Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05082116
Sponsor trial ID:	NN7088-4595
Official title of study:	A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A
Document date*:	05 Jul 2021

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

16.1.1 Protocol and protocol amendments

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Protocol

Protocol title: A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of turoctocog alfa pegol (N8-GP) when used for treatment and prophylaxis of bleeding episodes in previously treated Chinese patients with haemophilia A

Substance name: turoctocog alfa pegol (N8-GP)

Universal Trial Number: U1111-1235-5905

EudraCT Number: 2020-003001-58

Trial phase: 3b

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Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
Updated protocol with protocol amendment 3	05 Jul 2021	CN
Updated protocol with protocol amendment 2	22 Jan 2021	CN
Updated protocol with protocol amendment 1	28 Sep 2020	CN
Original Protocol	01 Jul 2020	CN

Protocol version 4.0 (05 Jul 2021)

Overall rationale for preparing protocol version 4.0:

The overall rationale for preparing the protocol, version 4.0 is to include neurological assessment categories that had been missed to include in prior protocol version, for the patients who have not had visit 2a at the time of implementation of protocol version 4.0 and clarifications on discontinuation of trial treatment and FVIII inhibitors. List changes in chronological order:

Section # and name	Description of change	Brief rationale
Section 4.1.4 Treatment of bleeding episodes Section 6.5.1 Prohibited Medication Section 7.1 Discontinuation of trial treatment Section 8.1.1 Bleeding Episodes	Update of exception criteria for discontinuation of trial treatment	The exception criteria on the use of other FVIII product between visit 2a and 2b does not apply for the trial, hence removed

Section # and name	Description of change	Brief rationale
Section 8.2.1.1 Neurological examination	Update to neurological examination criteria	Addition of missed categories for neurological examination
Section 8.6.1 FVIII inhibitors	Clarification on analysis of FVIII inhibitors	Clarification
Section 10.6 Appendix 6: Neurological examination checklist	Update to neurological examination checklist	Addition of missed categories for neurological examination

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1 Protocol summary

1.1 Synopsis

Rationale:

To accumulate sufficient exposure to N8-GP in order to document efficacy for treatment and prevention of bleeding episodes and to evaluate safety (including immunogenicity) and pharmacokinetics (PK) in previously treated Chinese patients with severe haemophilia A (FVIII activity <1%).

Objectives and endpoints:

Primary objective

- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeding episodes during prophylaxis) in Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products

Primary endpoint

Endpoint title	Time frame	Unit
Number of bleeding episodes	From start of treatment until visit 7	Count

Secondary objectives

In Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products:

- To evaluate the clinical efficacy of N8-GP when used for treatment of bleeding episodes
- To evaluate the consumption of N8-GP
- To evaluate the immunogenicity of N8-GP
- To evaluate the general safety of N8-GP
- To evaluate the pharmacokinetic properties of N8-GP

Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none)	From start of treatment until visit 7	Count
Consumption of N8-GP for treatment of bleeding episodes	From start of treatment until visit 7	IU/kg/bleed
Consumption of N8-GP for prophylaxis	From start of treatment until visit 7	IU/kg/year
FVIII trough activity during prophylaxis	From start of treatment (excluding the first exposure) until visit 7	IU/mL

Secondary safety endpoints

Endpoint title	Time frame	Unit
Incidence rate of confirmed FVIII inhibitors ≥0.6 BU	From start of treatment until visit 7	Rate
Number of adverse events (AEs)	From start of treatment until end of trial	Count
Number of serious adverse events (SAEs)	From start of treatment until end of trial	Count

Secondary pharmacokinetic endpoints

Endpoint title	Time frame	Unit
FVIII activity 30 min post-injection (C_{30min})	Single-dose: 30 min ± 5 min post-injection at visit 2a Steady-state: 30 min ± 5 min post-injection at visit 7	IU/mL
Incremental recovery (IR)	Single-dose: 30 min ± 5 min post-injection at visit 2a Steady-state: 30 min ± 5 min post-injection at visit 7	(IU/mL)/(IU/kg)
Area under the curve (AUC)	Single-dose: 0−inf post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	h*(IU/mL)
Terminal half-life ($t_{½}$)	Single-dose: 0−96 h post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	h
Clearance (CL)	Single-dose: 0−96 h post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	mL/h/kg
FVIII trough activity 96 h post-injection (C_{96h})	Single-dose: 96 h ± 8 h post-injection at visit 2a Steady-state: 96 h ± 8 h post-injection at visit 7	IU/mL

Overall design:

This trial is a multi-centre, open-label, non-randomised, single-arm phase 3b trial.
The trial population consists of previously treated Chinese patients ≥12 years of age with severe haemophilia A (FVIII activity <1%).

Inclusion criteria are:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male Chinese patient with severe congenital haemophilia A with a FVIII activity <1% according to medical records.
3. Aged ≥12 years at the time of signing informed consent.
4. History of at least 150 exposure days (EDs) to other FVIII products[1].
5. The patient and/or caregiver is capable of assessing a bleeding episode, keeping a diary, performing home treatment of bleeding episodes and otherwise following the trial procedures at the discretion of the investigator.

[1] Prophylaxis, prevention, on-demand and treatment during surgery counts as exposure days. If not possible to count the actual number of exposures in the medical chart, the investigator should make a written statement with an estimate

based on e.g., patient age, treatment frequency, medical history, discussion with previous doctor/transfer note and other relevant information. This statement should be filed either with the patient chart or separately with the investigator trial file.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

Exclusion criteria are:

1. Known or suspected hypersensitivity to trial product or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 5 half-lives or 30 days from screening, whichever is longer.
4. Known history of FVIII inhibitors based on existing medical records, laboratory report reviews and patient and/or caregiver interviews.
5. Current FVIII inhibitors ≥0.6 BU.
6. Congenital or acquired coagulation disorder other than haemophilia According to medical records.
7. HIV positive, defined by medical records, with CD4+ count ≤200/µL and a viral load >200 particles/µl or >400000 copies/mL within 6 months of the trial entry. If the data are not available in medical records within last 6 months, then the test must be performed at screening visit.
8. Previous significant thromboembolic events (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as defined by available medical records.
9. Hepatic dysfunction defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 times the upper limit of normal combined with total bilirubin >1.5 times the upper limit of normal at screening, as defined by central laboratory.
10. Renal impairment defined as estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 for serum creatinine measured at screening, as defined by central laboratory.
11. Platelet count $<50\times10^9$/L at screening based on central laboratory values at screening.
12. Ongoing immune modulating or chemotherapeutic medication.
13. Any disorder, except for conditions associated with haemophilia A, which in the investigator`s opinion might jeopardise the patient`s safety or compliance with the protocol.
14. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

Patients are screened at visit 1 and baseline assessments are performed at visit 2a which will take place approximately two weeks after visit 1. At visit 2a trial product is administered for the first time to all patients. Some patients will undergo single-dose PK assessments until visit 2b, which is 4 days after visit 2a. From visit 2b the treatment period consists of an additional 4 visits (visits 3-6) taking place 4, 8, 12, and 20 weeks after visit 2a. An end of treatment visit (visit 7) is placed 28 weeks after visit 2a. Patients who underwent single-dose PK assessments at visit 2a will undergo

steady-state PK assessments at visit 7. An end of trial (follow-up) visit (P8) is placed 30 days after the end of treatment visit (visit 7) (visit windows are not included in this description).

Major and minor surgery is allowed in the trial.

Number of patients:

Thirty-six (36) patients are planned to be included in the trial. At least 30 patients must complete the trial with ≥50 EDs to N8-GP (including treatment of bleeding episodes) during a period of ≥6 months (≥28 weeks) of prophylaxis with N8-GP. Among these, at least 12 patients will complete single-dose and steady-state PK assessments.

Treatment groups and duration:

All patients will receive prophylaxis with 50 IU/kg N8-GP every 4 days for a treatment period of at least 28 weeks (with the possibility of switching to twice-weekly dosing during the treatment period at the discretion of the investigator). Bleeding episodes will be treated with bolus injection(s) of 20−75 IU/kg N8-GP.
Dosing recommendation guidance for surgery recommends FVIII activity level of 30-60% for minor surgery and 80-100% for major surgery, until adequate wound healing is ensured.

Data monitoring committee: No

1.2 Flowchart

	Protocol Sections	Screening	Baseline[a, b]	Treatment period					End of treatment	Discontinuation of treatment	End of trial (Follow up)	Surgery
Visit		V1	V2a	V2b	V3	V4	V5	V6	V7	V7a	P8	
Timing of Visit (Weeks)		-2	0	4 days after visit 2a	4	8	12	20	28		30D	
Visit Window (Days)		-7	0	0	±7	±7	±7	±7	+7		+5	
Informed Consent and Demography	10.1.3	X										
Eligibility Criteria	5.1, 5.2	X	X									
Discontinuation Criteria	7, 7.1			X	X	X	X	X				X
Medical History/Concomitant Illness	8.2,	X	X									
History of surgery	8.2,	X										
Details of Haemophilia	8.2,	X										
Haemophilia treatment and bleed history	8.2,	X										
Date and time of last coagulation factor administration	8.2,	X	X									

	Protocol Sections	Screening	Baseline[a, b]	Treatment period					End of treatment	Discontinuation of treatment	End of trial (Follow up)	Surgery
Visit		V1	V2a	V2b	V3	V4	V5	V6	V7	V7a	P8	
Timing of Visit (Weeks)		-2	0	4 days after visit 2a	4	8	12	20	28		30D	
Visit Window (Days)		-7	0	0	±7	±7	±7	±7	+7		+5	
Concomitant Medication	6.5	X	X	X	X	X	X	X	X	X		X
Body Measurements	8.2.1	X	X		X	X	X	X	X	X		
Height	8.2.1	X										
Weight	8.2.1	X	X		X	X	X	X	X	X		
BMI	8.2.1	X										
Physical Examination	8.2.1	X	X				X		X	X		
Neurological examination	8.2.1.1	X	X				X[h]		X[h]	X[h]		
Target Joint	8.2.1	X	X				X		X	X		
Vital Signs	8.2.2	X	X		X	X	X	X	X	X		
ECG	8.2.3	X							X	X		

	Protocol Sections	Screening	Baseline[a, b]	Treatment period					End of treatment	Discontinuation of treatment	End of trial (Follow up)	Surgery
Visit		V1	V2a	V2b	V3	V4	V5	V6	V7	V7a	P8	
Timing of Visit (Weeks)		-2	0	4 days after visit 2a	4	8	12	20	28		30D	
Visit Window (Days)		-7	0	0	±7	±7	±7	±7	+7		+5	
Adverse Event	8.3			X	X	X	X	X	X	X	X	X
Bleeding Episode	8.1.1			X	X	X	X	X	X	X		X
Technical Complaints	10.5,8.3.7		X	X	X	X	X	X	X	X		X
Laboratory Assessments	8.1.2, 8.2.4, 10.2	X	X		X	X	X	X	X	X		X
Haematology	10.2	X	X		X	X	X	X	X	X		
Biochemistry	10.2	X	X		X	X	X	X	X	X		
Urinalysis	10.2	X	X									
Coagulation parameter	10.2	X										
Factor VIII Chromogenic Activity	10.2		X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X		X[c]
Hepatitis	10.2	X										

	Protocol Sections	Screening	Baseline[a, b]	Treatment period					End of treatment	Discontinuation of treatment	End of trial (Follow up)	Surgery
Visit		V1	V2a	V2b	V3	V4	V5	V6	V7	V7a	P8	
Timing of Visit (Weeks)		-2	0	4 days after visit 2a	4	8	12	20	28		30D	
Visit Window (Days)		-7	0	0	±7	±7	±7	±7	+7		+5	
HIV[d]	10.2	X										
Factor VIII Inhibitor in Plasma	10.2,8.6.1	X[e]	X[e]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Anti-N8-GP antibodies	8.6.2	X	X		X	X	X	X	X	X		
Anti-PEG antibodies	8.6.3		X						X	X		
Anti-HCP antibodies	8.6.4		X							X[g]		
PK[b]	1.2 8.5		X[e]						X			
Administration of Trial Product	4.1.1		X	X	X	X	X	X	X			X
Drug Dispensing	6.2		X	X	X	X	X	X	X	X		X
Dispensing Visit	6.2		X	X	X	X	X	X				X
Drug Accountability	6.2, 6.4		X	X	X	X	X	X	X	X		X

	Protocol Sections	Screening	Baseline[a, b]	Treatment period					End of treatment	Discontinuation of treatment	End of trial (Follow up)	Surgery
Visit		V1	V2a	V2b	V3	V4	V5	V6	V7	V7a	P8	
Timing of Visit (Weeks)		-2	0	4 days after visit 2a	4	8	12	20	28		30D	
Visit Window (Days)		-7	0	0	±7	±7	±7	±7	+7		+5	
IWRS session	6.2, 6.3	X	X	X	X	X	X	X	X	X		
Hand Out and Instruct in Diary	8.7		X	X	X	X	X	X				
Home treatment training	8.8		X	X								
Training in Devices	8.8		X	X								

Footnotes	Description
a	All screening assessments must be completed and evaluated by the investigator before the patient can be included in the trial.
b	Refer to Table 1-1 for patients that will participate in PK assessments
c	To be measured pre-injection and 30 min (±10min) post-injection.
d	If positive HIV test, then a HIV polymerase chain reaction (PCR) viral load assessment should be performed
e	Time from last treatment with current FVIII product should be at least 96 hours. The blood sample should be taken before any injection of N8-GP, if applicable.
f	Time from last treatment with N8-GP should be at least 96 hours. The blood sample should be taken before any injection of N8-GP, if applicable.
g	Only to be assessed in case of an acute severe allergic/anaphylactic reaction.
h	Neurological assessments should not be performed for the assessments not performed at baseline (visit 2a).

