previous FIX products but will reimburse trial sites for the cost of the products used at Visit 1.

9.3 Packaging and labelling of trial product(s)

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

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

Labelling will be in accordance with Annex 13[20], local law and trial requirements.

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.

9.4 Storage, handling, accountability and destruction of trial product(s)

The trial products (N9-GP Drug Product and 4.2 mL Histidine solvent) at the site must be stored in a secure place, for N9-GP Drug Product under refrigeration at 2-8°C, and for the Histidine solvent at 2-25°C, both protected against 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.

At home, the patient should store the trial products in a refrigerator until use. The site must carefully instruct the patient and parent(s)/caregiver in how to store the trial product. No temperature monitoring is required after the trial products are taken home by the patient.

The investigator must ensure the availability of proper storage conditions at the site and record and evaluate the temperature. The storage facilities must be checked frequently (at least once every working day) using a calibrated temperature logging device. A temperature log must be kept at the site. The investigator must ensure that the monitor is contacted in case of deviations outside the acceptable temperature range.

The temperature recorder should be either:

- Electronic with minimum interval of logging of 1 hour or;
- Manual with a min-max calibrated thermometer; the actual, minimum and maximum temperatures must be logged on working days

Dispensing and drug accountability

The IV/WRS will allocate the trial product in uniquely packed DUNs to the patient at each dispensing visit. The DUNs will be dispensed in accordance with the patient's body weight.

- No trial products should be dispensed to any person not enrolled in the trial
- Unused trial product must be stored separately from used trial product
- Once a patient is dosed, all trial drug product vials (used, partly used or unused, returned and lost/damaged) must be recorded in the Drug Accountability Module

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

Drug accountability must be performed for all delivered trial drug products. Trial product will be dispensed at dispensing or assessments visits, as appropriate.

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

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

The TMM, detailing the handling of the trial materials, will be provided by Novo Nordisk A/S.

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 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

All auxiliaries supplies used in this trial will be provided by Novo Nordisk A/S such as syringes, butterflies, sterile swabs, vial adapters etc.

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 voice/web response system

A trial specific IV/WRS will be set-up, and can be accessed at any time via internet or via telephone using toll-free telephone numbers. Some sessions may be available only as web sessions and can be accessed via internet. Accessibility to the IV/WRS must be restricted to and controlled by authorised persons. As a minimum, the system will be used for enrolling of patients, dispensing of trial product, controlling of expiry date of trial product, ordering of trial product, and screening failure data.

Since the trial product will not be shipped to the site before screening, the investigator should be encouraged to make a confirmation call in the IV/WRS as soon as the patient is deemed eligible for the trial and no later than two weeks prior to the planned Visit 2. Otherwise the trial product may not be available in time for dosing at Visit 2.

IV/WRS user documents, containing detailed descriptions, will be provided to the site.

11 Concomitant illnesses and concomitant medication

Definitions:

Concomitant illness: any illness that is present at the start of the trial (ie, at the first visit).
Concomitant medication: any medication, other than the N9-GP, that is taken during the trial, including the screening periods.

Details of all concomitant illnesses and medication must be recorded at trial entry (ie, at the first visit). Any changes in concomitant medication must be recorded at each visit. If a change is due to an AE then this must be recorded and reported according to Section 12. If the change influences the patient's eligibility to continue in the trial then the monitor must be informed.

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

11 Concomitant illnesses and concomitant medication:

Treatment of bleed in low titre inhibitor patients

Low titre inhibitor patients (<5 BU) who do not respond sufficiently to N9-GP treatment may be treated with activated recombinant factor VII (rFVIIa) for period of up to 4 weeks.

Prohibited medication

Plasma-derived prothrombin complex concentrates (pd-PCC) and plasma-derived activated prothrombin complex concentrates (pd-aPCC) are **not** allowed during the course of the trial.

- Coagulation Factors, not allowed in the 4 days prior to Visit 2: FVIII, FIX and coagulation factor VII (FVII) containing products other than N9-GP and other FIX-containing products like fresh frozen plasma or cryoprecipitate
- Anti-coagulants such as Heparin and vitamin-K antagonists except if they are used in relation to major surgery. Heparin is allowed for sealing of central venous access ports and cannulae according to local practice. An exception is when the ports are used for injection of N9-GP at dosing visits. In this case, heparin-sealed ports or cannulae have to be flushed and sealed with saline the evening before the visit. This procedure is not necessary prior to home treatment injections.

