# Cover Page for Protocol

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

# Protocol

**Protocol title: A multi-centre, open-label trial evaluating efficacy, safety and pharmacokinetics of nonacog beta pegol when used for treatment and prophylaxis of bleeding episodes in Chinese patients with haemophilia B**

**Substance name: Nonacog beta pegol**

**Universal Trial Number: U1111-1260-0438**

**EudraCT Number: 2021-004947-25**

**Trial phase: 3b**

In the following, Novo Nordisk A/S and its affiliates will be stated as "Novo Nordisk".

# Protocol amendment summary of changes table

| DOCUMENT HISTORY | |
|---|---|
| **Document version** | **Date** |
| Protocol version 2.0 | 22 September 2021 |
| Original Protocol | 21 January 2021 |

**Protocol version 2.0 (22 September 2021)**

Protocol version 2.0, dated 22 Sep 2021, has been prepared based on requirements from the Center for Drug Evaluation (CDE), China.

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Flowchart<br><br>Section 8.2.4 Electrocardiograms | Updated ECG evaluation to include Visit 10 (end of treatment) and Visit 10A (discontinuation of treatment). | In order to accommodate a request from China Center for Drug Evaluation (CDE). |
| Synopsis<br><br>Flowchart<br><br>Table 1-2<br><br>Section 8.1.3 Surgery<br><br>Section 8.6.2 FIX inhibitors | Added information that guidance is included and where.<br><br>Added a flowchart outlining the assessments and sampling relevant for patients undergoing surgery during the trial.<br><br>Specified in Section 8.1.3 what data will be recorded as well as timing of collection of samples for FIX activity and FIX inhibitors.<br><br>Update of text about timing of collection of blood samples for FIX inhibitors.<br><br>Update of definition of low- and high responders, respectively in accordance with current haemophilia guidelines. | In order to accommodate a request from China Center for Drug Evaluation (CDE). |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 9.4.5 Other analyses | Wording about analyses is updated. | |
| Flowchart<br><br>Appendix 2 Clinical laboratory tests | Added PEG plasma concentration assessment to be performed at baseline as well as visits 5, 7, 8, 9, 10 and 10A for Arm B. | In order to accommodate a request from China Center for Drug Evaluation (CDE). |
| Flowchart<br><br>Section 8.6.1 Anti-nonacog beta pegol and anti-PEG antibodies<br><br>Appendix 2 Clinical laboratory tests | Clarification that anti-PEG antibodies will be assessed. | In order to accommodate a request from China Center for Drug Evaluation (CDE). |
| Flowchart<br><br>Section 8.6.3 Anti-HCP antibodies<br><br>Appendix 2 Clinical laboratory tests | Added anti-HCP antibody laboratory assessments to be performed at Visit 2, Visit 10 and Visit 10A. | In order to accommodate a request from China Center for Drug Evaluation (CDE) and to align with previous trials. |
| Section 2.4.1 Risk assessment, Identified risks | Information about 'Allergic/hypersensitivity reactions' and 'Anaphylactic reactions' has been combined. | There is no separate identified risk for anaphylactic reactions related to nonacog beta pegol treatment and therefore information is combined with allergy and hypersensitivity reactions. |
| Section 2.4.1 Risk assessment, potential risks | Information about PEG accumulation has been updated. | Text updated to clarify and to align with text in Periodic Safety Update Report (PSUR). |
| Section 6.3 Measures to minimise bias: Randomisation and blinding | Specified that subject preference is also included in the evaluation of what treatment arm the subject will be allocated to. | Corrects an omission in protocol version 1.0. |

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 7.1 Discontinuation of trial product | Update of Discontinuation criteria number 5. | To specify that only severe allergy/anaphylaxis should result in discontinuation. |
| Section 8.2.2.1 Neurological examination<br><br>Section 9.4.4 Other safety analysis<br><br>Appendix 6: Neurological examination checklist | Update to neurological examination criteria, performance and analysis. | Addition of missed categories for neurological examination and correction of error in protocol version 1.0. |
| Appendix 2 Clinical laboratory tests | Added that urinalysis will be performed locally, and relevant results will be recorded in the eCRF. | Corrects an omission in protocol version 1.0. |

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# 1 Protocol summary

## 1.1 Synopsis

**Rationale:**

To investigate the efficacy, safety and pharmacokinetics of nonacog beta pegol used for treatment of bleeding episodes and for prophylaxis in Chinese patients with moderate to severe haemophilia B (FIX activity ≤2%) in order to enable a comparison of efficacy, safety and pharmacokinetic data from the current trial in Chinese patients with data from the global pivotal phase 3a trial with nonacog beta pegol (Trial NN7999-3747).

**Objectives and endpoints:**

**Primary objective**

- To evaluate the clinical efficacy of nonacog beta pegol in haemostasis (treatment of bleeding episodes during on-demand and prophylaxis [PPX]) in Chinese patients aged 12-70 years with moderate to severe haemophilia B

**Secondary objectives**

In Chinese patients aged 12-70 years with moderate to severe haemophilia B:

- To evaluate the clinical efficacy of nonacog beta pegol in PPX treatment (number of treated bleeding episodes during PPX)
- To evaluate the consumption of nonacog beta pegol
- To evaluate the immunogenicity of nonacog beta pegol
- To evaluate the general safety of nonacog beta pegol
- To evaluate the pharmacokinetic properties of nonacog beta pegol

**Primary endpoint**

| Endpoint title | Time frame | Unit |
|---|---|---|
| Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes during on-demand and PPX | From start of treatment (week 0) until end of treatment (up to week 50) | Count |

## Secondary efficacy endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of treated bleeding episodes during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | Count |
| Consumption of nonacog beta pegol for treatment of bleeding episodes | From start of treatment (week 0) until end of treatment (up to week 50) | IU/kg per bleed |
| Consumption of nonacog beta pegol for PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/kg per year |
| FIX trough levels during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/mL |

## Secondary safety endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of patients with inhibitory antibodies against FIX defined as titre ≥0.6 Bethesda units (BU) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of adverse events (AEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of serious adverse events (SAEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |

## Secondary pharmacokinetic endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Incremental recovery (IR) (Arm B only) | Single-dose: 30±10 minutes post-injection at week 0<br>Steady-state: 30±10 minutes post-injection at week 12 | (IU/mL)/(IU/kg) |
| Terminal half-life ($t_{½}$) (Arm B only) | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h |
| Clearance (CL) (Arm B only) | Single-dose: 0-168 hours post injection at week 0<br>Steady-state: 0-168 hours post injection at week 12 | mL/h/kg |
| Area under the curve (AUC) (Arm B only) | Single-dose: 0-168 hours post injection at week 0<br>Steady-state: 0-168 hours post injection at week 12 | h·IU/mL |

**Overall design:**

This is a multi-centre, open-label phase 3b trial evaluating the clinical efficacy, safety (including immunogenicity) and pharmacokinetics of nonacog beta pegol during on-demand and for prophylactic treatment in Chinese patients aged 12-70 years with haemophilia B and a FIX activity of ≤2%.

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 moderate to severe congenital haemophilia B with a FIX activity ≤2% according to medical records.
3. Aged 12-70 years (both inclusive) at the time of signing informed consent.
4. History of at least 100 EDs to products containing FIX.[1]
5. Patients currently on prophylaxis or patients currently treated on-demand with at least 6 bleeding episodes during the last 12 months or at least 3 bleeding episodes during the last 6 months.
6. The patient, legally authorised representative (LAR) and/or caregiver are capable of assessing a bleeding episode, keeping a diary, performing home treatment of bleeding episodes and otherwise following the trial procedures.

[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 FIX inhibitors based on existing medical records, laboratory report reviews and patient and LAR interviews.
5. Current FIX inhibitors ≥0.6 BU.
6. 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 the medical records within the last 6 months, then the test must be performed at the screening visit.
7. Congenital or acquired coagulation disorder other than haemophilia B.
8. Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records).
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.

10. Renal impairment defined as estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 $m^2$ for serum creatinine measured at screening.
11. Any disorder, except for conditions associated with haemophilia B, which in the investigator's opinion might jeopardise the patient's safety or compliance with the protocol.
12. Platelet count <$50\times10^9$/L at screening.
13. Immune modulating or chemotherapeutic medication.
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.

The trial will have two arms: Arm A (on-demand/PPX treatment arm) and Arm B (PPX treatment arm including single-dose and steady-state pharmacokinetic assessment). Patients are screened at Visit 1 and baseline assessments are performed at Visit 2, which will take place approximately 2 weeks after Visit 1.