Table 1-1 Flowchart for patients having PK evaluated at Visit 2a and Visit 7

Day(s)	0					0	1	2	3	4
Nominal Time	**Pre-dose**	**0**	**30**	**1 hr**	**4 hrs**	**12 hrs**	**24 hrs**	**48 hrs**	**72 hrs**	**96 hrs**
Visit Window	**-1h**		**± 5 min**	**± 5 min**	**± 30 min**	**±30 min**	**+ 8 hrs**	**+ 8 hrs**	**+ 8 hrs**	**+ 8 hrs**
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[h]		X	X	X	X	X	X	X	X
Vital signs	X		X							X
FVIII activity	X		X	X	X	X	X	X	X	X
Administration of N8-GP		X								

Footnotes	Description
h	Only applicable at visit 7

2 Introduction

2.1 Trial rationale

No Chinese haemophilia patients have yet been exposed to N8-GP as there were no patients from China included in the global N8-GP clinical development programme (NN7088, pathfinder™).

The rationale for this Phase 3b trial is to assess the effect of N8-GP in Chinese patients with severe haemophilia A (FVIII activity <1%) previously treated with other FVIII product(s) (PTPs). The aim is to accumulate sufficient exposure data in order to evaluate efficacy and safety of N8-GP in treatment and prevention of bleeding episodes and to obtain N8-GP PK data in this patient population.

The results of this trial will supplement results from the global N8-GP clinical development programme (pathfinder™).

2.2 Background

Haemophilia A is a rare, recessive X-linked congenital bleeding disorder caused by mutation in the blood-coagulation factor VIII (FVIII) gene on the long arm of the X-chromosome. The prevalence globally is approximately 1 in 5,000 male births.[1] According to the World Federation of Hemophilia (WFH), there are globally over 184,000 identified haemophilia patients of which 150,000 are diagnosed with haemophilia A.[2]

A meta-analysis in China has shown a prevalence of haemophilia of 5.5 per 100,000 males (3.6 per 100,000 males+females) and about 71% of these suffer from haemophilia A.[3] However, according to the WFH, about 12,500 patients with haemophilia A were registered in China in 2016.[2] Thus, only about 1/3 of the anticipated number of patients with haemophilia A in China are diagnosed[4] and there's a large number of patients who are either undiagnosed or untreated.

The most common manifestation of haemophilia A is bleeding into joints. Repeated bleeding into the same joint, referred to as a target joint, can prevent healing and thus cause chronic inflammation and musculoskeletal pain, reduced range of motion and diminished quality of life.[5] Incorrect or delayed diagnosis of haemophilia due to low disease awareness in the past years and the associated suboptimal treatment result in a high disease burden to the patients and their families as well to the society.[6] According to consensus of Chinese experts, about 70% of children with haemophilia suffer from joint disability when they have reached adulthood.[7] In the past years, however, the standard of care is rapidly improving in China and prophylaxis is becoming more and more available to the patients.

However, many patients consider prophylaxis to be a major burden as treatment requires frequent intravenous injections to maintain protective factor activity levels.[1, 8-11] Prophylaxis requires repeated venous access, which can be difficult and traumatic to obtain in some patients.[12, 13] In

addition, prophylactic treatment can be time consuming. While prophylaxis is the standard of care for haemophilia, patients often face challenges integrating prophylaxis dosing into their daily life. Thus, therapies that require less frequent dosing may reduce the overall burden of prophylaxis. Currently, there are no extended half-life rFVIII products available in China, therefore Chinese patients will still be facing the above-mentioned barriers.

With the well-established knowledge of N8-GP efficacy and PK properties obtained from the comprehensive global clinical development program in severe haemophilia A patients across all age groups,[14-16] N8-GP provides a new treatment option to significantly reduce the dosing frequency associated with regular prophylaxis, which fulfils the urgent unmet needs in Chinese patients.

Turoctocog alfa pegol (in this protocol referred to as 'N8-GP'), a 40-kDa glycoPEGylated human recombinant coagulation factor VIII (rFVIII) with an extended half-life, has been developed to offer patients with haemophilia A a more effective and less burdensome treatment versus standard FVIII products. N8-GP has improved PK properties including a 1.6-fold increase in terminal half-life compared with standard FVIII products, which offers the possibility of achieving FVIII levels in the range of moderate haemophilia A with a less-burdensome every fourth day treatment regimen.[14-16] With a better overall PK profile and the ability to sustain higher FVIII levels than standard therapies, N8-GP has the potential to improve prophylaxis and simplify management of bleeds as well as perioperative haemostatic control in patients with haemophilia A.

N8-GP has been approved in US, EU, Japan, Canada and Switzerland for on-demand and prophylaxis for patients with haemophilia A. The Global Regulatory file is based on the results from a comprehensive global clinical development programme (pathfinder™) including 270 unique PTPs (202 adults/adolescents and 68 children) with severe haemophilia A who have been exposed to N8-GP with a total of 79,446 EDs corresponding to 882 patient years of exposure (PYE). Overall, the haemostatic effect of N8-GP on prevention and treatment of bleeds was high and consistent across all phase 3 trials and age groups. Adults and adolescents had a median ABR of 1.18, and a median annualised spontaneous bleeding rate (AsBR) of 0.00, respectively, while 40% did not experience any bleeding episodes during prophylactic treatment with N8-GP in the pivotal parts of the Phase 3 trial. Another clinical benefit of N8-GP was observed in the treatment of bleeds. The overall success rate for the first treatment of a bleeding episode evaluated within 8 hours was 88 %.[15, 16] The vast majority of the bleeds were resolved with 1–2 injections. In addition, N8-GP was shown to provide haemostatic control during surgery (trial 3860), as the success rate for perioperative treatment was 96% in 45 major surgeries. Through the clinical development programme, N8-GP has demonstrated a safety profile similar to that of currently approved FVIII products. N8-GP was well tolerated, the AE pattern was considered typical for the patient population, and no safety concerns related to N8-GP have been identified. Across the clinical development programme of N8-GP, no discernible pattern has been observed when the response to N8-GP with regards to PK profile, efficacy (prevention and treatment of bleeds) and safety has been analysed by country, race, or ethnicity.

2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of N8-GP (turoctocog alfa pegol) may be found in the investigator's brochure).[17]

2.3.1 Risk assessment

Based on previous experience and knowledge from completed and ongoing phase 3 trials with N8-GP, development of inhibitory antibodies and allergic reactions have been classified as identified risks.

See Section 7.2 of the investigator's brochure[17] for further information on identified and potential risks with use of N8-GP and FVIII products.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Trial treatment: N8-GP		

Identified risks		
Development of inhibitory antibodies	The main safety issues identified with use of FVIII products are immunogenicity and lack of efficacy due to formation of neutralising antibodies against FVIII. See Section 7.2.1.1 of the investigator' brochure[17] for further details on identified risks, and Section 6.4.2.3 of the investigator's brochure[17] for results on inhibitor development in the N8-GP clinical trial programme.	For previously treated patients with no history of FVIII inhibitor development, the risk of inhibitor formation is low. As per inclusion criteria no.4 (see Section 5.1), only patients with a history of at least 150 EDs to other FVIII products are eligible. Also, exclusion criteria no. 4 excludes patients with a known history of FVIII inhibitors (Section 5.2). If reduced efficacy from treatment is suspected an assessment for FVIII inhibitors should be performed (see Section 8.6.1.
Allergic reactions	As with any intravenous product, allergic hypersensitivity reactions cannot be excluded. Allergic type hypersensitivity reactions, including anaphylaxis, have been observed in patients treated with marketed FVIII products. For results on allergic reactions reported in the N8-GP clinical trial programme, see Section 6.4.2.3 of the investigator's brochure.[17]	Patients are monitored carefully for allergic type hypersensitivity reactions, including anaphylaxis. Allergic type hypersensitivity reactions must be treated as per local practice and as per investigator's discretion.
Potential risks Thromboembolic events	Thromboembolic events is considered an important potential risk considering the fact that supra-physiologically elevated procoagulant levels may be associated with an increased risk of venous thrombosis. Few thromboembolic events have been observed in the N8-GP clinical trial programme; see Section 6.4.2.3 of the investigator's brochure.[17]	Thromboembolic events are monitored closely.

Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs.	There has been no indication of PEG accumulation after N8-GP treatment non-clinically or clinically. The possible clinical consequences of potential PEG accumulation are currently unknown. Potential effects of PEG accumulation are monitored closely.	Long-term safety including potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs are monitored in the clinical trials and post-marketing.
Trial procedures		

Intravenous injection (i.v.)	Wrong route of administration, e.g., intramuscular instead of intravenous	Administration of trial product at sites are performed by trained staff. The previously treated patients and/or caregivers have experience with i.v. injection and will be trained by site staff in use of trial product.
Physical examination and body measurements	No risks are expected to be associated with standard physical examination. Burden (embarrassment, discomfort, distress) associated with examinations that are related to sexual development (e.g., in adolescents) can be expected.	As this assessment is performed by physicians familiar with the patient population the burden is expected to be low.
Risk of COVID-19 infection in relation to participation in the trial.	Patients and caregivers may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low. To minimize the risk as much as possible, the following measures have been taken: On-site visits will be well-prepared and as short as possible. Physical contact between patients and site staff will be limited to the extent possible, and protective measures will be implemented such as masks sanitizers etc.
	If a patient is tested positive for COVID-19	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however if a patient is tested positive for COVID-19 then the investigator must ensure proper medical care and if possible site visits can be converted to telephone visits and if the patient recovers in time for the primary endpoint visit then the investigator should encourage the patient to visit the site for the primary endpoint visit. All necessary precautions must be taken for the site visit.

2.3.2 Benefit assessment

N8-GP has a longer half-life compared to standard FVIII coagulation products and thus has the potential to improve the quality of life for haemophilia A patients by offering a convenient prophylaxis treatment with a reduced treatment burden from less frequent injections.

2.3.3 Overall benefit-risk conclusion

No clinical safety issues have been identified that precludes further clinical development of N8-GP. AEs from the clinical trials that have been evaluated to be related to N8-GP are consistent with what has been observed, and what is expected, with use of other FVIII products. The potential benefits of N8-GP are considered to outweigh the identified and potential risks.

Taking into account the measures taken to minimise risk to patients participating in this trial, the potential risks identified in association with use of N8-GP are justified by the anticipated benefits that may be afforded to patient with haemophilia A.