12 Adverse events and technical complaints

12.1 Definitions

Adverse event (AE):

Any untoward medical occurrence in a patient administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

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

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

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

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

The following should not be recorded as AEs:

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

Serious adverse event (SAE):

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

- Death
- A life-threatening experience [a)]
- In-patient hospitalisation or prolongation of existing hospitalisation [b)]
- A persistent or significant disability/incapacity [c)]
- A congenital anomaly/birth defect
- Important medical events [d)] that may not result in death, be life-threatening [a)] or require hospitalisation may be considered a SAE when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- a) The term "life-threatening" in the definition of SAE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- b) The term "hospitalisation" is used when a patient is:

- Admitted to a hospital/in-patient (irrespective of the duration of physical stay), or;

- Not admitted to a hospital/not in-patient, but 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 neither be reported as AEs or SAEs. Likewise, hospital admissions for surgical procedures planned prior to trial inclusion are not considered AEs or SAEs.

- c) The term "disability/incapacity" means that following the event the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life.
- d) The term "important medical events" means events which may jeopardise the patient or require intervention to prevent a seriousness criterion. It can be AEs which suggest a significant hazard or puts the patient at risk, such as drug-interactions, contra-indications or precautions, occurrence of malignancies or development of drug dependency or drug abuse.

Non-serious adverse event:

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

Severity assessment definitions:

- Mild – No or transient symptoms, no interference with the 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.

Relationship to trial product (N9-GP) assessment definitions:

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

Outcome categories and definitions:

- Recovered – Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the patient signed the informed consent
- Recovering – The condition is improving and the patient is expected to recover from the event. This term should only be used when the patient has completed the trial

- Recovered with sequelae – As a result of the AE the patient suffered persistent and significant disability/incapacity (eg became blind, deaf, paralysed). If the sequelae meet seriousness criteria, the AE must be reported as an SAE
- Not recovered
- Fatal
- Unknown – This term should only be used in cases where the patient is lost to follow-up.

12.1.1 Technical complaints

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 products (e.g. discoloration, particles or contamination)
- All packaging material including labelling

12.1.2 Reporting of MESI and other reports for expedited reporting

12.1.2.1 MESI

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus.

A MESI should be reported following the same reporting requirements and timelines as for SAEs (see Section 12.2) irrespective of the MESI fulfils a SAE criterion.

The following are defined as MESIs in this trial:
1. Medication errors concerning trial products
   - The following should be reported:
   - Administration of wrong drug
   - Wrong route of administration, such as intramuscular instead of i.v.
   - Administration of an accidental overdose: more than 20% from the intended dose
2. Inhibitor formation against FIX is always considered a MESI. Blood samples for measurement of FIX inhibitors will be analysed at a central laboratory selected by Novo Nordisk A/S. However, if an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, this should also be reported as a MESI
3. Thromboembolic events (clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion, see definitions below)
4. Anaphylactic reaction as defined by Sampson et al 2006[21] (see below).

5. Allergic reaction including, but not limited to, any acute IgE mediated reaction or delayed type hypersensitivity (clinical signs may include various types of skin rashes) that does not meet the definition of anaphylaxis as described by Sampson et al[21]
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.

Medical events of special interest must always be reported to Novo Nordisk as a SAE. So the AE form in the eCRF should be filled in. If for any reason the electronic data capture (EDC) application is unavailable, then fax, telephone or email Novo Nordisk.

Also complete the Safety Information Form on paper case report forms (CRFs). Forward a copy electronically in PDF format by fax or courier to Novo Nordisk. Reporting timelines for a MESI are the same as a SAE (see section 12.2).

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:
   a. Ischaemic symptoms
   b. Subsequent development of pathologic Q waves on the ECG
   c. ECG changes indicative of ischaemia (ST segment elevation or depression)
   d. Coronary artery intervention (eg angioplasty)

2. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria a and b below are fulfilled):
   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, eg visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis.

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

Peripheral artery occlusion

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

Clinical criteria for diagnosing anaphylaxis (Sampson et al. 2006[21])

Anaphylaxis is highly likely when two or more of the following occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg generalised hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg dyspnea, wheese-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

c. Reduced BP or associated symptoms (eg hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting)

12.1.2.2 Other reports for expedited reporting

Other reports for expedited reporting should be reported following the same reporting requirements and timelines as for SAEs (see section 12.2) irrespective of the report fulfils a SAE criterion.