In Arm A, starting at Visit 2 patients will undergo a 28-week on-demand treatment period (including Visits 3-7 at 4, 8, 12, 20 and 28 weeks). This is followed by a PPX period until 30 EDs in trial including treatment of bleeds during the on-demand period as well as scheduled once-weekly PPX doses and treatment of breakthrough bleeds during the PPX period (including Visits 8 and 9 at 36 and 44 weeks).

In Arm B, starting with the first dose of trial product at Visit 2, patients will undergo a PPX treatment period lasting until 50 EDs to nonacog beta pegol (including treatment of breakthrough bleeds) and 50 weeks in trial (including Visits 3-9 at 4, 8, 12, 20, 28, 36 and 44 weeks). One single-dose and one steady-state pharmacokinetic profile (168 hours) will be obtained in patients in Arm B. The single-dose pharmacokinetic profile will start at first dosing (Visit 2), while the steady-state pharmacokinetic profile will be obtained at Visit 5.

Both treatment arms will end with an end of treatment visit (Visit 10), and an end of trial (follow-up) visit (Visit 11) is placed 30 days after the end of treatment visit.

Major and minor surgery is allowed in the trial.

**Number of patients:**

A total of 30 patients will be included in the trial (15 in each treatment arm). A minimum of 12 patients in each of the two treatment arms must complete the trial.

**Treatment groups and duration:**

The following trial product will be supplied by Novo Nordisk:

- nonacog beta pegol (N9-GP) 2000 IU/vial as a sterile, freeze-dried powder in a single-use vial of 2000 IU/vial to be reconstituted with 4 mL histidine solvent provided in a pre-filled syringe for i.v. injection.

During PPX treatment, one single bolus dose of 40 IU/kg nonacog beta pegol will be administered i.v. once weekly.

Bleeding episodes will be treated with i.v. injection of 40 IU/kg nonacog beta pegol (mild or moderate bleeds) or 80 IU/kg nonacog beta pegol (severe bleeds). Additional doses of 40 IU/kg can be given if there is no observed effect of the first dose.

Patients undergoing surgical procedures will receive trial product as bleeding preventive treatment according to standard practice at the clinical site and/or at the investigator's discretion. Guidance on assessments and dosing is included in a separate flowchart and in text sections.

The duration of the trial for each individual patient will be up to 64 weeks, i.e. 2 weeks screening period, up to 58 weeks treatment period (only applicable in Arm A in case a patient has no or few bleeds during the trial) and 30 days follow-up period.

**Data monitoring committee:**

No.

## 1.2 Flowchart

| Procedure | Protocol section | Screening | Baseline | Treatment period | | | | | | | End of treatment | Discontinuation of treatment | End of trial (follow-up) | Surgery[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V1 | V2 | V3 | V4 | V5 | V6 | V7[a] | V8[b] | V9[b] | V10 | V10A | V11 | |
| Timing of visit | | -2 weeks | 0 | 4 weeks | 8 weeks | 12 weeks | 20 weeks | 28 weeks | 36 weeks | 44 weeks | 50 weeks | | 30 days | |
| Visit window | | -7 days | | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | +56 days[c] | | +5 days | |
| Informed consent and demography | 10.1.3 | X | | | | | | | | | | | | |
| Informed consent obtained date | | X | | | | | | | | | | | | |
| Legal or authorised representative | | X | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | |
| Eligibility criteria | 5.1<br>5.2 | X | X | | | | | | | | | | | |
| Medical history/concomitant illness | 8.2 | X | X | | | | | | | | | | | |
| Details of haemophilia | | X | | | | | | | | | | | | |
| Haemophilia treatment and bleed history | | X | | | | | | | | | | | | |
| Concomitant medication | 6.5 | X | X | X | X | X | X | X | X | X | X | X | | X |
| Body measurements | 8.2.2 | X | X | | | X | | X | | | X | X | | |
| Body weight | | X | X | | | X | | X | | | X | X | | |
| Height | | X | | | | | | X[d] | | | X[d] | | | |
| Body mass index | | X | | | | | | | | | | | | |
| Vital signs | 8.2.3 | X | X | | | X | | X | | | X | X | | |

| Procedure | Protocol section | Screening | Baseline | Treatment period | | | | | | | End of treatment | Discontinuation of treatment | End of trial (follow-up) | Surgery[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V1 | V2 | V3 | V4 | V5 | V6 | V7[a] | V8[b] | V9[b] | V10 | V10A | V11 | |
| Timing of visit | | -2 weeks | 0 | 4 weeks | 8 weeks | 12 weeks | 20 weeks | 28 weeks | 36 weeks | 44 weeks | 50 weeks | | 30 days | |
| Visit window | | -7 days | | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | +56 days[c] | | +5 days | |
| Physical examination | 8.2.2 | X | X | | | X | | X | | | X | X | | |
| ECG | 8.2.4 | X | | | | | | | | | X | X | | |
| Neurological examination | 8.2.2.1 | X | X | | | X | | X | | | X | X | | |
| Target joint assessment | 8.2.2 | X | | | | | | | | | | | | |
| Discontinuation criteria | 7.1 | | X | X | X | X | X | X | X | X | | | | X |
| Adverse events | 8.3 | | | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events requiring additional data | 8.3 | | | X | X | X | X | X | X | X | X | X | X | X |
| Medication error, misuse and abuse | 8.3 | | | X | X | X | X | X | X | X | X | | X | X |
| Technical complaint | 8.3.8 | | | X | X | X | X | X | X | X | X | | X | X |
| Bleeding episode | 8.1.1 | | X[e] | X | X | X | X | X | X | X | X | X | | X |
| Laboratory assessments | 8.2.5 App. 2 | X | X | X | X | X | X | X | X | X | X | X | | X |
| Factor IX activity[f] | 8.1.2 8.5 | | X | X | X | X | X | X | X | X | X | X | | X |
| Anti-N9-GP antibodies/Anti-PEG antibodies | 8.6.1 | X | X | X | X | X | X | X | X | X | X | X | | |
| FIX inhibitor analysis | 8.6.2 | X | X | X | X | X | X | X | X | X | X | X | | X |

| Procedure | Protocol section | Screening | Baseline | Treatment period | | | | | | | End of treatment | Discontinuation of treatment | End of trial (follow-up) | Surgery[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V1 | V2 | V3 | V4 | V5 | V6 | V7[a] | V8[b] | V9[b] | V10 | V10A | V11 | |
| Timing of visit | | -2 weeks | 0 | 4 weeks | 8 weeks | 12 weeks | 20 weeks | 28 weeks | 36 weeks | 44 weeks | 50 weeks | | 30 days | |
| Visit window | | -7 days | | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | +56 days[c] | | +5 days | |
| Pharmacokinetics[g] | 8.5 | | X | | | X | | | | | | | | |
| Anti-HCP antibodies | 8.6.3 | | X | | | | | | | | X | X[i] | | |
| PEG plasma concentration[h] | 8.2.5 | | X | | | X | | X | X | X | X | X | | |
| Haematology | 10.2 | X | X | | | | | X | | | X | X | | |
| Biochemistry | 10.2 | X | X | | | | | X | | | X | X | | |
| Virology | 10.2 | X | | | | | | | | | | | | |
| Coagulation parameter | 10.2 | X | | | | | | | | | X | X | | |
| Lupus anticoagulant | 10.2 | X | | | | | | | | | | | | |
| Urinalysis | 10.2 | 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 | X | | | | X |
| Drug accountability | 6.4 | | X | X | X | X | X | X | X | X | X | X | | X |
| IWRS session | 6.2, 6.3 | X | X | X | X | X | X | X | X | X | X | X | | |
| Administration of trial product | 4.1 | | X[h] | X[h] | X[h] | X[h] | X[h] | X | X | X | | | | X |
| Home treatment training | 8.8 | | X | | | | | | | | | | | |

| Procedure | Protocol section | Screening | Baseline | Treatment period | | | | | | | End of treatment | Discontinuation of treatment | End of trial (follow-up) | Surgery[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V1 | V2 | V3 | V4 | V5 | V6 | V7[a] | V8[b] | V9[b] | V10 | V10A | V11 | |
| Timing of visit | | -2 weeks | 0 | 4 weeks | 8 weeks | 12 weeks | 20 weeks | 28 weeks | 36 weeks | 44 weeks | 50 weeks | | 30 days | |
| Visit window | | -7 days | | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | +56 days[c] | | +5 days | |
| End of treatment | 6.7<br>7.1 | | | | | | | | | | X | X | | |
| End of trial | 4.4 | | | | | | | | | | | | X | |
| Hand out ID card | | X | | | | | | | | | | | | |
| Hand out and instruct in diary | 8.7 | | X | X | X | X | X | X | X | X | | | | |
| Training in trial product | | | X | | | | | | | | | | | |

[a] In Arm A (On-demand/PPX), patients will switch from on-demand treatment to PPX treatment at Visit 7.