3 Objectives and endpoints

3.1 Primary and secondary objectives

Primary objective

- To evaluate the clinical efficacy of N8-GP in bleeding prophylaxis (number of bleeding episodes during prophylaxis) in Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products

Secondary objectives

In Chinese adolescent and adult patients with severe haemophilia A previously treated with other FVIII products,

- To evaluate the clinical efficacy of N8-GP when used for treatment of bleeding episodes
- To evaluate the immunogenicity of N8-GP
- To evaluate the general safety of N8-GP
- To evaluate the consumption of N8-GP
- To evaluate the pharmacokinetic properties of N8-GP

3.2 Primary and secondary endpoints

3.2.1 Primary endpoint

Endpoint title	Time frame	Unit
Number of bleeding episodes	From start of treatment until visit 7	Count

3.2.2 Secondary endpoints

3.2.2.1 Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none)	From start of treatment until visit 7	Count
Consumption of N8-GP for treatment of bleeding episodes	From start of treatment until visit 7	IU/kg/bleed
Consumption of N8-GP for prophylaxis	From start of treatment until visit 7	IU/kg/year
FVIII trough activity during prophylaxis	From start of treatment (excluding the first exposure) until visit 7	IU/mL

3.2.2.2 Secondary safety endpoints

Endpoint title	Time frame	Unit
Incidence rate of confirmed FVIII inhibitors ≥0.6 BU	From start of treatment until visit 7	Rate
Number of adverse events (AEs)	From start of treatment until end of trial	Count
Number of serious adverse events (SAEs)	From start of treatment until end of trial	Count

3.2.2.3 Secondary pharmacokinetic endpoints

Endpoint title	Time frame	Unit
FVIII activity 30 min post-injection (C_{30min})	Single-dose: 30 min ± 5 min post-injection at visit 2a Steady-state: 30 min ± 5 min post-injection at visit 7	IU/mL
Incremental recovery (IR)	Single-dose: 30 min ± 5 min post-injection at visit 2a Steady-state: 30 min ± 5 min post-injection at visit 7	(IU/mL)/(IU/kg)
Area under the curve (AUC)	Single-dose: 0−inf post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	h*(IU/mL)
Terminal half-life ($t_{½}$)	Single-dose: 0−96 h post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	h
Clearance (CL)	Single-dose: 0−96 h post-injection at visit 2a Steady-state: 0−96 h post-injection at visit 7	mL/h/kg
FVIII trough activity 96 h post-injection (C_{96h})	Single-dose: 96 h ± 8 h post-injection at visit 2a Steady-state: 96 h ± 8 h post-injection at visit 7	IU/mL

4 Trial design

4.1 Overall design

This trial is a multi-centre, open-label, non-randomised, single-arm phase 3b trial evaluating the clinical efficacy, safety (including immunogenicity) and PK of N8-GP when used for treatment and prevention (prophylaxis) of bleeding episodes in Chinese patients ≥12 years of age with severe haemophilia A (FVIII activity <1%). This trial design is overall similar to the design of the completed global, pivotal pathfinder™2 trial in adult and adolescent previously treated patients with severe haemophilia A (trial NN7088-3859).

Thirty-six (36) Chinese PTPs with severe haemophilia A, aged ≥12 years and with ≥150 exposure days (EDs) to other FVIII product(s), will receive prophylaxis with 50 IU/kg N8-GP every 4 days (with the possibility of switching to twice-weekly dosing during the treatment period at the discretion of the investigator). Bleeding episodes will be treated with bolus injection(s) of 20-75 IU/kg N8-GP.

The treatment period in the trial will be at least 28 weeks with N8-GP prophylaxis every 4 days where ≥50 EDs to N8-GP (including treatment of bleeding episodes) must be obtained. The screening period will be 2 weeks and the follow-up period will be 30 days.

At least 30 patients must complete the trial with ≥50 EDs to N8-GP (including treatment of bleeding episodes) and ≥6 months (≥28 weeks) of prophylaxis.

An overview of the trial design is given in Figure 4-1.

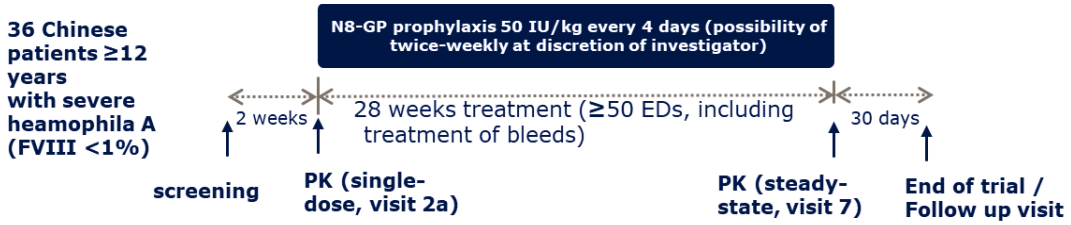

Figure 4-1 Overview of trial design

Efficacy of N8-GP prophylaxis (prevention of bleeds) will be assessed by the number of spontaneous and traumatic bleeding episodes observed (annualised bleeding rate). In addition, trough levels of the surrogate efficacy parameter, FVIII activity, will be evaluated.

The haemostatic effect of N8-GP in the treatment of bleeding episodes will be based on the treatment of all bleeding episodes (spontaneous and traumatic bleeding episodes) during prophylaxis (breakthrough bleeds), and will be assessed by total number, severity, cause of bleed, and by location of bleed (including target joints). The haemostatic response to N8-GP will be assessed using a four-point scale (excellent, good, moderate and none response) by counting excellent and good as success and moderate and none as failure. Amount and number of injections of N8-GP per bleeding episode will also be evaluated.

Major and minor surgery is allowed in the trial, and the haemostatic effect and consumption of N8-GP in relation to surgery will be evaluated.

Fifteen (15) of the 36 enrolled patients will participate in PK assessments to obtain at least 12 patients with two PK profiles of N8-GP (one single-dose PK profile and one steady-state PK profile). The single-dose PK assessments will be performed at first exposure to N8-GP after a preceding wash-out period of at least 4 days (96 hours). The steady-state PK assessments will be performed approximately 28 weeks after start of prophylaxis.

4.1.1 Treatment of patients

Patients will receive N8-GP as prophylaxis, for treatment of bleeding episodes, and in relation to surgery.

The trial product is N8-GP (turoctocog alfa pegol) produced by Novo Nordisk. The trial product is a recombinant FVIII product and is a lyophilised powder in vials, which is reconstituted with solvent for injection (see Section 6.1 for further details). Trial product will be administered as intravenous injections (i.v.) at home by the patient and/caregiver, at the trial site, or in exceptional cases in another clinic/hospital. To be able to train patients on home treatment of N8-GP at least the first treatment should be at the trial site.

Table 4-1 Treatment regimens

Treatment regimen	Age (years)	Dose (IU/kg)	Dose frequency
Prophylaxis	≥12	50	Once every 4 days (can be changed to twice-weekly at investigator's discretion)
Treatment of bleeds	≥12	20-75	When necessary
Surgery	≥12	At investigator's discretion	Pre-dose and when necessary

4.1.2 Maximum dose and daily administration of N8-GP

The maximum dose to be administered to a patient within 24 hours is 200 IU/kg. The dose is recommended to be divided and only considered under exceptional circumstance such as serious trauma or severe bleed. The maximum dose per injection must not exceed 100 IU/kg BW.

4.1.3 Prophylaxis

The N8-GP prophylaxis regimen chosen for this trial is based on clinical data from the global trial in adolescent and adult patients (pathfinder™2, NN7088-3859) where prophylaxis with 50 IU/kg N8-GP every 4 days was associated with low ABRs.

For prophylaxis, one single bolus dose of 50 IU/kg N8-GP will be administered i.v. every 4 days (96 hours interval). During the treatment period, a shortening of the dosing interval for prophylaxis to twice-weekly dosing may be undertaken at the investigator's discretion, if deemed necessary for the individual patient. If the dosing regimen is changed to twice weekly, doses should be separated with at least 3 calendar days and no more than 4 calendar days. Other changes of the dose or dosing interval for prophylaxis are not allowed in the trial. However, extra doses of N8-GP can be

administered if a patient experiences a treatment-requiring bleeding episode (see Section 4.1.4) or in case of surgery (see Section 4.1.5).

If a bleeding episode occurs on a planned prophylaxis dosing day before administration of the prophylaxis dose, or if a bleeding episode extends into such a day, the bleeding episode must be treated with the full prophylaxis dose (this dose should be recorded as treatment of a bleeding episode). The patient should at all times follow the original prophylaxis dosing scheme unless a dose has already been given to treat a bleeding episode during the same day.

4.1.4 Treatment of bleeding episodes

A treatment-requiring bleeding episode is defined as a bleed that requires treatment with N8-GP. If a patient experiences a treatment-requiring bleeding episode it must be treated as soon as it is identified. The investigator must always be contacted in case of a severe bleed and the patient should visit the site within 24 hours, or when possible. Mild/moderate bleeding episodes can be treated at home without contacting the site. Treatment should be started as soon as a bleed is identified.

For treatment of a mild or moderate bleeding episode, for example a joint bleed, N8-GP i.v. bolus injections at doses between 20-75 IU/kg BW should be administered to achieve a desired dose level based on the severity and location of the bleeding episode. Each unit of N8-GP will raise the FVIII level with approximately 2%. The required dose within the 20-75 IU/kg BW dosing range is determined by the investigator for every patient, using the recommendations in the World Federation of Haemophilia (WFH) guideline, FVIII activity should not fall below the lower range for the given plasma activity level (in % of normal or IU/dl) until the bleeding episode is resolved.

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

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

If a bleeding episode occurs on a planned prophylaxis dosing day before administration of the prophylaxis dose, or if a bleeding episode extends into such a day, the bleeding episode must be treated with the full prophylaxis dose (this dose should be recorded as treatment of a bleeding episode). The patient should at all times follow the original prophylaxis dosing scheme unless a dose has already been given to treat a bleeding episode during the same day.

If a haemostatic response cannot be achieved after 48 hours using adequate doses of N8-GP treatment when treating bleeding episodes, another FVIII product may be used at the discretion of

the investigator. The use of other FVIII products will result in discontinuation of the patient (exception: current FVIII product is allowed until 96 hours before visit 2a).

4.1.5 Treatment for surgery

Major and minor surgery can be performed while participating in the trial. Use of FVIII products other than N8-GP for surgery is not allowed. Patients undergoing surgical procedures will receive trial product as bleeding preventive treatment according to standard practice at the trial site and/or at the investigator's discretion.

For dosing guidance in patients who need to undergo surgical procedures during the trial, investigators could refer to Table 4-2 and WFH guidelines.[18] As these guidelines are recommendations, non-compliance with them will not require any protocol deviations. Achieving higher FVIII activity levels may be necessary depending on type of surgery and standard practice at the trial site. The rationale is to replace the FVIII activity in these patients up to FVIII activity levels that are effective in preventing bleeding during and after surgery.

Table 4-2 Guide for dosing for surgery

Type of surgical procedure	FVIII activity to achieve (%) (IU/dL)	Frequency of doses (hours)/ Duration of treatment (days)
Minor surgery (including tooth extraction)	30-60	Repeat every 24 hours if needed until adequate wound healing is achieved.
Major surgery	80-100 (pre-and postoperative)	Maintain factor VIII level by repeat injection every 8-24 hours until adequate wound healing is achieved, then adjust therapy for at least 7 more days to maintain a FVIII activity of 30% to 60% (IU/dL)

The specific treatment for each patient is decided by the investigator in collaboration with the surgeon. Surgery can be done at the trial site, in another clinical department of the site, or at another hospital. If a surgery takes place at another location than at the trial site, the surgeon must be informed that the patient is participating in the trial, and the investigator should give instructions to the surgeon about the dosing treatment, the handling of the trial product and the efficacy and safety evaluation. It must be ensured that there is enough available trial product for the surgery, including the post-operative period. Please note the medication that is not permitted during the trial and surgery, see Section 6.5.1.

The maximum dose to be administered to a patient within 24 hours is 200 IU/kg. The dose is recommended to be divided and only considered under exceptional circumstance such us serious trauma or severe bleed.

See Section 8.1.3.1 for definitions of major and minor surgery.

4.1.5.1 Administration of N8-GP on the day of surgery

Patients undergoing surgical procedures will receive trial product as bleeding preventive treatment according to standard practice at the trial site and/or at the investigator's discretion.

Preventive treatment with trial product should be administered before any surgical procedures are undertaken, including potential anaesthesia to avoid bleeding when being anaesthetised.

See Table 4-2 for dosing guidance for surgery.

4.1.6 Treatment during screening and follow-up periods

Patients should follow their normal treatment regimen during the screening and follow-up periods. Treatments will not be reimbursed by Novo Nordisk during these periods. Bleeds that occur during the screening and follow-up periods should be treated as per standard local practice and will not be assessed.

4.2 Scientific rationale for trial design

This trial is a Phase 3b trial with a trial design overall similar to the global, pivotal pathfinder™2 trial in adult and adolescent patients with severe haemophilia A (trial NN7088-3859), which is also in accordance with recommendations from Centre of Drug Evaluation (CDE) and guidelines.

The chosen trial design will provide information on efficacy, safety (including immunogenicity) and PK of N8-GP when used for prophylaxis and treatment of bleeding episodes in previously treated Chinese patients with severe haemophilia A (FVIII activity <1%), complementing the data collected in global pathfinder™2 trial.

Prophylaxis of bleeding episodes is the primary goal of therapy and must be the goal of all haemophilia care programmes until a cure is available.[18]

The trial will generate efficacy and safety data from ≥50 EDs and ≥6 months of prophylaxis to N8-GP for each patient completing the trial, equivalent to at least 28 weeks of prophylaxis.

The trial will not be controlled by a placebo group as it is considered unethical to administer an ineffective treatment to patients with haemophilia.

The rationale for choosing a multi-centre design is to ensure a sufficient screening pool of patients with a rare disorder.