The following is defined as other reports for expedited reporting in this trial:
1. Suspected transmission of an infectious agent via a trial product

Other reports for expedited reporting must always be reported to Novo Nordisk on the AE form in the eCRF.

12.1.3 Disease-related bleeding

Bleeding episodes and other symptoms (eg pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes that are evaluated by the investigator as part of the underlying disease should never 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 a fatal/life-threatening bleeding episode, it should always be reported as a SAE. All bleeding episodes and other symptoms related to the underlying disease will be captured in the eCRF or dairy.

12.2 Collection, recording and reporting of adverse events

All events meeting the definition of an AE must be collected and reported. Bleeding episode and other symptoms in connection with bleeding episodes that are evaluated by the investigator as part of the underlying disease must be collected from start of any trial related activity and reported according to Section 12.1.3. During each contact with the trial site (visit or telephone, excluding safety visits, where the patient is not seeing the investigator or his/her staff eg visits to the laboratory) the patient must be asked about AEs, eg, “Have you experienced any problems since the last contact?”.

All AEs, either observed by the investigator or reported by the patient, must be recorded by the investigator and evaluated.

Novo Nordisk’ assessment of expectedness is done according to the reference documents:
- IB, N9-GP, current version and any updates hereof[8].

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. Additionally, the IB is also used for the assessment of expectedness for reporting to the Investigator and the head of a site.

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

All AEs (including MESIs) must be recorded by the investigator on the standard AE form. If more than one sign or symptom is to be reported, use a separate AE form for each sign and symptom. For SAEs complete a safety information form for each event. However, if several symptoms or diagnosis occur as part of the same clinical picture, only one set of safety information form pages can be used to describe all the SAEs.

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

The investigator must report initial information on all SAEs and MESIs to Novo Nordisk within **24 hours** of obtaining knowledge about the event. Contact details (fax, telephone and e-mail) for reporting of SAEs and MESIs are provided in Attachment II.

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

- AE form in the eCRF **within 24 hours**
- Safety information form on the paper CRFs **within 5 calendar days** of obtaining knowledge about the SAE.

For AEs: Only AE form to be filled in. For SAEs/MESIs: AE form in the eCRF within 24 hours and SIF on the paper CRFs within 5 calendar days.

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

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

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

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

For Japan only: Novo Nordisk must inform the health authorities and the relevant parties of SAE information in accordance with the Japanese requirements in force and ICH GCP[22].

Investigators will be notified of trial-related SAEs in accordance with the local requirements in force and ICH GCP[22].

The monitor must be informed accordingly.

12.2.1 Follow-up of adverse events

During and following a patient's participation in a clinical trial, the investigator should ensure that adequate medical care is provided to the patient for any AE, including clinically significant laboratory values related to the trial. The investigator should inform the patient when medical care is needed for AE(s) of which the investigator becomes aware.

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

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

All non-serious AEs must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. AEs ongoing at time of death (where death is due to another AE) may be closed with an outcome of "recovering" or "not recovered".

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

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

Queries or follow-up requests from Novo Nordisk should be responded to within 14 calendar days, unless otherwise specified. The investigator must forward follow-up information on SAEs and MESIs within 5 calendar days of obtaining the information. This must be done by updating the AE form in the eCRF and/or completing a new safety information form marked follow -up on paper CRF and forwarding these to Novo Nordisk. If for any reason the EDC application is unavailable, then fax, telephone or e-mail to Novo Nordisk.

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

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

12.3 Technical complaints and technical complaint samples

12.3.1 Reporting of technical complaints

All technical complaints, on any of the following products:

- N9-GP 2000 IU/vial
- N9-GP 500 IU/vial
- Histidine solvent, 4,2 ml
- Novo Nordisk Trial Injection Kit

which occur from the time of first usage until the time of 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 AEs, SAEs and/or MESIs.
Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch or lot number must be completed

The investigator must complete and forward the technical complaint form by fax, e-mail or courier to Novo Nordisk, within the same timelines as for reporting AEs, SAEs and MESIs as follows (see Section 12.2):

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

12.3.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample 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 the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

If the technical complaint sample was not retained or collected, the investigator must specify on the technical complaint form why it was not retained.

- The investigator must ensure that the technical complaint sample is labelled with the batch number and, if available, the DUN number. All parts of the DUN should be returned.