[b] In Arm A (On-demand/PPX), Visits 8 and 9 will only be conducted in case the patient has not yet attained 30 EDs in the trial (including treatment of bleeds during the on-demand period as well as scheduled once-weekly PPX doses and treatment of breakthrough bleeds during the PPX period) (see Section 4.1 for details).

[c] The visit window of +56 days for Visit 10 is included to ensure that patients who have not achieved the required number of exposure days after 50 weeks of treatment can have the treatment period extended until maximum 58 weeks as needed (see Section 4.1 for details).

[d] Only in patients <18 years.

[e] Only bleeding episodes after first dose of trial product in Arm B.

[f] All patients will have FIX activity measurements pre-dosing and 30 minutes post-dosing at all dosing visits during PPX treatment and during surgery.

[g] For details on pharmacokinetic assessments, refer to Table 1-1.

[h] Only applicable in Arm B.

[i] Only to be assessed in case of an acute severe allergic/anaphylactic reaction.

[j] Please also see surgery specific flowchart in Table 1-2.

## Table 1-1 Flowchart for patients having pharmacokinetics evaluated at Visits 2 and 5 in Arm B

| **Day(s)** | **0** | | | | **1** | **2** | **4** | **7** |
|---|---|---|---|---|---|---|---|---|
| **Nominal time**[a] | **Pre-dose** | **0** | **30 min** | **8 h** | **24 h** | **48 h** | **96 h** | **168 h** |
| **Visit window** | **-60 min**[b] | **-** | **±10 min** | **±30 min** | **+ 8 h** | **+ 8 h** | **+ 8 h** | **±24 h** |
| Factor IX activity | X | | X | X | X | X | X | X |
| Administration of trial product | | X | | | | | | |

[a] Relative to completion of nonacog beta pegol administration.

[b] Time window of 60 min pre-dose is only applicable for blood samples (which should be drawn between 60 and 5 min prior to nonacog beta pegol administration). Any other assessments can be performed at any time prior to dosing.

## Table 1-2 Detailed flowchart of assessments and sampling performed for patients undergoing surgery

| **Day** | **Day of surgery** | | **Post-surgery Days 2, 5, 7, 14**[a] |
|---|---|---|---|
| **Nominal Time**[b] | Pre-surgery | Post-surgery | 48, 120, 168, 336 hours |
| Concomitant medication[c] | X | | X |
| Body measurements (weight) | X | | |
| Vital signs | X | | X |
| Surgery details, e.g. type, indication, location, date, start and stop time | X | | |
| Adm. of N9-GP[d] | X[e] | | X |
| Clinical evaluation of the haemostatic response during surgery | | X | |
| Clinical narrative surgery (incl. estimated blood loss, complications etc.) | | X | |
| Bleeding, drainage, and wound assessment | | X | X |
| **LABORATORY ASSESSMENTS**[f] | | | |
| FIX activity<br>-pre-dose<br>-post-dose (30 min) | <br>X<br>X | | <br>X<br>X |
| FIX inhibitor analysis | X | | X |

[a]Post-surgery assessments: only major surgery. Timing of assessments conducted in the post-surgery period is dependent on the type and outcome of surgery. Suggested nominal times are included for guidance. Please see Table 6-1 for further information.
[b]Time values refer to time relative to the start of surgery.
[c]Including allowed haemostatic medication and blood product transfusions.
[d]Frequency of nonacog beta pegol/N9-GP administration is dependent on the type and outcome of surgery.
[e]For major surgery 80 IU/kg of nonacog beta pegol/N9-GP is administered i.v. prior to surgery, 40 IU/kg for minor surgery. Dosing frequency of additional 40 IU/kg is dependent on the type and outcome of the surgery.
[f]FIX activity test is to be performed pre- and post-dose on the day of surgery, prior to every post-surgery dose, as well as upon return to assigned treatment. FIX inhibitor test is to be performed pre-surgery and at return to the assigned treatment.

# 2 Introduction

## 2.1 Background

Haemophilia B is a rare, X-linked recessive congenital bleeding disorder characterised by increased bleeding tendency due to mutations in the coagulation factor IX (FIX) gene. The prevalence of haemophilia B globally is approximately 1 in 25,000 male births.[1] According to the World Federation of Hemophilia, there are globally over 210,000 identified haemophilia patients of which 34,289 are diagnosed with haemophilia B.[2] Haemophilia B is classified as 'severe'(FIX activity <1%), 'moderate'(FIX activity 1 to <5%) or 'mild'(FIX activity ≥5%) according to endogenous FIX plasma activity level. Factor levels are generally correlated to the severity of bleeding.[3] Haemophilia care is based on prevention (prophylaxis; PPX) and/or episodic treatment (on-demand) of bleeding episodes with a haemostatic agent.[3]

PPX is the treatment by regular intravenous (i.v.) injection of FIX concentrate (FIX replacement therapy) to prevent anticipated bleeding and is the key to successful long-term outcomes in patients with haemophilia B.[4] Historically, the aim of PPX in haemophilia B has been to keep the FIX activity >1% to minimise spontaneous bleeds. However, the haemophilia community has recently recognised that factor activity levels of 1% may be insufficient to prevent spontaneous bleeds and joint damage, and a mean trough level of 15% has been proposed as a theoretical threshold for avoiding joint bleeds and micro-haemorrhages.[5-7] Thus, ideal prophylactic treatment in haemophilia B should aim to maintain high FIX activity for the entire dosing interval to prevent or delay the development of severe joint damage.

The dose regimen used for treatment of bleeds and the duration of treatment depend on the site and severity of bleeding. The aim of management of specific haemorrhages is not only to treat the bleed, but also to prevent bleed recurrence, limit complications and restore tissue and/or organ function to a pre-bleed state.[3] Reduced frequency of doses to treat bleeding episodes would represent a significant improvement to on-demand treatment.

The clinical manifestations of haemophilia B are bleeding episodes due to impaired haemostasis. The bleeding episodes in patients with severe haemophilia B typically occur spontaneously or after mild trauma in joints, muscles and soft tissues. The bleeding episodes often occur in muscles and weight bearing joints (elbows, knees and ankles) causing acute haemarthrosis. In repeated cases, this is followed by synovitis in the affected joint. Recurrent bleeding episodes in the same location, most commonly a weight-bearing joint, may lead to chronic arthropathy, muscular atrophy and disabling deformities. Bleeding may occur in all parts of the body including rare, but life-threatening events, e.g. bleeding in the central nervous system, throat, neck or retroperitoneum.[3]

## 2.2 Nonacog beta pegol

Nonacog beta pegol is a glycopegylated recombinant human FIX with an extended half-life, which was developed to offer a more effective and less burdensome treatment compared to standard FIX products. An improved overall pharmacokinetic profile provides the ability to sustain higher FIX levels than with standard therapies. Thus, nonacog beta pegol has the potential to improve prophylaxis and simplify management of bleeds as well as perioperative haemostatic control in patients with haemophilia B.

The clinical development programme for nonacog beta pegol was initiated in August 2009. Five trials have been completed in previously treated adolescent and adult patients: two phase 1 trials in adult patients (Trials 3639 and 4260) and three phase 3 trials in adolescent or adult patients (Trials 3747, 3773 and 3775). In addition, the main phase of Trial 3774 in previously treated paediatric patients has also been completed, whereas the extension phase is still ongoing. Finally, Trial 3895 in previously untreated paediatric patients is ongoing. In the phase 1 trials, 31 patients have been exposed to nonacog beta pegol. In Trials 3747, 3773, 3775 and 3774 (main phase), 105 unique previously treated patients have been exposed to nonacog beta pegol with a total of 8,785 exposure days (EDs).

The phase 1 Trial 3639 comparing nonacog beta pegol and patients' previous FIX product showed that nonacog beta pegol has a 5-fold prolonged half-life ($t_{½}$) compared to marketed plasma-derived and recombinant standard half-life FIX products.[8] In Trial 4260 comparing the single-dose pharmacokinetics of nonacog beta pegol with ALPROLIX®, both at a dose of 50 IU/kg, a statistically significantly longer $t_{½}$ (by 22%) was observed for nonacog beta pegol vs. ALPROLIX® (estimated ratio [95% confidence interval] nonacog beta pegol/ALPROLIX® 1.22 [1.09; 1.35]).[9]

In all phase 3 trials, nonacog beta pegol was effective in treatment of bleeds, using fixed doses of 40 IU/kg (mild/moderate bleeds) or 80 IU/kg (severe bleeds) without any dose adjustment. Furthermore, nonacog beta pegol provided effective prophylactic treatment with once-weekly dosing. Thus, in the prophylactic treatment regimen of Trials 3747 and 3774, the Poisson-estimated annualised bleeding rate (ABR) was 1.90 [1.27;2.84] for 40 IU/kg once weekly, which is lower than reported for other FIX products.[10-13] In relation to surgery, efficacy and post-operative complications with nonacog beta pegol were comparable to reports for surgeries in patients with haemophilia B as well as in non-haemophilia subjects.[14-19] The haemostatic effect of nonacog beta pegol during surgery was confirmed with a success rate of 100% in the 13 major surgeries in Trial 3773.