4.3 Justification for dose

This trial design is overall similar to the global, pivotal pathfinder™2 trial design. The frequency for the prophylaxis treatment regimen and the dose levels for prophylaxis and treatment of bleeding

episodes is identical to what was used in the pathfinder™2 trial. The treatment for major and minor surgery is identical to what was used in the pathfinder™3 trial (NN7088-3860).

4.4 End of trial definition

A patient is considered to have completed the trial if he has completed all visits of the trial including the last visit. The end of the trial is defined as the date of the last visit of the last patient in the trial.

5 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male Chinese patient with severe congenital haemophilia A with a FVIII activity <1% according to medical records.
3. Aged ≥12 years at the time of signing informed consent.
4. History of at least 150 exposure days (EDs) to other FVIII products[1].
5. The patient and/or caregiver is capable of assessing a bleeding episode, keeping a diary, performing home treatment of bleeding episodes and otherwise following the trial procedures at the discretion of the investigator.

[1] Prophylaxis, prevention, on-demand and treatment during surgery counts as exposure days. If not possible to count the actual number of exposures in the medical chart, the investigator should make a written statement with an estimate based on e.g., patient age, treatment frequency, medical history, discussion with previous doctor/transfer note and other relevant information. This statement should be filed either with the patient chart or separately with the investigator trial file.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

5.2 Exclusion criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to trial product or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 5 half-lives or 30 days from screening, whichever is longer.

4. Known history of FVIII inhibitors based on existing medical records, laboratory report reviews and patient and/or caregiver interviews.
5. Current FVIII inhibitors ≥0.6 BU.
6. Congenital or acquired coagulation disorder other than haemophilia According to medical records.
7. HIV positive, defined by medical records, with CD4+ count ≤200/µL and a viral load >200 particles/µl or >400000 copies/mL within 6 months of the trial entry. If the data are not available in medical records within last 6 months, then the test must be performed at screening visit. .
8. Previous significant thromboembolic events (e.g. myocardial infarction, cerebrovascular disease or deep venous thrombosis) as defined by available medical records.
9. Hepatic dysfunction defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 times the upper limit of normal combined with total bilirubin >1.5 times the upper limit of normal at screening, as defined by central laboratory.
10. Renal impairment defined as estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 for serum creatinine measured at screening, as defined by central laboratory.
11. Platelet count $<50\times10^9$/L at screening based on central laboratory values at screening.
12. Ongoing immune modulating or chemotherapeutic medication.
13. Any disorder, except for conditions associated with haemophilia A, which in the investigator`s opinion might jeopardise the patient`s safety or compliance with the protocol.
14. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

The criteria will be assessed at the investigator's discretion unless otherwise stated.

5.3 Lifestyle considerations

Normal lifestyle is considered to be restricted for PK patients when they will undergo PK assessments at visit 2a and visit 7 where blood sampling will be performed during a 96-hour period. It is not required that the patient stays overnight. See the flowchart in Section 1.2 for patients having PK evaluated at Visit 2a and Visit 7, and Section 8.5 for how PK assessments are performed.

5.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and laboratory results. A screen failure session must be made in the interactive web response system (IWRS).

Individuals who do not meet the criteria for participation in this trial may not be rescreened. Re-sampling is not allowed if the patient has failed one of the inclusion criteria or fulfilled one of the

exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6 Treatments

6.1 Treatments administered

Investigational medicinal product (IMP)

The following trial product will be supplied by Novo Nordisk:

- turoctocog alfa pegol (N8-GP) 2000 IU/vial as a sterile, freeze-dried powder in a single-use vial of 2000 IU/vial to be reconstituted with 4.3 mL of 0.9% sodium chloride (NaCl) for i.v. injection.

The reconstituted solution must not be further diluted. It is recommended to use the trial product immediately after reconstitution.

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

Trial drug will be administered as i.v. injections at sites or at home by the patient and/or caregiver themselves.

The investigator must document that directions for use are given to the patient/caregiver verbally and in writing at the first dispensing visit (visit 2a) (see Section 1.2).

Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S

Trial product name:	Turoctocog alfa pegol (N8-GP), 2000 IU/vial.
Dosage form	Solution for injection.
Route of administration	Intravenous (i.v.).
Dosing instructions	Prophylaxis: 50 IU/kg every 4 days. Treatment of bleeds: 20-75 IU/kg bolus injections. Minor surgery (dosing guidelines): 50-75 IU/kg N8-GP or a dose sufficient to increase the FVIII level to 100% (IU/dL) prior to the surgery. Major surgery (dosing guidelines): Maintain factor VIII level at 80-100% (IU/dL) by repeat injection every 8-24 hours until adequate wound healing, then adjust therapy for at least 7 more days to maintain a FVIII activity of 30-60% (IU/dL).
Packaging	Vial with freeze-dried powder to be reconstituted with 0.9% sodium chloride.

Non-investigational medicinal products (NIMP)

Sodium chloride 0.9% solution will be used to reconstitute the IMP. Sodium chloride 0.9% will come in a syringe with scale label (the NIMP) and will be provided by Novo Nordisk.

Auxiliary supplies

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

Only needles and syringes provided and/or approved by Novo Nordisk must be used for administration of trial product.

6.2 Preparation/handling/storage/accountability

Only patients enrolled in the trial may receive trial product (IMP and NIMP), and only the trial doctor and authorised site staff may supply and administer trial product.

Instructions for trial product storage, in-use conditions and in-use time will be available from the label and from the trial materials manual (TMM).

- Acceptable temperature ranges and conditions for storage and handling of trial product when not in use and when in use are described in the TMM.
- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and inclusion.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. If so, this trial product must not be dispensed to any patient before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.
- The investigator or designee is responsible for drug accountability and for recording maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the patient in what to return at next visit.
- The patient must return all used, partly used and unused trial product including empty packaging materials during the trial as instructed by the investigator or designee.
- Drug accountability for N8-GP (IMP) and sodium chloride 0.9% syringe (NIMP) is performed on a dispensing unit number (DUN) level using the IWRS drug accountability module to account for the status of each DUN.

- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned, unused, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

6.3 Measures to minimise bias: Randomisation and blinding

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

This is an open-label trial.

6.4 Treatment compliance

Drug treatment compliance

Throughout the trial, the investigator will remind the patients to follow the trial procedures and requirements to encourage patient compliance.

When patients are dosed at the site, they will receive trial product directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents.

When patients self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available. Any missed dose should be discussed with the patient and followed up to ensure patient is compliant to trial product and trial procedures. If any suspicion of non-compliance arises i.e., the patient missed ≥5 doses of any consecutive 25 doses site must enter into a dialogue with the patient, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product, visual inspection of vials
- Review of dosing diaries
- Questioning of patients

Treatment start dates, stop dates and all doses will be recorded in the electronic case report form (eCRF).

6.4.1 In-use time

Investigator/investigator designee must train the subject on in-use time of the trial product at first dispensing, At each site visit investigator/ investigator designee must review use of trial product with the subject and document in the subject medical record if the subject exceeds in-use time of the trial product.

6.5 Concomitant medication

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) other than the trial product(s) that the patient is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Start and stop dates
- Total daily dose

Changes in concomitant medication must be recorded at each visit. If a change in concomitant medication is due to an AE/SAE, then this must be reported according to Section 8.3.

6.5.1 Prohibited Medication

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

- Bypassing products: activated recombinant factor VII (rFVIIa), plasma-derived prothrombin complex concentrates (pd-PCC) and plasma-derived activated prothrombin complex concentrates (pd-aPCC).
- Coagulation Factors: FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products like fresh frozen plasma or cryoprecipitate (exception: current FVIII is allowed until 96 hours before Visit 2a).
- Anti-coagulants such as Heparin and vitamin-K antagonists. Heparin is allowed for sealing of central venous access devices according to local practice.

6.6 Dose modification

Treatment with N8-GP for prophylaxis, treatment of bleeding episodes, and surgery is found in Sections 4.1.3, 4.1.4 and 4.1.5, respectively.

The possibility of changing the prophylaxis regimen in an individual patient from every 4 days dosing with 50 IU/kg N8-GP to twice-weekly dosing with 50 IU/kg N8-GP at the discretion of the investigator is described in Section 4.1.3.

6.7 Treatment after end of trial

When discontinuing trial product at visit 7 or 7a (i.e., before the End of trial/Follow-up visit), the patient should be transferred to a suitable marketed product at the discretion of the investigator.

7 Discontinuation of trial treatment and patient withdrawal

Treatment of a patient may be discontinued at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Even if treatment with trial product has been discontinued, the patient should continue to follow the planned visit schedule until having completed the end of treatment visit (Visit 7). Efforts must be made to have the patients who discontinue trial product attend and complete all scheduled visit procedures according to Section 1.2. Patients should stay in the trial irrespective of lack of adherence to the treatment, lack of adherence to visit schedule or missing assessments.

If the patient, who has been discontinued from treatment with trial product, declines the request to continue in the trial, then efforts must be made to have the patient attend Visit 7a (discontinuation of treatment visit) (see Section 1.2).

Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

7.1 Discontinuation of trial treatment

A patient who does not fulfil the eligibility criteria (inclusion/exclusion criteria) must not be included in the trial. Inclusion in violation of any of the eligibility criteria is non-compliant with Good Clinical Practice (GCP) procedures and must be reported to the sponsor without delay. This will be handled as an important protocol deviation, and the independent ethics committee (IEC)/ institutional review board (IRB) and regulatory authorities must be notified according to local requirements. If there are no safety concerns for the patient, trial treatment may be continued or resumed at the discretion of the investigator after agreement with the sponsor´s global medical expert.

A patient may be discontinued from treatment with N8-GP at the discretion of the investigator due to a safety concern.

The trial product must be discontinued, if any of the following applies for the patient:

1. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial.
2. Haemostasis not achievable with N8-GP: The bleed cannot be controlled after 48 hours using adequate doses of N8-GP.
3. FVIII inhibitor (≥0.6 and ≤5 BU) as confirmed by re-testing by Central Laboratory that makes treatment (prophylaxis and/or treatment of bleeding episodes) with N8-GP clinically ineffective. see section 8.6

4. FVIII inhibitor (>5 BU) as confirmed by re-testing by Central Laboratory.

5. Allergy/anaphylaxis to the trial product.

6. Use of Coagulation Factors FVIII, FIX and FVII-containing products other than N8-GP and other FVIII-containing products such as fresh frozen plasma or cryoprecipitate (**Exception**: FVIII is allowed until 96 hours before visit 2a).

7. Incapacity or unwillingness to follow the trial procedures.

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

See Section 1.2 for data to be collected at the time of treatment discontinuation (discontinuation of treatment visit; Visit 7a) and follow-up and for any further evaluations that need to be completed.

The purpose of the end of trial (follow-up) visit is to collect information about adverse events. For convenience of the patient the visit can be performed as a telephone contact.

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

If a patient discontinues treatment prior to Visit 7, Visit 7a should be performed as soon as possible after the last dose of trial product has been administered, and prior to starting treatment with another marketed product. The follow-up visit (Visit P8) should be performed 30 +5 days after the last dose of trial product has been administered. Even if treatment with trial product has been discontinued, after Visit P8 the patient should continue to follow the planned visit schedule until having completed the end of treatment visit (Visit 7).

After Visit 7a, the following procedures/assessments should not be performed for patients who discontinue treatment:

- Trial product administration
- FVIII activity
- Medication error
- Technical complaint
- Drug dispensing and drug accountability

7.1.1 Temporary discontinuation of trial treatment

Temporary discontinuation of treatment with trial product is not allowed in the trial.

7.2 Patient withdrawal from the trial

A patient may withdraw consent at any time at his own request or at the request of the caregiver.

If a patient withdraws consent, the investigator must ask the patient for willingness, as soon as possible, to have assessments performed according to Visit 7a (discontinuation of treatment visit). See Section 1.2 for data to be collected at Visit 7a (discontinuation of treatment visit) after treatment with trial product has been discontinued.

Final drug accountability must be performed even if the patient is not able to come to the site. A treatment discontinuation session must be made in the IWRS.

If the patient withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, the patient may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a patient is not obliged to give the reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end-of-trial form in the eCRF.

7.2.1 Replacement of patients

Patients who discontinue trial product or withdraw from the trial will not be replaced.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a patient fails to return to the site for a required visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, at least three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's source document.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the trial with a primary reason of `lost to follow-up'.

8 Trial assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowcharts in Section 1.2.

Informed consent must be obtained before any trial related activity, see Section 10.1.3.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, patients will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the trial design requirements, including those specified in the flowchart in Section 1.2, is essential and required for trial conduct.

Review of e.g., diaries and laboratory reports must be documented either on the documents or in the patient's source documents. If clarification of entries or discrepancies in the documents is needed, the patient must be questioned, and a conclusion made in the patient's source documents. Care must be taken not to bias the patient

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Refer to Appendix 2 for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowcharts in Section 1.2.