Storage and shipment of the technical complaint sample should be done in accordance with the conditions described for the product (see Section 9).

12.4 Pregnancies in partners of trial patients

In the case of an AE (with a causal relationship evaluated as possible or probable by the investigator) in the foetus, newborn infant(s) or infant(s)/toddler(s) of a trial patient's partner, who is potentially exposed to the trial product via the trial patient, the pregnancy and the AE should be reported on pregnancy form Part A and Part B and an AE form.

12.5 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 BP. 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.

If an overdose is suspected and in case of a safety concern, further N9-GP administration should be stopped and the patient be withdrawn from the trial. The patient should receive treatment as appropriate according to the hospital practice and guidelines.

12.6 Safety committee

12.6.1 Internal Novo Nordisk safety committee

Novo Nordisk will constitute an internal safety committee to perform ongoing safety surveillance of N9-GP in all phase 3 trials (pivotal [NN7999-3747], surgery [NN7999-3773], extension [NN7999-3775] and paediatric [NN7999-3774]). 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.

12.6.2 Stopping rules

Any event occurring after administration of N9-GP fulfilling the SAE/MESI criteria must be reported to Novo Nordisk within 24 hours. If one of the below mentioned stopping criteria is fulfilled, enrolment of additional patients will be placed on hold. All investigators will be informed in writing. An urgent safety committee meeting will be called for to decide whether or not the trial can continue with or without modifications. Dosing of patients on treatment may continue while further evaluation of the SAE/MESI is made by the safety committee, unless otherwise decided by the safety committee. The evaluation of fulfilment of the below stopping rules by the safety committee will take into consideration whether or not the patient was dosed according to protocol.

- Inhibitor formation (Bethesda Unit of ≥0.6 BU) in two patients. A patient has inhibitor formation if the patient has been tested positive for inhibitors at two consecutive tests fro m the central laboratory
- Anaphylaxis in two patients after trial product administration[21]
- Occurrence of two significant thromboembolic events in two different patients (eg myocardial infarction, pulmonary embolism, cerebral thrombosis/infarction or oth er significant thromboembolic event)
- Death related to trial product assessed by Novo Nordisk or by the investigator

13 Case report forms

Novo Nordisk will provide a system for EDC. This system and support services to the system will be supplied by a vendor. The activities of this vendor will be under the direction and supervision of Novo Nordisk. Paper CRFs will be used for collection of data from major surgeries.

13.1 Rules for completing eCRFs

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

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

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

13.2 Corrections to eCRFs

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

If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the case book then the case book must be signed again by the investigator.

13.3 eCRF flow

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

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

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

13.4 Paper CRFs for major surgery

Data recorded for major surgery batch will be captured in paper CRF. Original paper CRF will be collected by monitor, and a copy must be retained at site.

Please ensure using legible print and use of ballpoint when completing the paper CRF. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If an assessment or test 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 indicate this by writing "NA" (not applicable) in the appropriate answer field. Investigator must ensure that all information is consistent with the source documentation by signing the affirmation statement and confirming that information in the CRF and related forms is complete and correct.

13.4.1 Corrections to paper case report forms

Corrections to the data in 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 was crossed out. Each correction must be initialled, dated and explained (if necessary). If corrections are made by the investigator's authorised staff after the date of the investigator's signature on the affirmation statement, the affirmation statement must be signed and dated again by the investigator. Corrections necessary after the CRFs have been removed from the trial site must be documented on a data clarification form (DCF) or a monitor-initiated discrepancy form (MIDF). If the affirmation statement for the subject has not yet been signed, any corrections must be approved by the investigator or her/his authorised staff. If the affirmation statement for the subject has already been signed, the investigator must approve any correction.

13.4.2 Paper case report form flow

The investigator must ensure that data is recorded in the CRF as soon as possible after the visit

13.5 eDiaries

Novo Nordisk will provide patients and/or parent(s)/LAR with an eDiary for electronic recording of details of their bleeding episodes, see Section 8.10.3. The eDiary and related support services will be supplied by a vendor that will be working under the direction and supervision of Novo Nordisk.

At Visit 3, the patients will be provided with the eDiary and trained in the use thereof. The eDiary will be returned by the patient at either Visit 11 (for patients not continuing in the extension phase) or at the EOT visit.