In children with haemophilia B, as compared to adults and adolescents, there were no apparent differences for the haemostatic response, while a difference between age groups was observed for the ABR, where rates were lowest in the small children (0-6 years) and increased for patients in the older age groups.

No unexpected safety issues have been identified during the clinical development programme with nonacog beta pegol. Furthermore, the safety profile of nonacog beta pegol appeared comparable between children and adults.

A new drug application for nonacog beta pegol has been approved in the United States (May 2017) and the European Union (June 2017) and subsequently in Switzerland, Canada, Japan, Australia, Taiwan, Argentina and India.

## 2.3 Trial rationale

A meta-analysis in China has shown a prevalence of haemophilia of 5.5 per 100,000 males (3.6 per 100,000 males and females) and about 16% of these suffer from haemophilia B.[20] However, according to the WFH, a total of 2,460 patients with haemophilia B were registered in China in 2018, corresponding to 0.18 per 100,000 inhabitants.[2] Thus, less than 1/3 of the anticipated number

of patients with haemophilia B in China are diagnosed and there is a large number of patients who are either undiagnosed or untreated.[21]

With the rapidly improving standard of care in China, an increasing number of patients with haemophilia B in China are expected to be diagnosed and to be managed in the future. Consequently, optimal prophylactic treatment needs to become more readily available to the patients. This will significantly increase the demand for FIX products in China in the future. Currently, there are no extended half-life rFIX products available in China. Therefore, Chinese patients still face the challenges associated with frequent and repeated i.v. injections.

The rationale for this phase 3b trial is to investigate the efficacy, safety and pharmacokinetics of nonacog beta pegol used for treatment of bleeding episodes and for prophylaxis in Chinese patients with moderate to severe haemophilia B (FIX activity ≤2%) in order to enable a comparison of efficacy, safety and pharmacokinetic data from the current trial in Chinese patients with data from the global pivotal phase 3a trial with nonacog beta pegol (Trial NN7999-3747).

## 2.4 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 nonacog beta pegol may be found in the investigator's brochure.[22]

### 2.4.1 Risk assessment

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| **Trial treatment: Nonacog beta pegol** | | |
| **Identified risks** | | |
| Allergic/hypersensitivity reactions | As with any intravenous product, allergic/hypersensitivity including anaphylactic reactions cannot be excluded. Allergic-type hypersensitivity reactions have been reported in patients treated with marketed FIX products.<br>For results on allergic reactions reported in the nonacog beta pegol clinical trial programme, see Section 6.4.2.3 of the investigator's brochure.[22] | Patients are monitored carefully for allergic/hypersensitivity reactions. Patients are monitored carefully for anaphylactic reactions as defined by Sampson et al.[23] (see Section 10.3.3). Allergic/hypersensitivity/anaphylactic reactions must be treated as per local practice and as per investigator's discretion. |
| FIX inhibitors | The main safety issues identified with use of FIX products are immunogenicity and lack of efficacy due to formation of neutralising antibodies against FIX.<br>See Section 7.2.1.1 of the investigator's brochure[22] for further details on identified risks, and Section 6.4.2.4 of the investigator's brochure[22] for results on inhibitor development in the nonacog beta pegol clinical trial programme. | For previously treated patients with no history of FIX inhibitor development, the risk of inhibitor formation is low. As per inclusion criterion no. 4 (see Section 5.1), only patients with a history of at least 100 EDs to products containing FIX are eligible. Also, exclusion criterion no. 4 excludes patients with a known history of FIX inhibitors (Section 5.2). If reduced efficacy from treatment is suspected, an assessment |

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| | | for FIX inhibitors should be performed (see Section 8.6.2). |
| **Trial treatment: Nonacog beta pegol (continued)** | | |
| **Potential risks** | | |
| Thromboembolic events | Thromboembolic events are considered an important potential risk considering the fact that supraphysiologically elevated procoagulant levels may be associated with an increased risk of venous thrombosis.<br>No thromboembolic events have been observed in the nonacog beta pegol clinical trial programme; see Section 6.4.2.3 of the investigator's brochure.[22] | Thromboembolic events are monitored closely. |
| Accumulation of polyethylene glycol (PEG) in the brain (choroid plexus) and in other tissues/organs after long-term treatment | There has been no indication of PEG accumulation beyond steady state after nonacog beta pegol treatment non-clinically or clinically. The possible clinical consequences of potential PEG presence are currently unknown.<br>Potential effects of PEG accumulation are monitored closely. | Long-term safety including potential effects of PEG accumulation in the choroid plexus and other tissues/organs are monitored in the clinical trials and post-marketing. |
| **Trial procedures** | | |
| Intravenous (i.v.) injection | 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 their caregivers have experience with i.v. injection and will be trained by site staff in use of the 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. |

| Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| **Trial procedures (continued)** | | |
| 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 minimise 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. If possible, site visits can be converted to telephone visits. 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. |

### 2.4.2 Benefit assessment

Nonacog beta pegol has a longer half-life compared to standard FIX products. The longer half-life of nonacog beta pegol allows for PPX treatment with a reduced injection frequency and higher FIX activity trough levels, which subsequently will lead to better compliance with a prophylactic regimen and improved joint health. Furthermore, the prolonged effect of nonacog beta pegol allows on-demand treatment as well as surgical haemostatic coverage with a reduced frequency of dosing and duration of therapy as compared with other standard half-life FIX products. Thus, nonacog beta pegol has the potential to improve the quality of life for haemophilia B patients by offering a convenient treatment with a reduced treatment burden from less frequent injections.

### 2.4.3 Overall benefit-risk conclusion

No clinical safety issues have been identified that precludes further clinical development of nonacog beta pegol. AEs from the clinical trials that have been evaluated to be related to nonacog beta pegol are consistent with what has been observed, and what is expected, with use of other FIX products. The potential benefits of nonacog beta pegol 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 nonacog beta pegol are justified by the anticipated benefits that may be afforded to patients with haemophilia B.

# 3 Objectives and endpoints

## 3.1 Primary and secondary objectives

### Primary objective

- To evaluate the clinical efficacy of nonacog beta pegol in haemostasis (treatment of bleeding episodes during on-demand and prophylaxis [PPX]) in Chinese patients aged 12-70 years with moderate to severe haemophilia B

### Secondary objectives

In Chinese patients aged 12-70 years with moderate to severe haemophilia B:

- To evaluate the clinical efficacy of nonacog beta pegol in PPX treatment (number of treated bleeding episodes during PPX)
- To evaluate the consumption of nonacog beta pegol
- To evaluate the immunogenicity of nonacog beta pegol
- To evaluate the general safety of nonacog beta pegol
- To evaluate the pharmacokinetic properties of nonacog beta pegol

## 3.2 Primary and secondary endpoints

### 3.2.1 Primary endpoint

| Endpoint title | Time frame | Unit |
|---|---|---|
| Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes during on-demand and PPX | From start of treatment (week 0) until end of treatment (up to week 50) | Count |

### 3.2.2 Secondary endpoints

#### 3.2.2.1 Secondary efficacy endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of treated bleeding episodes during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | Count |
| Consumption of nonacog beta pegol for treatment of bleeding episodes | From start of treatment (week 0) until end of treatment (up to week 50) | IU/kg per bleed |
| Consumption of nonacog beta pegol for PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/kg per year |
| FIX trough levels during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/mL |

### 3.2.2.2 Secondary safety endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of patients with inhibitory antibodies against FIX defined as titre ≥0.6 Bethesda units (BU) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of adverse events (AEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of serious adverse events (SAEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |

### 3.2.2.3 Secondary pharmacokinetic endpoints

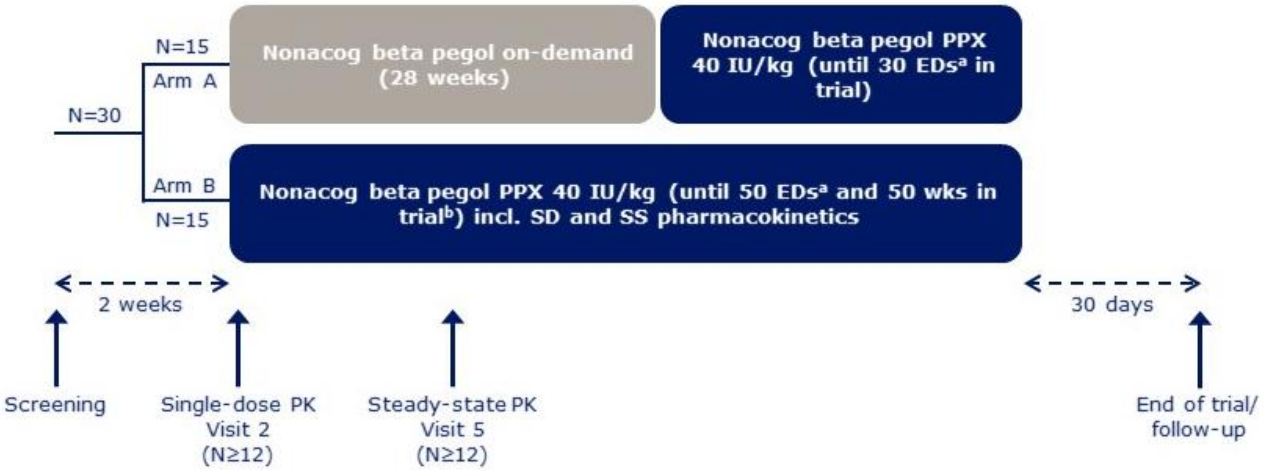
| Endpoint title | Time frame | Unit |
|---|---|---|
| Incremental recovery (IR) (Arm B only) | Single-dose: 30±10 minutes post-injection at week 0<br>Steady-state: 30±10 minutes post-injection at week 12 | (IU/mL)/(IU/kg) |
| Terminal half-life ($t_{½}$) (Arm B only) | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h |
| Clearance (CL) (Arm B only) | Single-dose: 0-168 hours post injection at week 0<br>Steady-state: 0-168 hours post injection at week 12 | mL/h/kg |
| Area under the curve (AUC) (Arm B only) | Single-dose: 0-168 hours post injection at week 0<br>Steady-state: 0-168 hours post injection at week 12 | h·IU/mL |

# 4 Trial design

## 4.1 Overall design

This is a multi-centre, open-label phase 3b trial evaluating the clinical efficacy, safety and pharmacokinetics of nonacog beta pegol during on-demand and for prophylactic treatment in Chinese patients aged 12-70 years with haemophilia B and a FIX activity of ≤2%.

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




[a] Including treatment of bleeds during the on-demand period as well as scheduled once-weekly PPX doses and treatment of breakthrough bleeds during the PPX period

[b] Both 50 EDs and 50 weeks in trial must be fulfilled for a patient to complete the trial

ED, exposure day; N, number of patients; PK, pharmacokinetics; PPX, prophylaxis; SD, single-dose; SS, steady-state; wks, weeks

**Figure 4-1 Overview of trial design**

A total of 30 patients will be included in the trial and a minimum of 24 patients must complete the trial. The trial will have two arms: Arm A (on-demand/PPX treatment arm) and Arm B (PPX treatment arm including single-dose and steady-state pharmacokinetic assessment). Patients will not be randomised to Arm A and Arm B. Whether a patient will be in Arm A or Arm B is the choice of the patient and the investigator and will be decided at the screening visit. A minimum of 12 patients in each of the two treatment arms must complete the trial.

In Arm A (on-demand/PPX), the on-demand treatment period will be 28 weeks. For a patient in Arm A, 30 EDs to nonacog beta pegol in the entire trial must be fulfilled to complete the trial (including treatment of bleeds during the on-demand period as well as scheduled once-weekly PPX doses and treatment of breakthrough bleeds during the PPX period).

In Arm B (PPX), 50 EDs to nonacog beta pegol (including treatment of breakthrough bleeds) and 50 weeks in trial must be fulfilled to complete the trial. One single-dose and one steady-state pharmacokinetic profile will be obtained in patients in Arm B. The single-dose pharmacokinetic profile will start at first dosing (Visit 2), while the steady-state pharmacokinetic profile will be obtained at Visit 5. The steady-state pharmacokinetic profile may be postponed but must be conducted between Visit 5 and Visit 9.

In both treatment arms, the screening period will be 2 weeks (+7 days) and the follow-up period will be 30 days (+5 days).

The duration of the trial for each individual patient will be up to 64 weeks, i.e. 2 weeks screening period, up to 58 weeks treatment period (only applicable in Arm A in case a patient has no or few bleeds during the trial) and 30 days follow-up period.

The clinical efficacy assessment of nonacog beta pegol in the treatment of bleeding episodes will be based on the treatment of all bleeding episodes in Arm A and Arm B (including specific information on target joints as defined at baseline). The haemostatic response to nonacog beta pegol will be assessed by the patient/caregiver 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 nonacog beta pegol per bleeding episode will also be recorded.

Efficacy of prophylaxis treatment with nonacog beta pegol will be assessed by the number of spontaneous and traumatic treated bleeding episodes observed in Arm B (annualised bleeding rate will be estimated). In addition, trough levels of the surrogate efficacy parameter, FIX activity, will be evaluated (in Arm B only).

Major and minor surgery is allowed in the trial, and information on the haemostatic effect and consumption of nonacog beta pegol in relation to surgery will be collected as applicable.

The safety of nonacog beta pegol will be evaluated based on the following safety assessments: AEs, safety laboratory parameters, physical examination and vital signs.

The pharmacokinetics will be evaluated by measurement of plasma FIX activity in blood samples collected pre-dosing and 30 minutes, 8, 24, 48, 96 and 168 hours post-dosing. All patients will have FIX activity measurements pre-dosing and 30 minutes post-dosing at all dosing visits during PPX treatment and during surgery. The analysis of plasma FIX activity will be performed at a central laboratory in China selected by Novo Nordisk.

### 4.1.1 Treatment of patients

Patients will receive nonacog beta pegol as prophylaxis, as on-demand for treatment of bleeding episodes and in relation to surgery (Table 4-1).

The trial product is nonacog beta pegol (N9-GP) produced by Novo Nordisk. The trial product is a recombinant FIX product and is a sterile, freeze-dried powder in vials, which is reconstituted with histidine solvent for injection (see Section 6.1 for further details). Trial product will be administered as i.v. injections at home by the patient and/or caregiver, at the trial site, or in exceptional cases in another clinic/hospital. All patients should be trained in home treatment of nonacog beta pegol. In Arm A, the first two doses of the trial product should be administered at the trial site or at a hospital/clinic as agreed with the investigator under supervision of medically qualified personnel. In Arm B, the first two doses of the trial product should be administered at the trial site.

**Table 4-1 Treatment regimens**

| Treatment regimen | Age (years) | Dose | Dose frequency |
|---|---|---|---|
| Prophylaxis | 12-70 years | 40 IU/kg | Once-weekly |
| Treatment of bleeds | 12-70 years | Mild and moderate bleeds: 40 IU/kg<br>Severe bleeds: 80 IU/kg<br>Additional doses of 40 IU/kg can be given if there is no observed effect of the first dose. | When necessary |
| Surgery | 12-70 years | At investgator's discretion (the following dosing guidelines can be used).<br>Minor surgery: 40 IU/kg prior to the surgery. Additional doses can be given if needed.<br>Major surgery: 80 IU/kg prior to the surgery. Two repeated doses of 40 IU/kg (in 1- to 3-day intervals) within the first week after surgery. Thereafter, the frequency of dosing may be extended to once weekly until bleeding stops and healing is achieved. | Pre-dose and when necessary |

### 4.1.2 Maximum dose and daily administration of nonacog beta pegol

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

### 4.1.3 Prophylaxis

During PPX treatment, one single bolus dose of 40 IU/kg nonacog beta pegol will be administered i.v. once weekly. If a dose for treatment of bleeding is taken, the next PPX dose should still be taken on the planned day.

Additional doses of nonacog beta pegol 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 PPX dosing day before administration of the PPX dose, or if a bleeding episode extends into such a day, the bleeding episode must be treated with the full PPX dose (this dose should be recorded as treatment of a bleeding episode). The patient should always follow the original PPX 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 is treated with haemostatic drugs. 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, a single dose of 40 IU/kg nonacog beta pegol i.v. should be administered. If there is no observed effect of 40 IU/kg,

the investigator should be contacted prior to administration of a second dose of 40 IU/kg. A severe bleeding episode should be treated immediately at home or at a local emergency room with 80 IU/kg, and the clinical site must be contacted immediately thereafter for further instructions or transport.

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

If a bleeding episode occurs on a planned PPX dosing day before administration of the PPX dose, or if a bleeding episode extends into such a day, the bleeding episode must be treated with the full PPX dose (this dose should be recorded as treatment of a bleeding episode). The patient should always follow the original PPX 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 nonacog beta pegol treatment when treating bleeding episodes, another FIX product may be used at the discretion of the investigator. The use of other FIX products will result in discontinuation of trial treatment.