8.1.1 Bleeding Episodes

From Visit 2a (inclusion of the patient and first administration of trial product) and during the entire trial period all treatment-requiring bleeding episodes (also referred to as ‘bleeding episodes’ or ‘bleeds’) must be entered by the patient or caregiver in the patient’s diary. In case a patient is unable to enter a bleeding episode in the diary or is hospitalised, the investigator will report the bleeding episode in the eCRF (refer to Section 8.7 for reporting in the diary and eCRF).

If a patient experiences a bleeding episode at home, treatment with N8-GP should be initiated irrespective of severity of the bleeding episode (refer to Section 8.8 for training in home treatment). If the bleed is mild/moderate, the treatment responsibility is with the patient, patient’s caregiver(s) and/or the investigator. For severe bleeding episodes, the treatment responsibility is always with the investigator and the patient should contact the site for further instructions. Treatment of severe

bleeding episodes should be initiated as soon as possible by the patient or caregiver. It is the responsibility of the investigator to assess the severity of the bleeding episodes and to ensure that all data is recorded correctly in the patient's diary.

Any discrepancy observed by the investigator or site staff must be documented in the patient's medical record and the patient must be retrained on completion of the diary completion, if required.

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

A need for haemostatic rescue therapy with another FVIII product will be assessed by the investigator via phone or during the site visit. Patients treated with FVIII products other than N8-GP must be discontinued from treatment with N8-GP (exception: the patient's current FVIII product is allowed until 96 hours before visit 2a).

8.1.1.1 Definition of severity of bleeding episodes

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

8.1.1.2 Definition of Haemostatic Response:

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

8.1.1.3 Classification of a bleeding episode

Table 8-1 Definitions of bleeding episodes

Category	Comment
Spontaneous	Not linked to a specific event
Traumatic	Caused by a specific, known action or event (e.g. injury or exercise)
Surgical bleed	Bleeds after surgery from the surgical wound. Bleeding episodes during surgery does not fall under this category and will be evaluated in the surgical haemostatic evaluation

8.1.2 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowcharts in Section 1.2 and the laboratory manual.

8.1.3 Surgery

Surgical procedures should be performed by a surgeon in collaboration with the investigator. Surgery should preferably be scheduled early in the week and early in the day for optimal conditions, e.g., support from the blood bank. Access to sufficient quantities of N8-GP should be ensured before undertaking surgery.

Blood samples for analysis of FVIII activity will be collected on the day of surgery; pre-dosing (trough) and 30±5 min (recovery) post-administration of the dose for surgery. These sampling time points are relative to completion of N8-GP administration, and actual time must be documented.

The analysis of plasma FVIII activity will be performed using a chromogenic assay at a central laboratory selected by Novo Nordisk.

8.1.3.1 Definition of surgery

Surgery type	Definition
Major surgery	Major surgery is any invasive operative procedure where any one or more of the following occur A body cavity is entered. A mesenchymal barrier (e.g. pleura, peritoneum or dura) is crossed. A fascial plane is opened. An organ is removed. Normal anatomy is operatively altered These procedures may be performed using general anaesthesia, spinal anaesthesia, epidural anaesthesia, conscious sedation or with a combination of these modalities
Minor surgery	Minor surgery is any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated. Examples of minor surgery include vascular cutdown for catheter/fistula placement, implanting pumps or CVAD in subcutaneous tissue, biopsies or placement of probes, leads, or catheters requiring the entry into a body cavity only through a needle/guidewire. Dental surgery will be classified as minor or major based on above definitions

8.1.3.2 Haemostatic response during surgery

Table 8-2 Haemostatic response during surgery

Category	Definition
Excellent	blood loss less than expected
Good	blood loss as expected
Moderate	blood loss more than expected
None	uncontrolled bleeding

This evaluation must be performed by the surgeon and the investigator should ensure to document it in the eCRF.

8.1.3.3 Surgery visit

Surgery must be performed at a dedicated surgery visit. See Section 1.2 for procedures and assessments to be performed during a surgery visit.

8.2 Safety assessments

Planned time points for all safety assessments are provided in Section 1.2.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the patient experienced prior to the time point from which AEs are collected.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form.

8.2.1 Physical examinations

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

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

Target joints: Patients will be asked about number and location of target joints. Target joints are defined as 3 or more bleeding episodes in the same joint within 6 months.

Any changes in the examination between the visits which fulfil the criteria of an AE must be recorded as such (see Appendix 3 in Section 10.3).

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

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body weight

Body weight will be measured in kilos (kg) with one decimal without shoes and wearing only light clothing. Body weight should be measured preferably at the same time of the day and by using the same calibrated scale throughout the trial, if possible.

Height

Height is measured without shoes in centimetres or inches and recorded in the eCRF to nearest ½ cm or ¼ inch.

Body Mass Index

Body mass index will be calculated by the investigator at the screening visit 1 and documented in the subject medical record.

8.2.1.1 Neurological examination

The following neurological examinations will be performed by the investigator (haematologist) or an appropriately trained designee under their supervision upon the outline specified in Appendix 6 (this outline has been developed with guidance from a neurologist):

- General neurology including level of consciousness
- Cranial nerves in relation to sight including reaction to light, visual fields and acuity, and eye movements, facial sensation and movement, hearing, palate sound and tongue movement, and trapezius muscle function
- Tone of upper and lower extremity right and left
- Strength of upper and lower extremity right and left
- Reflexes of the biceps, triceps, knee and ankle right and left
- Sensory aspect of cold, pin prick, light touch and proprioception (toe up/down)
- Gait with regards to walking, running, on heels and toes, tandem (toe/heel walk), stand/hop on one leg/foot right and left, and Romberg sign
- Coordination and Fine Motor including finger-to-nose, rapid index finger tab and rapid finger movement right and left

If a patient have not had a specific neurological examination at baseline (visit 2a) then that examination item should not be performed during subsequent visits as per flowchart Table 1-1.

8.2.2 Vital signs

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

Vitals signs include assessment of:

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

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

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

8.2.3 Electrocardiograms

12-lead ECG will be obtained at the screening visit and at the end of treatment visit. For the ECG recording, the patients must be resting and in a horisontal position. Any irregularities observed during the ECG, e.g. cough, should either induce a re-run of the ECG and/or be annotated in the eCRF page with description of the occurrence. Printouts must include date, time, patient's identification, and initials of the investigator, and at least 2 complexes for each lead and a single rhythm strip of 6 beats. Electronic capture of these measurements may also be performed.

The evaluation should be made by the investigator or delegated to a cardiologist.

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

8.2.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Section 1.2). An investigator must sign, date and categorise the laboratory results. Categorisation will be either "normal", "out of normal range, not clinically significant" or "out of normal range, clinically significant". Clinically significant findings at Visits 1 and 2a must be recorded as Concomitant Illness, while clinically significant findings from Visit 2b until Visit 7 (included) must be recorded as AEs. Abnormalities should only be recorded as AEs if not present or worsened from baseline/previous assessments. Laboratory results are considered as source data and must be signed and dated by the investigator to verify that the data has been reviewed and that any AEs have been reported.

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

8.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

The definition of AEs and SAEs can be found in Appendix 3, along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant events, together with AESIs, are listed in Table 8-3.

Table 8-3 AEs requiring additional data collection (serious and non-serious AEs) and AESIs

Event type	AE requiring additional data collection	AESIs
Medication error	X	
Misuse and abuse	X	
Hypersensitivity	X	
FVIII inhibitors		X
CNS-related AEs		X
Renal or hepatic AEs		X
Thromboembolic events		X

A detailed description of the events mentioned in the above table can be found in Appendix 3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the first administration of trial product at Visit 2a and until the end of the trial (follow-up visit) at the time points specified in the flowchart in Section 1.2.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3. All SAEs must be recorded and reported to Novo Nordisk or designee within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the trial product or related to trial participation, the investigator must promptly notify Novo Nordisk.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about events.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or the patient is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure[17] and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female partners of male patient will be collected after first exposure to trial product and until end of trial (follow-up) visit.

If a female partner of a male patient becomes pregnant **and** the outcome of the pregnancy is abnormal, the investigator should inform Novo Nordisk within 14 calendar days of learning of the abnormal outcome and should follow the procedures outlined in Appendix 4.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as an AE or SAE

The following disease-related events (DREs) are common in patients with haemophilia A and can be serious/life threatening:

- Bleeding episodes.

Bleeding episodes

Because bleeding episodes are typically associated with the disease under study, they will not be reported according to the standard process for reporting of AEs/SAEs, even though the episodes may meet the definition of an AE/SAE. These episodes will be recorded in the patient diary and eCRF. These DREs will be monitored by Novo Nordisk on a routine basis.

Note: The bleeding episode must be recorded and reported both as a DRE and as an AE/SAE if one of the following applies:

- The bleeding episode is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.
- The investigator considers that there is a reasonable possibility that the bleeding episode was related to treatment with the IMP.
- The bleeding episode is considered life-threatening (see Appendix 4 for definition of life-threatening).
- The bleeding episode results in death.

8.3.7 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form.

Instructions for reporting technical complaints can be found in Appendix 5.

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Treatment of overdose

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 for further details.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAE.

For more information on overdose, also consult the current version of the turoctocog alfa pegol (N8-GP) investigator's brochure.[17]

8.5 Pharmacokinetics

Patients will be administered a single i.v. bolus injection of 50 IU/kg of N8-GP at Visit 2a and at Visit 7. The PK sessions extends over 96 hours. Overnight stay is not required. After completion of the PK sessions the patients will return to prophylaxis treatment with the next visit in line.

Patients must not have received current FVIII product for at least 4 days (96 hours) prior to the administration of trial product for the single-dose PK session at visit 2a, (i.e., a wash-out period of at least 96 hours must be applied before visit 2a).

There is no wash-out period for the steady-state PK session at visit 7, however administration of trial product at visit 7 should be approximately 96 hours after the previous N8-GP dose.

Patients must not be actively bleeding during the pharmacokinetic sessions.

The lines/tubes must be flushed immediately after administration of the trial product.

The pharmacokinetic endpoints (see Section 3.2.2.3) will be based on assessments performed from 1 hour prior to and up to 96 hours after administration of N8-GP at Visit 2a (single-dose PK assessments) and Visit 7 (steady-state PK assessments) (see flowchart for PK assessments in Section 1.2).

8.5.1 Visit 2a for patients undergoing PK assessments

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

At Visit 2a the patients will receive their first dose of N8-GP (50 IU/kg) at the site and nine PK samples will be taken during the following 96 hours. If a bleeding episode occurs between Visit 2a and 2b the patient must contact the site and preferably come to the site for treatment with N8-GP. Further blood sampling for PK will be stopped. If the patient experiences a bleeding episode at home that requires immediate treatment, or if the investigator judges it as necessary, the patient must treat himself at home with his previous FVIII product. Treatment with previous FVIII product

must lead to immediate stop of PK assessments and the patient must be discontinued from treatment with trial product.

Assessments at visit 2a are outlined in Section 1.2 and additional assessments and sampling for PK patients are outlined in Table 1-1.

The lines must be flushed immediately after administration of the trial product.

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

The samples taken 30 min post dose must not be taken from the same vein as used for administration of N8-GP.

8.5.2 Visit 2b for patients undergoing PK assessments

The second dose of N8-GP will be administered at the site after the last PK sample in relation to Visit 2a is taken.

Assessments at visit 2b are outlined in Section 1.2 and additional assessments and sampling for PK patients are outlined in Table 1-1.

8.5.3 Visit 7 for patients undergoing PK assessments

Patients who underwent a single-dose PK assessment at Visit 2a must also undergo a steady-state PK assessment at Visit 7. The steady-state PK session should be performed approximately 96 hours after the previous N8-GP dose. Overnight stay is not required during the PK evaluation. Blood sampling for PK should be stopped if a treatment requiring bleeding episode occurs during the PK session.

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

The lines used for injection must be flushed immediately after administration of the trial product.

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

Assessments at visit 7 and additional assessments and sampling for PK patients are outlined in Section 1.2.

8.6 Immunogenicity assessments

8.6.1 FVIII inhibitors

All patients will be examined for the development of FVIII inhibitors at scheduled visits (see Section 1.2). If FVIII inhibitor development is suspected (e.g., increased number of bleeding episodes, bleeding episodes difficult to treat, N8-GP recovery and trough levels below expected values) during the course of the trial, additional inhibitor tests can be taken. All inhibitor tests must be analysed by the central laboratory.