Data will be entered by the patient or parent(s)/LAR in the eDiary device. All data entered will be automatically transferred from the device to the electronic patient reported outcomes (ePRO) database, where it is kept as a certified copy of the source data. Data entered in the device will upon confirmation of a successful back-up be deleted from the device.

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

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

Data in the ePRO database will be viewable to relevant sites and Novo Nordisk personnel on a secure, password protected web portal. Data will be transferred to the Novo Nordisk trial database at defined intervals. For details on eDiary data flow, see Figure 13-1.

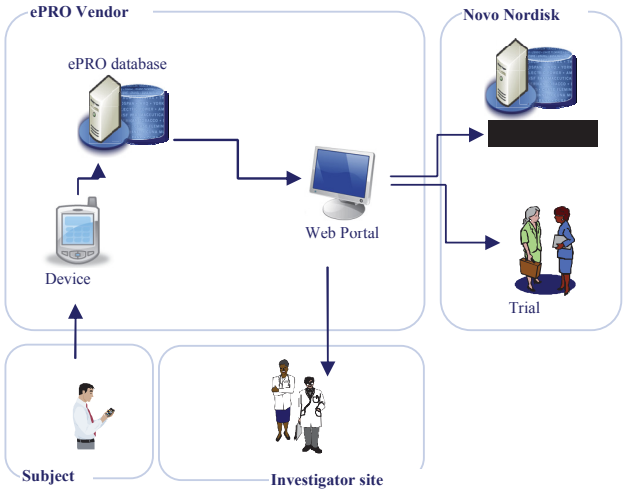

Figure 13-1 eDiary data flow

13.6 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 these assessments will be collected on paper forms.

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

13.7 Paper diaries for major surgery

The patient will be provided with a paper diary by Novo Nordisk A/S that is to be completed during the period where regular N9-GP prophylaxis is paused due to major surgery. During this period the eDiary must be stored at site and not returned to the patient until regular prophylaxis is resumed.

Original paper diaries will be collected by monitor, and a copy must be retained at site.

14 Monitoring procedures

During the course of the trial the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP. The monitor should visit a site soon after a patient has been screened. The intervals between monitoring visits must not exceed 28 weeks whilst patients are in the trial.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the trial. In addition, the investigator should be available for discussions with the monitor eg by telephone.

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. All data entered in the eCRF will be transferred into the trial database.

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

Information on prophylactic home treatment and treatment of bleeding episodes will be collected in the eDiaries (refer to Section 8.3.7). The completed eDiaries are considered source data. The patient will only be identified by patient number and the monitor will verify and ensure that the eCRFs and eDiaries are completed.

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

15 Data management

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

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

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

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

Data will be entered and delivered in an [redacted] file and loading into [redacted]

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

The system for neurocognitive testing and support services for the system will be supplied by a CRO. The CRO will collect, query and process data from Structured Developmental History and Haemophilia History as well as Neurocognitive Assessments. The CRO will transfer assessment results and outcomes from the External Review Panel to NovoNordisk.

16 Computerised systems

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

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

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

The eDiary , and the electronic devices 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). After trial completion, each trial site will be supplied with CDs. These 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.

17 Evaluability of patients for analysis

All main descriptions and analysis of efficacy and PK data will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines[23]. The FAS includes all patients with efficacy data after exposure 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.

Pharmacokinetics analyses will be done on the FAS although it may be decided prior to database lock in exceptional cases to exclude patients or observations from these analyses based on protocol deviations and relevant overviews and listings (based on the trial database) prepared by the trial statistician. The decisions will be documented and the documentation will be stored together with the remaining trial documentation.

18 Statistical considerations

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

The main statistical reporting of the trial will be performed when 10 patients in each age group have completed the initial main phase (52 weeks) with at least 50 EDs. Data from patients that have entered the extension phase at this point will be included up to this cut-off date. This reporting will form the basis for the submission for approval.

The entire extension phase will be reported separately when it is completed.

18.1 Sample size calculation

No formal sample size calculations have been performed. The sample size is based on the requirements in the EMA guideline[3].

18.2 Statistical methods

18.2.1 General considerations

Except for the confidence interval for inhibitor rate , for annualised bleeding rate the evaluation of data will be based on descriptive statistics, ie summary tables, listings and figures.Multiple bleeding locations occurring from the same event (eg, due to a bicycle accident) or at the same time point will be counted as one bleeding episode.

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 8.5.3).