### 4.1.5 Treatment for surgery

Major and minor surgery can be performed while participating in the trial. Use of FIX products other than nonacog beta pegol for surgery is not allowed. Patients undergoing surgical procedures will receive trial product as bleeding preventive treatment according to standard practice at the clinical 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 4-1 and WFH guidelines.[3] As these guidelines are recommendations, non-compliance with them will not require any protocol deviations. Achieving higher FIX activity levels may be necessary depending on type of surgery and standard practice at the clinical site. The rationale is to replace the FIX activity in these patients up to FIX activity levels that are effective in preventing bleeding during and after surgery.

The specific treatment for each patient is decided by the investigator in collaboration with the surgeon. Surgery can be done at the clinical site, in another clinical department of the site or at another hospital. If a surgery takes place at another location than at the clinical 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 7.1.

The maximum dose to be administered to a patient within 24 hours is 200 IU/kg, with a maximum individual dose of 80 IU/kg to be administered no more frequently than every hour.

### 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

The trial design will provide information on efficacy, safety and pharmacokinetics of nonacog beta pegol in Chinese patients with haemophilia B and a FIX activity of ≤2%. Efficacy, safety and pharmacokinetic data from the current trial in Chinese patients will be compared with data from the global pivotal phase 3a trial with nonacog beta pegol (Trial NN7999-3747).

The age of the patients (12-70 years) is in accordance with the China guideline on clinical trials of recombinant human FIX,[24] while still allowing for the planned comparison with data from the global pivotal phase 3a trial with nonacog beta pegol (Trial NN7999-3747), which included patients aged 13-70 years.

The purpose of the on-demand treatment period is to ensure that sufficient bleeding treatment data for nonacog beta pegol are collected in the trial. It is considered acceptable to offer on-demand treatment to patients who are comfortable with and prefer this treatment option.

The purpose of the PPX periods is to ensure sufficient exposure to nonacog beta pegol to provide efficacy data for nonacog beta pegol in prophylaxis and to evaluate the immunogenicity of nonacog beta pegol. The PPX treatment arm will generate safety data from at least 50 EDs for each patient, equivalent to approximately 50 weeks of continuous treatment in haemophilia B patients. The PPX period of the on-demand/PPX treatment arm will provide additional safety data without the need to increase the required number of patients.

The duration of treatment in the PPX treatment arm (≥50 EDs and ≥50 weeks in trial) is based on the requirement of ≥50 EDs and ≥6 months of efficacy evaluation for PPX treatment in the China guideline on clinical trials of recombinant human FIX.[24]

The duration of treatment in the on-demand treatment period (28 weeks) is based on the requirement of ≥6 months of efficacy evaluation for on-demand treatment in the China guideline on clinical trials of recombinant human FIX.[24] The duration of the PPX period of the on-demand/PPX treatment arm (until the patient has attained 30 EDs to nonacog beta pegol in the entire trial) is chosen in order to provide additional safety data on PPX treatment, while at the same time considering the robust data already available from the clinical trials included in the global clinical development programme for nonacog beta pegol.

Randomisation will not be carried out, since the two separate treatment arms will not be compared.

The trial will not be controlled by a placebo group as it is considered unethical to administer an ineffective treatment to patients with haemophilia. An active control group will not be included as this is not specified in the China guideline on clinical trials of recombinant human FIX.[24]

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

The dose levels chosen for the current trial are based on clinical data from all completed trials in the global population. In all trials investigating efficacy, nonacog beta pegol at fixed doses of 40 IU/kg (mild and moderate bleeds) or 80 IU/kg (severe bleeds) was safe and efficacious in treatment of bleeds. Overall, 93.2% of the bleeds were successfully treated with nonacog beta pegol without any dose adjustment. When administered at the PPX dose of 40 IU/kg once weekly, nonacog beta pegol was associated with low annualised bleeding rates. Mean FIX trough levels above 15% was achieved for all age groups, which has been mentioned as a theoretical threshold for avoiding joint bleeds and micro haemorrhages.[6] Nonacog beta pegol was generally well tolerated in all trials, and no unexpected patterns in the reported AEs were observed.

Based on an investigation of the pharmacokinetics, efficacy and safety characteristics of nonacog beta pegol in Asian patients compared with the global population, it has been concluded that nonacog beta pegol is unlikely to be sensitive to ethnic factors. Consequently, the dose levels of nonacog beta pegol used in the completed global clinical trials will also be used in the current trial in Chinese patients.

## 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 moderate to severe congenital haemophilia B with a FIX activity ≤2% according to medical records.
3. Aged 12-70 years (both inclusive) at the time of signing informed consent.
4. History of at least 100 EDs to products containing FIX.[1]
5. Patients currently on prophylaxis or patients currently treated on-demand with at least 6 bleeding episodes during the last 12 months or at least 3 bleeding episodes during the last 6 months.
6. The patient, legally authorised representative (LAR) and/or caregiver are capable of assessing a bleeding episode, keeping a diary, performing home treatment of bleeding episodes and otherwise following the trial procedures.

[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 FIX inhibitors based on existing medical records, laboratory report reviews and patient and LAR interviews.
5. Current FIX inhibitors ≥0.6 BU.
6. 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 the medical records within the last 6 months, then the test must be performed at the screening visit.
7. Congenital or acquired coagulation disorder other than haemophilia B.
8. Previous arterial thrombotic events (e.g. myocardial infarction and intracranial thrombosis) or previous deep venous thrombosis or pulmonary embolism (as defined by available medical records).

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.
10. Renal impairment defined as estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 $m^2$ for serum creatinine measured at screening.
11. Any disorder, except for conditions associated with haemophilia B, which in the investigator's opinion might jeopardise the patient's safety or compliance with the protocol.
12. Platelet count <$50\times10^9$/L at screening.
13. Immune modulating or chemotherapeutic medication.
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 patients having pharmacokinetics evaluated when they will undergo pharmacokinetic assessments at Visit 2 and Visit 5 where blood sampling will be performed during a 168-hour period. It is not required that the patient stays overnight. See the flowchart for patients having pharmacokinetics evaluated at Visit 2 and Visit 5 (Table 1-1), and Section 8.5 for how pharmacokinetic 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 inclusion/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. If the patient has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. 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:

- nonacog beta pegol (N9-GP) 2000 IU/vial as a sterile, freeze-dried powder in a single-use vial of 2000 IU/vial to be reconstituted with 4 mL histidine solvent provided in a pre-filled syringe for i.v. injection.

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

The trial product should be administered as a slow bolus i.v. injection over several minutes (from start to completion of injection) for all trial product administrations. The rate of administration should be determined by the patient's comfort level up to a maximum injection rate of 4 mL/min.

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 2) (see Section 1.2).

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

| **Trial product name** | Nonacog beta pegol (N9-GP) 2000 IU/vial (IMP, test product) | Histidine solution (Solvent) |
|---|---|---|
| **Dosage form** | Powder for solution for injection | Solvent for solution for injection |
| **Route of administration** | Intravenous | Intravenous |
| **Dosing instructions** | Prophylaxis: 40 IU/kg once weekly.<br>Treatment of bleeds: Single dose of 40 IU/kg (mild or moderate bleeds) or 80 IU/kg (severe bleeds). Additional doses of 40 IU/kg can be given if there is no observed effect of the first dose.<br>Minor surgery (dosing guidelines): Single dose of 40 IU/kg prior to the surgery. Additional doses can be given if needed.<br>Major surgery (dosing guidelines): Single dose of 80 IU/kg prior to the surgery. Two repeated doses of 40 IU/kg (in 1- to 3-day intervals) within the first week after surgery. Thereafter, the frequency of dosing may be extended to once weekly until bleeding stops and healing is achieved. | Not applicable |
| **Packaging** | Vial | Pre-filled syringe with scale label |

### 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 allocated to treatment may use trial product and only delegated site staff may supply and administer trial product.

Instructions for preparation of trial products, in-use conditions and in-use time will be available on 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 allocation to treatment arms.
- 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. The 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 record 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 nonacog beta pegol and histidine solvent 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, un-used, 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. At baseline, allocation to treatment arm A or B will be decided by the investigator and the subject based on the subject's medical history and preference. 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 the patient is compliant to trial product and trial procedures. If any suspicion of non-compliance arises, i.e. the patient missed ≥3 doses of any consecutive 15 doses, the 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

The investigator/investigator designee must train the patient on in-use time of the trial product at first dispensing. At each site visit, the investigator/investigator designee must review use of trial product with the patient and document in the patient medical record if the patient 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 products 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
- Dates of administration including start and stop dates or continuation
- Total daily dose

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

## 6.6 Dose modification

Information on dose levels during treatment with nonacog beta pegol for prophylaxis, treatment of bleeding episodes and surgery is found in Section 4.1 and the rationale for the doses is provided in Section 4.3.