A positive inhibitor test is defined as ≥0.6 BU. In the event that a previously inhibitor negative patient has a positive inhibitor test (≥0.6 BU), the patient will be requested to visit the site for additional sampling preferably within 2 weeks. In addition, the following tests should be performed: anti-N8-GP antibodies, anti-PEG antibodies, FVIII trough (pre-dose), FVIII recovery (30 min post-dose) and lupus anticoagulant. These samples should preferably be taken prior to any change of treatment, and after approximately 96 hours wash-out period. If the second (confirmatory) inhibitor test is also positive, the patient must be discontinued from trial treatment if FVIII inhibitor >5 BU or if FVIII inhibitor ≥0.6 and ≤5 BU that makes treatment (prophylaxis or treatment of bleeding episodes) with N8-GP clinically ineffective, by discontinuing trial product and attending the discontinuation of treatment visit (visit 7a) within 1 week after the result is available.

If the second (confirmatory) inhibitor test is positive and ≤5 BU and the investigator judges that the inhibitor does not clinically interfere with N8-GP treatment (prophylaxis or treatment of bleeding episodes), the patient can stay in the trial and continue treatment as per-protocol treatment.

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

For patients discontinued from treatment with N8-GP: A follow-up visit must be scheduled 30(+5) days after the discontinuation of treatment (Visit 7a) and additional follow-up contact(s) (e.g., phone calls) may be arranged as long as clinically warranted up to 3 months after the EOT Visit.

For patients continuing in the trial with inhibitor (≥0.6 and ≤5 BU): the patient must follow per-protocol treatment schedule and the scheduled visits as described in Section 1.2. Additional visits can be scheduled if closer monitoring is needed. Closer monitoring is highly recommended but this decision will be at investigator's discretion. In the event of a concern about reduced treatment efficacy a PK session may be performed. Blood sampling during the PK profile session can be performed at the following time points: pre-dose, 30 minutes (± 10 min), 24h (± 8 hours), 48h (± 8 hours), 72h (± 8 hours) and 96h (± 8 hours).

A confirmed positive inhibitor is considered to have disappeared if the inhibitor titre is <0.6 BU on 2 consecutive inhibitor tests (performed at 2 consecutive visits) and the FVIII recovery is ≥66% of expected values. A patient with repeated positive inhibitor test result will count only once in the determination of the inhibitor incidence rate.

Patients who develop an inhibitor should be classified as high responders (peak inhibitor titre >5 BU), low responders (peak inhibitor titre ≤5 BU), and whether the inhibitor is transient (disappearing (inhibitor titre <0.6 BU on ≥2 consecutive measurements) spontaneously within 6 months without a change in treatment regimen), or not.

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

Any single positive inhibitor test must be reported as an AESI (see Section 10.3.3).

If the second (confirmatory) inhibitor test is positive then the event must be reported as an SAE (see Section 10.3.5).

Blood samples for measurement of inhibitors towards FVIII will be analysed according to the Nijmegen modification of the Bethesda assay.[15] Any sampling for the inhibitor test must be performed at least 96 hours after last administration of N8-GP to allow for maximum wash-out of the drug.

The patient may discontinue the trial including an EOT Visit and FU Visits or remain in the trial as described above. A patient having an initial positive inhibitor test and a second negative inhibitor test will be regarded as inhibitor negative and can continue in the trial.

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

In the event that a patient is discontinued from trial treatment due to development of inhibitors, Novo Nordisk A/S will cover costs of associated treatment if the inhibitor development is considered a trial related injury in accordance with Chinese law.

8.6.2 Anti-N8-GP antibodies

N8-GP binding antibodies will be assessed using a radioimmunoassay that is validated according to internationally recognised guidelines.[19-23] Samples measured above the assay cut-point of antibody reactivity will be subject to a confirmation test, where the presence of anti-N8-GP antibodies will be confirmed by addition of excess of unlabelled N8-GP and cross-reactivity to rFVIII will be measured using excess of unlabelled rFVIII. Only samples positive in the confirmatory assay will

be characterised as anti-N8-GP or anti-rFVIII antibody positive. The analyses will take place at the end of the trial.

8.6.3 Anti-PEG antibodies

Anti-PEG antibodies will be measured at baseline and at end of treatment using a direct ELISA validated according to internationally recognised guidelines.[19-23] Samples measured above the assay cut-point of antibody reactivity will be subject to a confirmation test, where the presence of anti-PEG antibodies will be confirmed by addition of excess of unlabelled PEG. The analysis will take place at the end of the trial.

8.6.4 Anti-HCP antibodies

All patients at baseline and subsequently any patient who experiences an acute severe allergic/anaphylactic reaction (see Section 10.3.3 for definition) that cannot be assigned to anti-N8-GP antibodies will be assessed for anti-HCP antibodies. The blood sample for assessment of anti-HCP antibodies should be drawn within 4 weeks (and preferably 2-4 weeks) after the AE of acute severe allergic/anaphylactic reaction.

8.7 Diary

The patient/caregiver will be provided with a diary for recording of bleeding episodes and the home treatment hereof. All the treatments, administered at home (see section 8.8 and 8.1.1) must also be recorded in the diary. All bleeding episodes including the bleeding episodes that are experienced while at site must be recorded in the diary. At visit 1, the patient/caregiver will receive the first diary and they will be trained in the use by the investigator.

The diary is split into a bleed and a treatment diary. The diaries must be returned at every scheduled visit and new diaries will be handed out to the patient/caregiver. During trial site visits, the diaries must be reviewed together with the patient/caregiver and evaluate together with the patient/caregiver the correctness of the haemostatic efficacy for treatment of bleeds. The severity rating of the bleeding episode and the treatment type must be entered by the trial site staff, if necessary, into the diaries. Afterwards the diary data must be recorded in the eCRF by the investigator or the designee.

Patient diaries must be reviewed by the investigator at every scheduled visit to ensure that AEs, including any change in health and concomitant medication, are reported. Furthermore, the diaries must also be reviewed for accuracy, completeness and consistency with the requirements defined in this protocol, see section 6.4. This review must be documented in the patient's medical record.

Only the patient or caregiver is allowed to change entries in the diary except for the severity rating and treatment type if they are entered into the diary by the site.

If clarification of entries or discrepancies in the diary that are entered by the patient is needed, the patient must be questioned, and a conclusion made in the patient's medical record. Care must be taken not to bias the patient. A correction is done by both changing the entry in the paper diary and the entry in the eCRF.

8.8 Home treatment training

Home treatment training with injection of N8-GP (turoctocog alfa pegol) can start after injections of the first dose at the trial site, and should continue until the patient or caregiver is comfortable with the reconstitution and injection process. The training must be documented in the medical records.

A home treatment guide for the reconstitution and injection process must be handed-out to the patient or caregiver at every dispensing visit.

If the patient does not follow the planned dosing schedule, the investigator must retrain the patient and/or caregiver.

9 Statistical considerations

9.1 Statistical hypotheses

No confirmatory hypotheses are planned to be tested due to the low number of patients to be included in this trial.

9.2 Sample size determination

No formal sample size calculations have been performed. Based on meeting communication with CDE and with the supplement data from the global pivotal trial NN7088-3859 which also included Asian patients, a total number of 30 Chinese patients to complete this trial is considered sufficient to evaluate efficacy and safety in the Chinese population.

Fifteen (15) patients will participate in PK assessments sessions to ensure at least 12 patients with complete single-dose and steady-state PK profiles.

9.3 Populations for analyses

All patients exposed to N8-GP in this trial will be included in the full analysis set and the safety analysis set.

Exceptional outlier pharmacokinetic profiles and/or individual plasma FVIII activities may be excluded when analysing pharmacokinetic endpoints based on the FAS. The rules to exclude data points from analysis of pharmacokinetic endpoints are described in the statistical analysis plan (SAP), and the decision of data exclusion will be made during a review prior to database lock. Any excluded data points will be documented in the database lock minutes and also in the clinical trial report (CTR).

9.4 Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to first-patient-first visit (FPFV), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoint. There are no confirmatory secondary endpoints specified in this trial.

9.4.1 General considerations

Novo Nordisk will be responsible for the statistical analyses.

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

In general, all summaries and analyses will also be prepared by age subgroup (12-17 and 18-70 years of age).

9.4.2 Primary endpoint

Endpoint title	Time frame	Unit
Number of bleeding episodes	From start of treatment until visit 7	Count

The primary endpoint will be analysed by a Poisson regression model allowing for over-dispersion (using Pearson's chi-square divided by the degrees of freedom) with the logarithm of duration of actual prophylaxis treatment with N8-GP used as offset. Estimates of the annualised bleeding rate (ABR) will be provided with 95% confidence intervals.

Only the observed bleeding episodes will be counted and the offset will be the duration of actual prophylaxis treatment with N8-GP.

A sensitivity analysis based on negative binomial regression model with the logarithm of duration of actual prophylaxis treatment with N8-GP used as offset will also be performed.

Another sensitivity analysis will be performed imputing the number of bleeding episodes for patients that discontinue treatment. For patients prematurely discontinuing treatment, the number of bleeding episodes counting in the analysis will be imputed up to what they could be expected to have had if they had completed the trial on treatment. If e.g. a patient withdraws after 2 months with 3 bleeding episodes, but the patient should have been in the study for 6 months, then this patient will in the analysis count as having had 9 bleeding episodes in 6 months. This is similar to last observation carried forward (LOCF) and will avoid positive bias occurring from patients with many bleeding episodes withdrawing early. For patients withdrawing within 1 month this method is

considered to give too uncertain LOCF values, hence imputation will not be attempted for such patients. Instead only the observed bleeds and the observed duration will be used.

ABRs will be summarised in total, by cause of bleed, and by location of bleed (including ABR in baseline target joints).

Bleeding episodes in relation to surgery will not be included in the analysis.

9.4.3 Secondary endpoints

9.4.3.1 Secondary efficacy endpoints

Endpoint title	Time frame	Unit
Haemostatic effect of N8-GP when used for treatment of bleeding episodes, assessed on a four-point scale for haemostatic response (excellent, good, moderate and none) by counting excellent and good as success and moderate and none as failure.	From start of treatment until visit 7	Count
Consumption of N8-GP for treatment of bleeding episodes	From start of treatment until visit 7	IU/kg/bleed
Consumption of N8-GP for prophylaxis	From start of treatment until visit 7	IU/kg/year
FVIII trough activity during prophylaxis	From start of treatment (excluding the first exposure) until visit 7	IU/mL

Haemostatic effect of N8-GP

Haemostatic effect of N8-GP when used for treatment of bleeding episodes is assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and none). Excellent and good counts as success and moderate and none as failures. In addition, any bleeding episodes with missing response information will be counted as failures.

Specifically, this will be done by a logistic regression. The analysis will be performed by use of Proc Genmod in SAS. Correlation within patients will be taken into account using a Generalized Estimation Equations approach with a working correlation matrix with a compound symmetry structure.

Response as measured by the four point scale will also be summarised and listed.

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

The haemostatic effect will be summarised in total, by cause of bleed and by location of bleed (including haemostatic effect in target joints).

Haemostatic effect for bleeding episodes in relation to surgery will not be included in the analysis.

Consumption of N8-GP for treatment of bleeding episodes

The number of injections per bleed will be summarised and listed.

The number of IU/Kg per bleed will be summarised and listed.

Consumption of N8-GP for prophylaxis

The number of injections for prophylaxis will be summarised and listed.

The number of IU/Kg per month and per year will be summarised and listed.

FVIII trough activity during prophylaxis

The trough and recovery FVIII activity levels will be analysed by a mixed model on the log-transformed plasma FVIII activity with age group as fixed effect and patient as a random effect. The mean trough and recovery levels will be presented back-transformed to the natural scale together with the 95% confidence interval.

The following rules will be implemented for the analysis of trough and recovery levels:

- Pre-dose and post-dose values will be excluded if post-dose activity is ≤ pre-dose activity.
- Pre-dose and post-dose values taken more than ±2 days outside of dosing interval will be excluded.
- Pre-dose and post-dose values taken less than twice the prophylaxis treatment interval after last treatment of a bleeding episode will be excluded.
- Pre-dose and post-dose values taken within 2 weeks after surgery will be excluded.
- Pre-dose and post-dose values taken in relation to the first exposure will be excluded.
- FVIII activity measured in defrosted plasma samples will be excluded.

Furthermore, trough and recovery (30 minutes post-dose) levels measured at scheduled visits will be summarised and listed. Incremental recoveries will be calculated and presented in summary tables and plots.

9.4.3.2 Secondary safety endpoints

Endpoint title	Time frame	Unit
Incidence rate of confirmed FVIII inhibitors ≥0.6 BU	From start of treatment until visit 7	Rate
Number of adverse events (AEs)	From start of treatment until end of trial	Count
Number of serious adverse events (SAEs)	From start of treatment until end of trial	Count

Incidence Rate of Confirmed FVIII-inhibitors ≥0.6 BU

A patient is said to have FVIII-inhibitors if two consecutive tests, preferably within 2 weeks, are positive (≥0.6 BU). The rate of 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 inhibitor rate the nominator will include all patients with neutralising antibodies while the denominator will include all patients with a minimum of 50 exposures plus any patients with less than 50 exposures but with neutralising inhibitors.