In general all summaries and analyses will also be made by age subgroup (0-6 and 7-12 years of age).

18.2.2 Primary endpoint

Incidence of inhibitory antibodies against FIX defined as ≥0.6 BU

The primary objective and endpoint will be evaluated when the main phase of the trial is completed and will include all data from patients already having entered the extension phase up to that cut-off date.

The rate of neutralising inhibitors 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 EDs plus any patient with less than 10 EDs but with inhibitors. Adequate safety with regard to inhibitors will be concluded if the observed rate is lower than or equal to 5%, corresponding to at most 1 inhibitor observed.

When the extension phase is completed, inhibitors in the extension phase will be listed.

18.2.3 Confirmatory secondary endpoints

The trial has no confirmatory secondary endpoints.

18.2.4 Supportive secondary endpoints

18.2.4.1 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.

AE's occurring in the time period between the patients stops weekly prophylaxis treatment to go to major surgery and to the date and time when patient resumes weekly prophylaxis treatment will be presented in a listing.

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 eGFR (estimated glomerular filtration rate), and physical examinations, including neurological assessments, will be summarised and listed.

18.2.4.2 Efficacy endpoints

Number of bleeding episodes during prophylaxis

Number of bleeding episodes during prophylaxis will also be presented by type (spontaneous, traumatic or other origin).

Annualised bleeding rate will be summarised and a 95% two sided confidence interval will be provided based on a Poisson regression model adjusting for exposure time and allowing for over-dispersion.

Bleeding episodes occurring in the time period between the patients stops weekly prophylaxis to go to major surgery and to the date and time when patient resumes weekly prophylaxis treatment will be presented in a listing and will not be included in the estimation of the annualised bleeding rate during prophylaxis treatment.

As sensitivity analysis data from patients withdrawing prematurely (but after more than 1 month on prophylaxis) will be imputed using a last observation carried forward (LOCF) approach. If patients drop out due to ineffective prophylaxis this may give a more correct estimate of the treatment effect.

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

Haemostatic effect of N9-GP in treatment of bleeding episodes

Summaries of this endpoint will include bleeding episodes from both the main phase and the extension phase up to the cut-off date since they will be treated in the same manner. Summaries will however also be provided for the main phase and the extension phase separately.

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

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

Acute efficacy, efficacy when treating bleeding episodes, will also be summarised by type of bleeding and by age group as well as for the main phase and the extension phase separately as mentioned above.

FIX consumption

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

18.2.4.3 Pharmacokinetic endpoints

Pharmacokinetic endpoints, except trough steady state and C_{30min} steady state, are assessed after a single dose (Visit 2). Steady state trough and C_{30min} will be assessed at Visit 4 - Visit 10 during the main phase of the trial.

- IR_{30min} ([IU/mL] / [IU/kg])

- Trough level (IU/mL) (single dose and steady state)
- AUC (Uxh/mL)
- Terminal half-life ($t_{1/2}$), (h)
- CL (mL/h/kg)
- MRT (h)
- V_{ss} (mL/kg)
- C_{30min} (IU/mL) (single-dose and steady state)

Table 18-1 Definition and calculation of PK parameters

Parameter	Description	Calculation
IR_{30min}	Peak activity recorded 30 minutes after end of injection and reported as [IU/mL]/[IU/kg]	The incremental recovery is calculated by dividing the pre-dose subtracted FIX activity (IU/mL) measured in plasma 30 minutes after dosing by the dose injected at time 0 expressed as IU/kg body weight
Trough level (single dose)	Lowest activity recorded at Visit 2, 168 hours post-dose (immediately before next dose is given) and reported as (IU/mL)	
Trough level (steady state)	Lowest activity recorded immediately before next dose is given (after Visit 3) and reported as (IU/mL)	
$t_{1/2}$	Terminal half-life (h)	$t_{1/2} = \ln(2)/\lambda_z$, where λ_z is the terminal elimination rate. The terminal elimination rate will be estimated using linear regression on the terminal part of the log(activity) versus time profile
CL	Total plasma clearance of drug after intravenous administration (mL/h/kg)	CL= Dose/AUC
AUC	Area under the activity versus time profile from time zero to infinity. Measure of total plasma exposure (Uxh/mL)	$AUC = AUC_{(0-t)} + C_{(t)}/\lambda_z$, where $C_{(t)}$ is the last measurable activity.
MRT	Mean residence time (h)	MRT = AUMC/AUC, where AUMC is the area under the first moment curve, ie, the area under the curve $txC_{(t)}$, calculated with the same method as AUC (linear trapezoidal method + extrapolated area)
V_{ss}	Apparent volume of distribution at steady-state (mL)	Vss = CLxMRT
C_{30min} (single-dose)	The FIX activity recorded 30 minutes after end of injection (IU/mL) at Visit 2	
C_{30min} (steady state)	The FIX activity recorded 30 minutes after end of injection (IU/mL) at Visit 4 -Visit 10	