## 6.7 Treatment after end of trial

When discontinuing trial product at Visit 10 or 10A (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 10). Efforts must be made to have the patients who discontinue trial product attend and complete all scheduled visit procedures according to the flowchart in 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 10A (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 nonacog beta pegol 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 nonacog beta pegol: The bleed cannot be controlled after 48 hours using adequate doses of nonacog beta pegol.
3. FIX inhibitors ≥0.6 and ≤5 BU, as confirmed by re-testing by central laboratory, which makes treatment (prophylaxis and/or treatment of bleeding episodes) with nonacog beta pegol clinically ineffective (see Section 8.6.2).
4. FIX inhibitors >5 BU as confirmed by re-testing by central laboratory.
5. Severe allergy/anaphylaxis to the trial product.
6. Use of coagulation factors FVIII, FIX and FVII-containing products other than nonacog beta pegol and other FIX-containing products such as fresh frozen plasma or cryoprecipitate (**Exception:** FIX is allowed until 120 hours before visit 2).
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).
9. Use of emicizumab.
10. Anti-fibrinolytics except for local/topical use. Use of single systemic doses is allowed after careful benefit-risk evaluation.

See the flowchart in Section 1.2 for data to be collected at the time of treatment discontinuation (discontinuation of treatment visit; Visit 10A) 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 AEs. 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 10, Visit 10A should be performed at least 7 days after the last dose of trial product has been administered, and prior to starting treatment with another marketed product. The follow-up visit (Visit 11) 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 11 the patient should continue to follow the planned visit schedule until having completed the end of treatment visit (Visit 10).

After Visit 10A, the following procedures/assessments should not be performed for patients who discontinue treatment:

- Trial product administration
- FIX 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 this trial.

## 7.2 Patient withdrawal from the trial

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

If a patient withdraws consent, the investigator must ask the patient if he is willing, as soon as possible, to have assessments performed according to Visit 10A (discontinuation of treatment visit). See the flowchart in Section 1.2 for data to be collected at Visit 10A (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, he 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 his 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 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. Please 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 flowchart in Section 1.2.

### 8.1.1 Bleeding episodes

From Visit 2 (inclusion of the patient) 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 Sections 8.3.6 and 8.7 for reporting in the diary and eCRF).

If a patient experiences a bleeding episode at home, treatment with nonacog beta pegol 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, if required.

A need for haemostatic rescue therapy with another FIX product will be assessed by the investigator via phone or during the site visit. Patients treated with FIX products other than nonacog beta pegol must be discontinued from treatment with nonacog beta pegol (exception: the patient's current FIX product is allowed until 120 hours before Visit 2).

**Definition of target joints**

Joint bleeds are either categorised as target joint or non-target joint bleeds. Target joints are defined as 3 or more spontaneous bleeding episodes in the same joint within 6 months.

#### 8.1.1.1 Definitions of bleeding episodes

- **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.

#### 8.1.1.2 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 (>3 g/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 hospitalised, 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.

#### 8.1.1.3 Definition of stop of bleeding episodes

- **Stop time is:** When the patient or caregiver experiences/observes signs of cessation of the active bleed, such as pain relief, no increase in swelling/limitation of motion and improvement in other objective signs of the bleeding episode.
- **Stop time is not:** When pain and objective signs of the bleeding episode are completely resolved.

#### 8.1.1.4 Definition of haemostatic response

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

### 8.1.2 Clinical efficacy laboratory assessments

Protocol-required efficacy laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the flowchart in Section 1.2 and the laboratory manual.

### 8.1.3 Surgery

Surgery should be performed at a dedicated surgery visit. See Section 1.2 (flowchart and Table 1-2) for procedures and assessments to be performed during and following a surgery visit. The following information will be recorded for each surgery:

- Type of surgery
- Indication for surgery
- Location of surgery
- Date of surgery and start and stop time

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 nonacog beta pegol should be ensured before undertaking surgery.

Blood samples for analysis of FIX 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 nonacog beta pegol administration, and actual time must be documented. Furthermore, blood samples for analysis of FIX activity (pre- and post-dose) will be collected for every post-surgery dose and upon return to assigned treatment at the end of the surgery period.

Blood samples for analysis of FIX inhibitors will be collected on the day of surgery and again upon return to assigned treatment at the end of the surgery period.

#### 8.1.3.1 Definition of surgery

- **Major surgery:** 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:** 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 central venous access devices 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

- **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.

### 8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart 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 Details of haemophilia and haemophilia treatment history

**Details of haemophilia (including history)**

- Diagnosis of haemophilia B (date)
- Classification of haemophilia B and FIX activity level (%) from medical history
- Inhibitor status (yes/no), age at inhibitor diagnosis, highest titre, duration of time with inhibitors and immune tolerance
- History of switching FIX products (type of products [from/to] and age at switching) if available

**Haemophilia treatment history**

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

- Number of bleeding episodes within the last 6 and 12 months (number of treatment requiring bleeds/number of non-treatment requiring bleeds)
- Number of months on prophylaxis
- Dose and frequency of dosing
- Recombinant or plasma FIX product
- Estimated amount and number of doses used to treat a bleeding episode

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

- Number of bleeding episodes within the last 6 and 12 months (number of treatment requiring bleeds/number of non-treatment requiring bleeds)
- Recombinant or plasma FIX product
- Estimated amount and number of doses used to treat a bleeding episode

For all patients, the following should be recorded:

- Surgeries within the last 5 years
  - Date of surgery
  - Indication (surgery)
  - Recombinant or plasma FIX product
- Number of EDs prior to trial entry:
  - If it is not possible to count the actual number of exposures in the patient's 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
- Registration of all current target joints, including number of bleedings for the last 12 months in each current target joint. A target joint is defined as 3 or more spontaneous bleeding episodes in the same joint within 6 months. When there has been no bleed in this same joint for 12 months, such a joint is no longer considered a target joint.

### 8.2.2 Physical examinations

A physical examination will be performed according to local procedure and will include assessments of:

- 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 spontaneous 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).

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 kilo (kg) with one decimal without shoes and wearing only light clothing and recorded in the eCRF. 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 and documented in the subject medical record.

#### 8.2.2.1 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

Each aspect of the neurological examination will be categorised into normal, abnormal (pre-existing or new) or not evaluated.

### 8.2.3 Vital signs

Before measurement of vital signs, the patient must rest comfortably for at least 3 min 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 (BP)
- 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.

### 8.2.4 Electrocardiograms

12-lead ECG will be obtained at screening as well as at End of Treatment visit (Visit 10) and in case of Discontinuation of treatment (Visit 10A). 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.

### 8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the protocol flowchart in 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 2 must be recorded as concomitant illness, while clinically significant findings from Visit 2 until Visit 10/10A (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 nonacog beta pegol 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 nonacog beta pegol.

## 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 of special interest (AESIs) and 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 are listed below in Table 8-1 together with AESIs.

**Table 8-1 AEs requiring additional data collection (serious and non-serious AEs) and AESIs**

| Event type | AE requiring additional data collection | AESI[a] |
|---|---|---|
| Medication error | X | |
| Misuse and abuse | X | |
| FIX inhibitors | | X |
| Allergic reactions | | X |
| Anaphylactic reactions | | X |
| CNS-related AEs | | X |
| Thromboembolic events | | X |
| Renal AEs | | X |

[a] Must follow the same reporting timelines as for SAEs.

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 2 and until the end of 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 (SUSARs).

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[22] and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.5 Pregnancy

Details of pregnancies in female partners of male patients will be collected after first exposure to trial product and until the 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 B 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 event 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 event was related to treatment with the IMP.
- The event is considered life-threatening (see Appendix 4 for definition of life-threatening).
- The event results in death.

### 8.3.7 Adverse event of special interest

Please refer to Section 8.3 and Appendix 3.

### 8.3.8 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 AEs/SAEs.

For more information on overdose, also consult the current version of the nonacog beta pegol investigator's brochure.[22]

## 8.5 Pharmacokinetics

Patients in Arm B (PPX) will be administered a single i.v. bolus injection of 40 IU/kg of nonacog beta pegol at Visits 2 and 5. The pharmacokinetic sessions extend over 168 hours after dosing. After completion of the pharmacokinetic sessions, the patients will return to PPX treatment with the next visit in line.

Patients must not have received current FIX product for at least 96 hours prior to the administration of trial product for the single-dose pharmacokinetic session at Visit 2 (i.e. a wash-out period of at least 96 hours must be applied before Visit 2).