Adverse Events (AEs) and Serious Adverse Events (SAEs) reported during the trial

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

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

9.4.3.3 Secondary pharmacokinetic endpoints

Table 9-1 Definition and calculation of PK Parameters

Title	Time frame	Unit	Details
Incremental Recovery	30 min ± 5 min post-injection at visit 2a and visit 7	(IU/mL)/(IU/kg)	The incremental recovery is calculated by subtracting the FVIII activity (IU/mL) measured in plasma at time 0 from that measured at time 30 min after dosing and dividing this difference by the dose injected at time 0 expressed as IU/kg BW
FVIII activity 30 min post-injection (C_{30min})	30 min ± 5 min post-injection at visit 2a and visit 7	IU/mL	The FVIII activity recorded 30 min after end of injection. Expected to be the maximum FVIII activity observed.
FVIII trough activity 96 h post-injection (C_{96h})	96 h ± 8 h post-injection at visit 2a and visit 7	IU/mL	The FVIII activity recorded immediately before next dose is given. Expected to be the minimum FVIII activity observed.
$AUC_{(0\text{-}inf)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	Area under the activity versus time profile from time zero to infinity. Measure of total plasma exposure. $AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_{(t)} / \lambda_z$, where $C_{(t)}$ is the last measurable activity.
$AUC_{(0\text{-}t)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	Area under the plasma activity versus time profile from time zero to the last measurable activity. Measure of plasma exposure in the time interval 0 to last measurable activity. $AUC_{(0\text{-}t)}$ is calculated using the linear trapezoidal method from time 0 to the time for the last measurable activity. The activity at time 0 will be estimated by log-linear back extrapolation of the two initial post-administration activities. If the second value is not lower than the first value, the concentration at time 0 will be defined as the highest of these two.
$AUC_{(0\text{-}96h)}$	0−96 h post-injection at visit 2a and visit 7	h*(IU/mL)	$AUC_{(0\text{-}96h)}$ is calculated using the linear trapezoidal activities. If FVIII activities are not available up to 96 hours post-dose, the area under the missing terminal part of the curve will be

Title	Time frame	Unit	Details
			determined by interpolation or extrapolation using a similar principle as for $AUC_{(0\text{-inf})}$, where the terminal elimination rate constant, λ_z, is used given that there are sufficient measurements for the determination of the terminal elimination rate constant.
Accumulation ratio	0−96 h post-injection at visit 7		Accumulation ratio is calculated as $AUC_{(0\text{-}96h)}$ at steady state/$AUC_{(0\text{-}96h)}$ at single dose.
Terminal half-life ($t_{½}$)	0−96 h post-injection at visit 2a and visit 7	h	$t½ = \ln(2) / \lambda z$, where λz 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.
Clearance (CL)	0−96 h post-injection at visit 2a and visit 7	mL/h/kg	CL= Dose / AUC. Using $AUC_{(0\text{-inf})}$ for single dose and $AUC_{(0\text{-}96h)}$ for steady state.
Vz	0−96 h post-injection at visit 2a and visit 7	mL/kg	Apparent volume of distribution based on the terminal phase. $Vz = CL/\lambda z$
Vss	0−96 h post-injection at visit 7	mL/kg	Apparent volume of distribution at steady-state. Vss = CL*MRT
%extrap	0−96 h post-injection at visit 2a and visit 7	%	Percentage of $AUC_{(0\text{-inf})}$ determined by extrapolation. $AUC_{(t\text{-inf})}/(AUC_{(0\text{-inf})})$
MRT	0−96 h post-injection at visit 2a and visit 7	h	Mean Residence Time. MRT = $AUMC/AUC_{(0\text{-inf})}$, where AUMC is the area under the first moment curve, i.e. the area under the curve $t{\cdot}C_{(t)}$, calculated with the same method as $AUC_{(0\text{-inf})}$ (linear trapezoidal method + extrapolated area)
λz	0−96 h post-injection at visit 2a and visit 7	1/h	Terminal elimination rate constant. The terminal elimination rate constant will be estimated using linear regression on the terminal part of the log(activity) versus time profile

Single dose PK will be based on the PK session at visit 2a, and steady state PK will be based on the PK session at visit 7.

The PK parameters will be calculated using plasma FVIII activity obtained from the chromogenic assay. The PK parameters will be derived according to a non-compartmental method, as described in Table 9-1. The actual time points will be used in the calculations.

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

Specifically, which data points and profiles that will be excluded will be defined prior to database lock. It should exclude profiles with pre-dosing activity > 5% (possibly indicating inadequate wash out) at visit 2a and profiles that are not indicative of a normal intravenously injection (i.e. clearly increasing plasma FVIII activity initially). If a patient is treated with an additional dose during the PK session, the plasma FVIII activities after the occurrence will then be excluded. Furthermore, if the profile shows indications of an additional dose (e.g. clearly increased plasma FVIII activity), the plasma FVIII activities after the occurrence will then also be excluded.

All pharmacokinetic endpoints (except MRT, Vss, Vz, percentage of $AUC_{(0\text{-inf})}$ determined by extrapolation and terminal elimination rate constant) will be analysed using mixed effects model on log-transformed parameters including patient as random effect. Estimates of each endpoint with 95% confidence intervals will be provided back-transformed to the natural scale.

Individual and mean PK profiles will be presented graphically.

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

9.4.4 Other safety analyses

Changes in vital signs (blood pressures, pulse, temperature, respiratory rate)

These endpoints will be presented in summary tables and plots.

Other safety parameters

All additional safety parameters such as laboratory parameters, vital signs, ECG and physical examinations will be presented in summary tables and plots.

9.4.5 Other analyses

Surgery

In relation to surgery the following will be recorded:

- Haemostatic effect evaluated on the four-point scale (excellent, good, moderate and none) and assessed by the investigator/surgeon on the day of surgery (Day 1) and on the last day in the post-operative period the patient is at the trial/surgery site.
- Loss of blood and requirements for transfusion on the day of surgery (Day 1) and during the post-operative period Days 2-7 or until the last day the patient is at the trial/surgery site, whatever comes first.

All records will be summarised and listed.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[24] and applicable ICH Good Clinical Practice (GCP) Guideline.[25]
- Any trial procedure conducted in China mainland should comply with "Regulations on management of Human Genetic Resources of People's Republic of China" and relative guideline.
  - Applicable laws and regulations.
  - The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
  - Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
  - Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial patients.
  - Before a site is allowed to start screening patients, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities.
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.
- ensuring submission of the CTR synopsis to the IRB/IEC.
- reporting any potential serious breaches to the sponsor immediately after discovery.

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the patient and/or the patient's caregiver and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.
- Patients must be informed that their participation is voluntary.
- Patients must be informed about their privacy rights.
- Patients or their caregiver will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines,[25] Declaration of Helsinki[24] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Patients and/or their caregiver must be re-consented to the most current version of the informed consent form*(s)* during their participation in the trial.
- A copy of the informed consent form(s) must be provided to the patient or the patient's caregiver.

10.1.4 Information to patients during trial

The site will be offered a communication package for the patient during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the patients. The written information will be translated and adjusted to local requirements and distributed to the patient at the discretion of the investigator. The patient may receive a "thank you for your participation letter" after completion of the trial. Further, the patient may receive other written information during the trial.

All written information to patients must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

- Patients will be assigned a 6-digit unique identifier, a patient number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the patient are transferred to Novo Nordisk.
- The patient and any biological material obtained from the patient will be identified by patient number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients as required by local, regional and national requirements.
- The patient must be informed about his/her privacy rights, including that his/her personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by auditors or other authorised staff appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial-independent *ad hoc* group will be established in order to maintain the blinding of the trial staff.

10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at 'chinadrugtrials.org.cn', 'clinicaltrials.gov', www.clinicaltrialsregister.eu, 'novonordisk-trials.com'. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[26], the Food and Drug Administration Amendment Act (FDAAA)[27], European Commission Requirements[28-30] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last patient first treatment + 28 weeks, corresponding to visit 7 (end of treatment visit). If the last patient is withdrawn early (i.e., withdraws informed consent), the PCD is considered the date when this last patient would have completed visit 7. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All patient data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
    - Safety information forms
    - Technical complaint forms
    - AE forms
- Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.
- The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site staff are accurate, complete and verifiable from source documents; that the safety and rights of patients are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the patient's medical records and other source data, e.g. the diaries, to ensure consistency and/or identify omissions compared to the eCRF.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

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

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation other than the eCRF.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the site staff making the entry.

- All data entered in the eCRF must be verifiable in source documentation other than the eCRF.
- The original of the completed diaries must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on a paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify patient's medical history in source documents, such as patient's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.
- Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.
- Site specific data should only be stored at site.
- Long term storage of Chinese Patients' Trial Data is not allowed in other entities.

10.1.11 Trial and site closure

Novo Nordisk reserves the right to close the site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the patients promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines.
- inadequate recruitment of patients by the investigator.
- discontinuation of further trial product development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients.

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

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the patient identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

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

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

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

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

10.1.13 Indemnity statement

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

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

Novo Nordisk accepts liability in accordance with Chinese law and regulations.

10.1.14 Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as 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 investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[31]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

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

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

For a multicentre 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. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

10.1.14.4 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research patients' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

The assessments detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory (except for urinalysis; see below).

At visits where it is not possible to perform the required blood sampling, re-scheduling of the visit within the visit (see Section 1.2) should be done. The timing of sampling in relation to trial drug administration should always be followed.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.

The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

Urinalysis will be performed locally with sticks provided by the central laboratory. Results of urinalysis should be recorded in the eCRF. Results from the urinalysis other than those listed in Table 10-2 should not be reported to Novo Nordisk. Clinically significant findings must be recorded as concomitant illness at screening and as AEs at the following visits if it is a new finding or a change relative to a previous visit.

Laboratory samples will be destroyed no later than at finalisation of the CTR.

The inhibitor samples will be stored at a central laboratory after end of trial and until marketing authorisation approval or until the research project terminates, after which they will be destroyed.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	*Parameters*
FVIII activity	• Chromogenic assay using PSS as calibrator

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	*Parameters*
Antibody assessments	• FVIII inhibitors • Anti-N8-GP • Anti-PEG • Anti-HCP
Haematology	• Erythrocytes • Haemoglobin • Leucocytes • Thrombocytes
Biochemistry	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Bilirubin, total • C-reactive protein (CRP) • Creatinine • Urea
Serology	• Hepatitis B surface antigen (HBsAg) • Hepatitis C virus antibody • HIV 1+2 screen (if positive test, then a confirmatory test is performed. If the confirmatory test is also positive, then assessment of viral load is performed) • *CD4+ T cell count (only at screening)*
Coagulation parameters	• aPTT • INR • PT • Lupus anticoagulant
Urinalysis (dip stick)	• pH • Protein • Glucose • Bilirubin • Blood
Other tests	• eGFR calculated by the central laboratory based on the creatinine value using the MDRD or the Schwartz equation depending on the age of the patient
Notes: Details of required actions for increased liver parameters are given in Section 10.3 (Hy's Law).	

10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

10.3.1 Definition of AE

AE definition

An AE is any untoward medical occurrence in a clinical trial patient that is temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events meeting the AE definition

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent

A "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE. Also, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT meeting the AE definition

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is an AE that fulfils at least one of the following criteria:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' 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.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • Hospitalisation signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment (e.g. elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. Note: • Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. • Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Important medical event:
• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
• The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
  • Suspicion of transmission of infectious agents via the IMP
  • Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law)

10.3.3 Description of AESIs and AEs requiring additional data collection

Description of AESIs and AEs requiring additional data collection (on specific event form)

AESIs

FVIII inhibitor development

CNS-related AEs
CNS-related adverse events, including but not limited to any learning and behavioural deficits.

Renal or hepatic AEs
Renal or hepatic adverse events including new onset of renal or hepatic disorder or impairment.

Thromboembolic events
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) are defined as follows:

- **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 (e.g. angioplasty)

2. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria a and b below are fulfilled):
   a. Increase in troponin T above the "diagnostic" limit: i.e. > 0.03 µg/L
   b. Patients with:
      - ST-segment elevation: New ST-segment elevation at the J point in two or more contiguous leads with the cut-off points >= 0.2mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)
      - No ST-segment elevation: ST-segment depression and or T-wave inversion in two or more contiguous leads >= 0.1 mV

- **Definition of pulmonary embolism**

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

1. Positive findings in ventilation/perfusion scan
2. Positive findings in a spiral(helical) computed tomography or angiography
3. Positive findings in a magnetic resonance imaging
4. Positive findings in a pulmonary angiography

- **Definition of cerebral thrombosis/infarction**

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

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

- **Deep vein thrombosis**

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

- **Definition of other clinically significant thromboembolic events**

Sign or suspicion of clinically significant thromboembolic event, e.g. visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis.