PK endpoints will be summarised and listed. PK will also be summarised by age group. All PK endpoints will be calculated based on baseline corrected plasma concentration.

Trough level (steady state)

Mean FIX trough activity levels during prophylaxis will be calculated as a mean of patient means. FIX trough activity levels of the main phase will be summarised. Plasma concentrations below lower limit of quantification (LLOQ) will be set to half the value of the LLOQ.

Only measurements taken at least 5 days and no more than 10 days after last dose as well as measurements taken at least 14 days after last bleeding episode will be included in the calculation of steady state trough.

C_{30min} (steady state)

Mean C_{30min} during prophylaxis will be calculated as a mean of patient means. C_{30min} levels of the main phase will be summarised.

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

18.4 Interim analysis

The main phase of the trial will be analysed and reported before the extension phase is completed. All main conclusions from the trial will be based on this reporting. The interim analysis will cover all endpoints. 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.

Some inspections of the data will be performed in the course of the trial in order to comply with various health authorities requests. Safety and PK data for the first five patients in the age group 7-12 years will be summarised and evaluated before dosing can commence in the age group 0-6 years. PK data from the first five patients in the age group 0-6 years will be summarised and

evaluated for the purpose of adjusting the dose level if the PK profile is found to have a clinically relevant difference from adults.

18.5 Sequential safety analysis/safety monitoring

Novo Nordisk A/S will constitute an internal safety committee to perform ongoing safety surveillance. The trial will be subject to stopping rules evaluated by this safety committee (Section 12.6.2).

18.6 Reporting of *F9* genotype

Information about underlying gene defects of *F9* will be listed in the clinical trial report. No statistical analysis will be performed.

18.7 Pharmacokinetic and/or pharmacodynamic modelling

Population PK is not a part of the planned statistical analysis.

18.8 Health economics and/or patient reported outcome

Health economic data and changes in PRO data (from the screening visit) will be summarised and listed using descriptive statistics. In case a new age fitted PRO questionnaire was introduced at V17 this will be used to calculate change from V17 to Visit 22/23/24. The PRO used at visit 17 will also be used at Visit 22/23/24 (the relevant visit where neurocognitive assessment s are performed for the first time for each patient)

Health economic calculations will be performed separately by the Novo Nordisk Health Economic Department.

19 Ethics

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

After completion of the main phase, patients will continue with prophylaxis in the extension phase. If the patient does not wish to continue in the extension phase, he will consult with the investigator to decide on the best available treatment.

19.1 Informed consent form for trial patients

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

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

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

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

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

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

The responsibility for seeking informed consent must remain with the investigator or an adequately medically qualified person delegated by the investigator. The written informed consent must be signed and personally dated, including time, by the parent(s)/LAR, and by the person who seeks the informed consent.

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

***F9* genotype testing/collection of previous genotype documentation**

Genotype testing is offered to the patients participating in this trial. If documentation of the patients' genotype already exists, the patient and/or the patient's parent(s)/LAR must give their consent before the data can be collected for trial purpose. Prior to any trial-related activity, the investigator must provide the patient with the possibility to abstain from the genetic testing/collection of previous documentation, but still be able to participate in the trial.

Only the *F9* 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.

19.2 Data handling

If the patient or the patient's parent(s)/LAR withdraws the previously given informed consent, if the patient dies and no consent is available from a patient's parent(s)/LAR, or if the patient is lost to follow up, the patient's data will be handled as follows:

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

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

19.3 Institutional review board/independent ethics committee

Prior to commencement of the trial, the protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient, patient recruitment procedures (incl. advertisement), if any, IB, available safety information, information about payments and compensation available to patients if not mentioned in the patient information, the investigator's current curriculum vitae (CV) and/or other documentation evidencing qualifications, and other documents as required by the local IRB/IEC should be submitted. The submission letter should clearly identify the trial identification number, version, EudraCT no., title and/or the date of the documents that have been submitted to the IRB/IEC. Written approval/favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

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

Substantial protocol amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate immediate hazards to the patients.

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

19.4 Regulatory authorities

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

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

19.5 Information to patient during 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 intended for distribution to the patients. The letters will be translated and adjusted to local requirements and distributed to the patient and/or the patient's parent(s)/LAR(s) by the investigator. The patient and/or the patient's parent(s)/LAR(s) may receive letters during the trial and a "thank you for your participation letter" after completion of the trial.

All written information to patient will be submitted to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

20 Premature termination of the trial/trial site

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

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

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

21 Protocol compliance

Deviations from the protocol should be avoided.

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

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

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

21.1 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk internal Quality Audit System or an inspection from domestic or foreign regulatory authorities. The investigator and the site staff as well as Novo Nordisk clinical staff have an obligation to cooperate and assist in such audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents relevant to the conduct of the clinical trial at the site.

22 Critical documents

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

- regulatory approval and/or notification as required
- curricula vitae of investigator and sub-investigator(s) (current, dated and signed and/or supported by an official regulatory document)
- signed receipt of IB
- signed and dated agreement on the final protocol
- signed and dated agreement on any substantial protocol amendment(s), if applicable
- approval/favourable opinion from IEC/IRB clearly identifying the documents reviewed: the protocol, any substantial protocol amendments, patient information/informed consent form and any other written information to be provided to the patient, patient recruitment procedures
- copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement
- list of IEC/IRB members/constitution
- financial agreement(s)(for US: verification under disclosures per CFR of Financial Conflict of Interest[25]).
- FDA financial disclosure form or local equivalent, as applicable
- laboratory reference ranges
- laboratory certification/QA scheme/other documentation
- laboratory methods
- **for US sites:** FDA form 1572 must be completed by each investigator and individual clinical trial staff, if directly involved in the treatment or evaluation of research making a direct and significant contribution to the data

FDA form 1572:

For US sites:

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

For sites outside the US:

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

As documented in writing by protocol signature, all investigators will fully comply ICH GCP[22], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[24].

23 Responsibilities

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

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

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law.

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

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

24 Reports and publications

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

The investigator to be designated with the responsibility to review and sign the clinical trial report (signatory investigator) will be a member of the Advisory Board and investigator in this trial.

24.1 Communication and publication

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

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

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

24.1.1 Authorship

Authorship of publications should be in accordance with guidelines from The ICMJE Uniform Requirements (sometimes referred to as the Vancouver Criteria[26]).

24.1.2 Publications

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

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

event of any disagreement about the content of any publication, both the investigators' and Novo Nordisk's opinions shall be fairly and sufficiently represented in the publication.

In a multi-centre trial based on the collaboration of all trial sites, any publication of results must acknowledge all trial sites.

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

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

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

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

24.2 Investigator access to data and review of results

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

Individual investigator(s) will have their own research participants' data after the investigator results meeting.

25 Retention of clinical trial documentation and human biospecimens

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

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

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

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

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

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

25.1 Retention of human biospecimens

Antibody samples (samples for binding antibodies and inhibitors) and all remaining blood samples will be stored until the trial has been evaluated by appropriate authorities or until the project terminates, but no longer than 15 years from end of trial. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of 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 hypothesis at initiation of the 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 hypothesis at initiation of the trial.

The samples will be stored at Novo Nordisk designated central laboratory (biorepository) 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 b e marked and identified by a unique sample ID. No direct identification of the patient will be stored together with the samples. The analyses will not have any medical consequences for the patients or their relatives. Only Novo Nordisk staff and central laboratory personnel (if applicable) will have access to the stored bio specimens.

In the event that the collected biospecimens (plasma, serum and genotype samples) will be used in the future, the investigator will become directly informed by Novo Nordisk ab out the results if the findings are deemed clinically and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of subject specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious genetically hereditary diseases, other untreatable diseases, or any other abnormal findings could be part of the observations. Patients or parent(s)/LAR may at any time contact the investigator if they wish to be informed about results derived from stored biospecimens obtained from their own body.

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

26 Indemnity statement

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

Novo Nordisk assumes no liability in the event of negligence, or any other liability by the clinics or doctors conducting experiments, or by persons for whom the said clinic or doctors are responsible.

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

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

27 References

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