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

- **Peripheral artery occlusion**

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

Adverse events requiring additional data collection

Medication error

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the patient, such as:

- administration of wrong drug.
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous.
- accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial

patient were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g. overdose to maximise effect).
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm).

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence, this must be reported on an additional AE form.

Hypersensitivity

Hypersensitivity type reactions, incl. anaphylactic reactions.

Clinical criteria for diagnosing anaphylaxis

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):

- Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue- uvula)
- Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
- Reduced Blood pressure or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the eCRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event (see Section 8.3 for details).
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all patient identifiers, with the

exception of the patient number, will be redacted on the copies of the source documents before submission to Novo Nordisk.

- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess severity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with a SAE. Both AEs and SAEs can be assessed as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.
- Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:
  - Probable - Good reason and sufficient documentation to assume a causal relationship.
  - Possible - A causal relationship is conceivable and cannot be dismissed.
  - Unlikely - The event is most likely related to aetiology other than the IMP.
- Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator should use the investigator's brochure[17] for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**
- The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome
The investigator will select the most appropriate outcome: • **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented • **Recovering/resolving:** The condition is improving, and the patient is expected to recover from the event. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE). • Note: For SAEs, this term is only applicable if the patient has completed the follow-up period and is expected to recover. • **Recovered/resolved with sequelae:** The patient has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE. • **Not recovered/not resolved:** The condition of the patient has not improved, and the symptoms are unchanged, or the outcome is not known. Note: This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE). • **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he died should be assessed as “recovered/resolved”, “recovering/resolving”, “recovered/resolved with sequelae” or “not recovered/not resolved”. An AE with a fatal outcome must be reported as an SAE. • **Unknown:** This term is only applicable if the patient is lost to follow-up.

Follow-up of AE and SAE
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the eCRF.

10.3.5 Reporting of SAEs

SAE reporting via eCRF
• Relevant forms (AE and safety information form) must be completed in the eCRF. • For reporting and sign-off timelines, see Figure 10-1. • If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below). • The site will enter the SAE data into the eCRF as soon as it becomes available. • After the trial is completed, the trial database will be locked, and the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after eCRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

AE and SAE reporting via paper CRF
• Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5. • For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in Figure 10-1): • AE form within 24 hours • Safety information form within 5 calendar days • Both forms must be signed within 7 calendar days after first knowledge by the investigator. • The specific event form for AEs requiring additional data collection within 14 calendar days

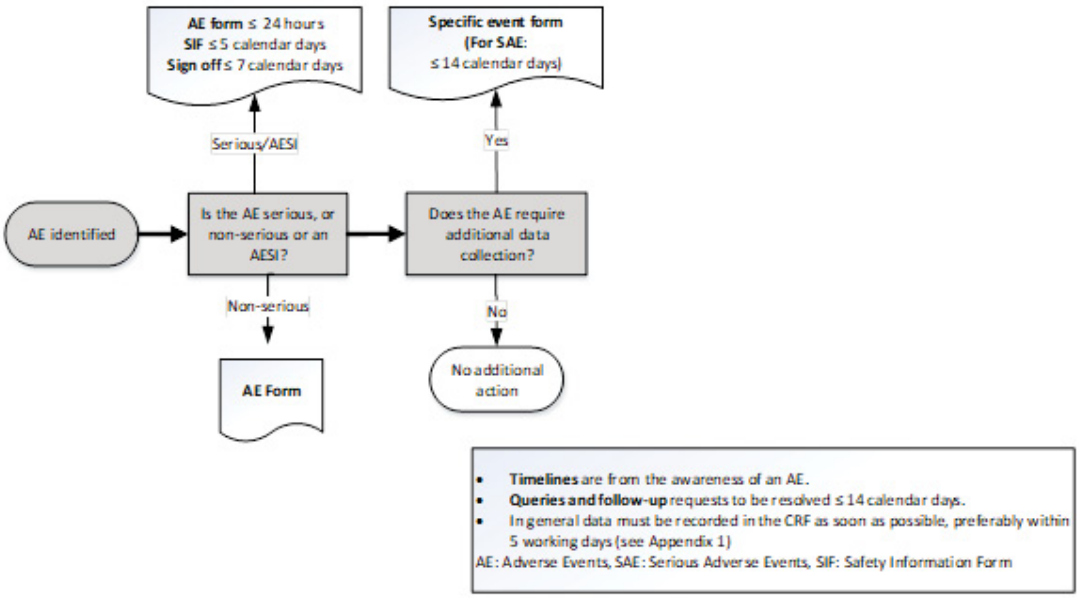

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines

Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Collection of pregnancy information

Male patients with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while male patient is participating in this trial. The pregnancy should be documented in the medical record of the male patient. Only in case of abnormal outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) of the pregnancy and in case the male patient receives IMP, should the investigator inform Novo Nordisk.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Novo Nordisk within 14 calendar days of learning of the abnormal outcome of the partner's pregnancy (see Figure 10-2). Information on the status of the mother and child will be included.
- Generally, follow-up will be 1 month following the delivery date.

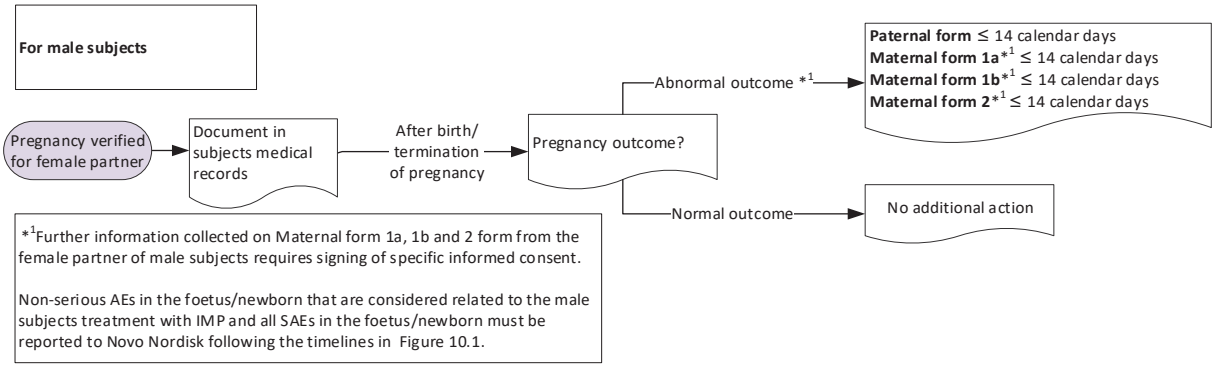

Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy

10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.5.1 Definition of technical complaint

Technical complaint definition
• 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:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- Problems with packaging material including labelling

Time period for detecting technical complaints
All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.5.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk
Contact details for Customer Complaint Center, please refer to Attachment I. Technical complaints must be reported on a separate technical complaint form: 1. One technical complaint form must be completed for each affected DUN. 2. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the eCRF within: • 24 hours if related to an SAE • 5 days calendar for all other technical complaints If the eCRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to patient, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.6 Appendix 6: Neurological examination checklist

Unless otherwise stated, each aspect of the neurological examination will be categorised into normal, abnormal or not evaluated.

General
Level of consciousness

Cranial Nerves
Pupillary reaction to light
Visual fields
Visual acuity (normal, corrected, abnormal, not evaluated)
Eye movements
Facial sensation
Facial movement (smile)
Hearing (finger rub)
Palate/gag (say “ahhh”)
Tongue movement
Trapezius (shoulder shrug)

Tone
Upper Extremity Left
Upper Extremity Right
Lower Extremity Left
Lower Extremity Right

Strength
Upper Extremity Left
Upper Extremity Right
Lower Extremity Left
Lower Extremity Right

Reflexes
Biceps Left
Biceps Right
Triceps Left
Triceps Right
Knee Left
Knee Right
Ankle Left
Ankle Right

Sensory
Cold
Pin prick
Light touch
Proprioception (toe up/down)

Gait
Gait walking
Gait running
Gait on heels
Gait on toes
Tandem (toe/heel walk)
Stand on one leg (right)
Stand on one leg (left)
Hop on one foot (right)
Hop on one foot (left)
Rhomberg sign (normal [absent], abnormal [present], not applicable)

Coordination and Fine Motor
Finger-to-nose (right)
Finger-to-nose (left)
Rapid index finger tap (right)
Rapid index finger tap (left)
Rapid finger movement (right)
Rapid finger movement (left)

Adapted from Paediatric Stroke Outcome Measure (PSOM)[32]

10.7 Appendix 12: Country-specific requirements

The following items are applicable for China.

Item	Section	Section title	Local requirement
1	5.1 and 5.2	Inclusion/Exclusion criteria	The criteria will be assessed at the investigator's discretion unless otherwise stated.
2	10.1	Appendix 1: Regulatory, ethical, and trial oversight considerations	Any trial procedure conducted in China mainland should comply with“Regulations on management of Human Genetic Resources of People’s Republic of China” and relative guideline. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm
3	10.1.10	Retention of clinical trial documentation	Site specific data should only be stored at site. Long term storage of Chinese Patients’ Trial Data is not allowed in other entities.
4	10.5	Appendix 12: Country-specific requirements	The samples which are tested at central lab will be destroyed as biological waste according to local regulation and lab manual. The laboratory samples for Chinese patients will be destroyed no later than the finalization of the clinical trial report, or according to local regulatory requirement.

10.8 Appendix 13: Abbreviations

ABR	annualised bleeding rate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CRF	case report form
CTR	clinical trial report
DFU	directions for use
DMC	data monitoring committee
DRE	disease related event
DUN	dispensing unit number
ECG	electrocardiogram
eCRF	electronic case report form
ED	exposure day
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
GCP	Good Clinical Practice
HCP	host cell protein
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
i.v.	intravenous(ly)
IWRS	interactive web response system
LAR	legally acceptable representative (also referred to as ‘caregiver’)
LOCF	last observation carried forward

LPLV	last patient last visit
MDRD	Modification of Diet in Renal Disease
MIDF	monitor-initiated discrepancy form
NIMP	non-investigational medical product
PCD	primary completion date
PEG	polyethylene glycol
PTP	previously treated patient
rFVIII	recombinant factor VIII
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent AE
TMM	trial materials manual
WFH	World Federation of Hemophilia
WOCBP	woman of child bearing potential

10.9 Appendix 14: Protocol amendment history

The Protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 2.0 (28 Sep 2020)

The overall rationale for preparing the protocol version 2.0 was to correct inconsistencies and editorial errors observed.

Section # and name	Description of change	Brief rationale
Synopsis section 1.1 and Section 5.2 Exclusion criteria	Exclusion criterion 7 updated	The criterion updated for more clarity.
Section 1.2 Flow chart and Table 1-1	Addition of Height, weight and BMI to the flow chart. Deletion of drug dispensing at visit 7 and other minor updates	Added for clear instruction on assessments and duplicate coagulation parameter assessment removed and other typographical errors corrected
Section 4.1.1 Treatment of patients Section 8.1.1.1 Definition of severity of bleeding episodes Section 8.5.1 visit 2a for patients undergoing PK assessments. Section 8.5.3 visit 7 for patients undergoing PK assessments Section 8.7 Diary Section 8.8 Home treatment training Section 10.17 Dissemination of clinical trial data	Minor updates	Typo corrected and minor information added
Section 6.1 Treatments administered	Some text deleted	Text deleted to align with trial material manual
Section 6.3 Measures to minimise bias: Randomisation and blinding	Some text deleted	Section updated to reflect the actual scenario in the trial.
Section 6.4.1 In-use time	New section added	Added to highlight importance of in-use time of the trial product

Section # and name	Description of change	Brief rationale
Section 7.1 Discontinuation of trial treatment	Errors corrected in this section	Section updated and errors corrected.
Section 7.2 Patient withdrawal from the trial	Text corrected	Text aligned with section 7.1 and duplicate text removed
Section 8.2.1 physical examination	Additional information on Height, Weight and BMI assessments added	Information was missed previously
Section 8.2.3 Clinical safety laboratory assessments	Duplicate text deleted	Duplicate text deleted as the text is already available in appendix 2.
Section 8.6.1 FVIII inhibitors	Text added with information about inhibitor liability and some text corrected	Text added for more clarity
Section 10.2, Appendix 2	Blood volume in table 10.1 and 10.2 corrected and other minor updates	Information corrected
Section 10.3.3 Description of AESI and AEs requiring additional data collection	Definition of anaphylactic reaction updated	Missing text added
Section 10.3.5 Reporting of SAEs	Figure 10.1 updated with missing timelines	Typo corrected

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16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

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

Content: Global key staff and Country key staff.