There is no wash-out period for the steady-state pharmacokinetic session at Visit 5. However, administration of trial product at Visit 5 should be approximately 168 hours after the previous nonacog beta pegol dose.

Patients must not be actively bleeding during the pharmacokinetic sessions.

The pharmacokinetic endpoints (see Section 3.2.2.3) will be based on assessments performed from 1 hour prior to and up to 168 hours after administration of nonacog beta pegol at Visits 2 (single-dose pharmacokinetic assessments) and 5 (steady-state pharmaockinetic assessments) (see the flowchart for pharmacokinetic assessments in Table 1-1).

### 8.5.1 Visit 2 for patients undergoing pharmacokinetic assessment

Visit 2 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 pharmacokinetic evaluation.

At Visit 2, the patients will receive their first dose of nonacog beta pegol (40 IU/kg) at the site and 7 pharmacokinetic samples will be taken during the following 168 hours. The lines must be flushed immediately after administration of the trial product. The blood sample taken pre-dose may be taken from the same arm as the one used for nonacog beta pegol administration. The blood sample taken 30 min post-dose must not be taken from the same vein as used for administration of nonacog beta pegol.

If a bleeding episode occurs between trial product administration and the last pharmacokinetic blood sample at 168 hours, the patient must contact the site and preferably come to the site for treatment with nonacog beta pegol. Further blood sampling for pharmacokinetic 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 nonacog beta pegol.

Assessments at Visit 2 are outlined in Section 1.2 and additional assessments and sampling for patients having pharmacokinetics evaluated are outlined in Table 1-1.

The second dose of nonacog beta pegol will be administered at the site after the last pharmacokinetic sample at 168 hours post-dose is taken.

### 8.5.2 Visit 5 for patients undergoing pharmacokinetic assessment

Patients who underwent a single-dose pharmacokinetic assessment at Visit 2 must also undergo a steady-state pharmacokinetic assessment at Visit 5. The steady-state pharmacokinetic session should be performed approximately 168 hours after the previous nonacog beta pegol dose. Overnight stay is not required during the pharmacokinetic evaluation.

At Visit 5, the patients will receive a dose of nonacog beta pegol (40 IU/kg) at the site and 7 pharmacokinetic samples will be taken during the following 168 hours. The lines must be flushed immediately after administration of the trial product. The blood sample taken pre-dose may be taken from the same arm as the one used for nonacog beta pegol administration. The blood sample taken 30 min post-dose must not be taken from the same vein as used for administration of nonacog beta pegol.

Blood sampling for pharmacokinetics should be stopped if a bleeding episode occurs during the pharmacokinetic session.

Assessments at Visit 5 are outlined in Section 1.2 and additional assessments and sampling for patients having pharmacokinetics evaluated are outlined in Table 1-1.

The next dose of nonacog beta pegol will be administered at the site after the last pharmacokinetic sample at 168 hours post-dose is taken.

## 8.6 Immunogenicity assessments

### 8.6.1 Anti-nonacog beta pegol and anti-PEG antibodies

Nonacog beta pegol binding antibodies will be assessed using a bridging ELISA that is validated according to internationally recognised guidelines.[25-29] Samples measured above the assay cut-point will be subject to a confirmation test, where the presence of anti-nonacog beta pegol antibodies will

be confirmed by addition of excess of unlabelled nonacog beta pegol and cross-reactivity to rFIX will be measured using excess of unlabelled rFIX. Samples measured positive in the confirmatory assay will be titrated to assign the level of antibodies.

Samples that are confirmed positive for anti-nonacog beta pegol antibodies but do not cross-react to rFIX will be defined as being positive for anti-PEG antibodies. The rationale for assessing anti-PEG antibodies with this method is that it was shown during the validation that anti-PEG antibodies could be detected by the anti-nonacog beta pegol binding antibody assay. Furthermore, data from the global pivotal nonacog beta pegol trials did not show any unexplained variation in PK during trial conduct that would indicate an immune response towards nonacog beta pegol.

The antibody analyses will take place at the end of the trial.

### 8.6.2 FIX inhibitors

All patients will be examined for the development of FIX inhibitors at scheduled visits (see Section 1.2). Blood samples for analysis of FIX inhibitors will be collected on the day of surgery and again upon return to assigned treatment at the end of the surgery period.

Blood samples for measurement of inhibitors towards FIX will be analysed according to the Nijmegen modification of the Bethesda assay.

If FIX inhibitor development is suspected (e.g. increased number of bleeding episodes, bleeding episodes difficult to treat, nonacog beta pegol recovery and trough levels below expected values) during 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. If 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. These samples should preferably be taken prior to any change of treatment. In addition, the following tests should be performed:

- FIX trough (pre-dose)
- FIX recovery (30 min post-dose)
- Lupus anticoagulant.

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

Inhibitor positive patients must be discontinued from trial treatment if FIX inhibitors >5 BU or if FIX inhibitors ≥0.6 and ≤5 BU that makes treatment (prophylaxis and/or treatment of bleeding episodes) with nonacog beta pegol clinically ineffective, by discontinuing trial product and attending the discontinuation of treatment visit (visit 10A) 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 nonacog beta pegol treatment (prophylaxis and/or

treatment of bleeding episodes), the patient can stay in the trial and continue treatment as per protocol.

For patients discontinued from treatment with nonacog beta pegol, the follow-up visit (Visit 11) must be scheduled 30 +5 days after the discontinuation of treatment, and additional follow-up contact(s) (e.g. phone calls) may be arranged as long as clinically warranted up to 3 months after Visit 11.

For patients continuing in the trial with inhibitors (≥0.6 and ≤5 BU), the patient must follow the 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 the investigator's discretion. In the event of a concern about reduced treatment efficacy, a pharmacokinetic session may be performed. Blood sampling during the pharmacokinetic session can be performed as described in Table 1-1.

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

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

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.

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.

A positive inhibitor test must be reported as a serious AESI (see Section 10.3.3). When the result of the second (confirmatory) inhibitor test is available, the serious AESI must be updated with this information.

If more than 1 patient is verified inhibitor positive, an ad hoc Safety Committee Meeting will be called by Global Safety, and a decision whether to continue, modify or stop the trial will be 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.

### 8.6.3 Anti-HCP antibodies

All patients will be assessed for anti-HCP antibodies at baseline (Visit 2) and at the end of treatment visit (Visit 10). The anti-HCP antibodies will be measured using a validated anti-HCP antibodies ELISA platform. Samples measured above the assay cut-point will be subject to a confirmation test, where the presence of anti-HCP antibodies will be confirmed by addition of excess of unlabelled

HCP. Samples measured positive in the confirmatory assay will be titrated to assign the level of antibodies.

In addition, any patient who experiences an acute severe allergic/anaphylactic reaction (see Section 10.3.3 for definition) that cannot be assigned to anti-nonacog beta pegol antibodies will also 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 and preferably before initiation of other treatment.

## 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 Sections 8.1.1 and 8.8) 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. Furthermore, the correctness of the haemostatic efficacy for treatment of bleeds must be evaluated together with the patient/caregiver. 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

For patients in Arm A, home treatment training with injection of nonacog beta pegol will be carried out at Visit 2 until the patient or caregiver is comfortable with the reconstitution and injection process. The training must be documented in the medical records.

For patients in Arm B, home treatment training with injection of nonacog beta pegol can start after injection 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 Visit 2. Retraining on home treatment should be given based on the investigator's discretion at the following dispensing visits.

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, a total number of 24 Chinese patients to complete this trial is assessed to be sufficient to evaluate efficacy and safety in the Chinese population, considering that data are also available from the global pivotal trial NN7999-3747, which included Asian patients. In order to account for withdrawn patients, 30 patients will be started on trial product (15 patients in Arm A [on-demand/PPX] and 15 patients in Arm B [PPX]).

All 15 patients in Arm B will participate in the pharmacokinetic evaluation to ensure that at least 12 patients will complete single-dose and steady-state pharmacokinetic profiles.

## 9.3 Populations for analyses

All patients exposed to nonacog beta pegol in this trial will be included in the full analysis set (FAS) and the safety analysis set (SAS).

Exceptional outlier pharmacokinetic profiles and/or individual plasma FIX activity values may be excluded when analysing pharmacokinetic endpoints based on the FAS. The rules to exclude data points from analysis of pharmacokinetic endpoints will be 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

### 9.4.1 General considerations

Novo Nordisk will be responsible for the statistical analyses. The SAP will be finalised prior to first patient first visit.

Unless otherwise stated, all endpoints will be presented in total and by treatment regimen/period as applicable (on-demand period in Arm A; PPX period in Arm A; and Arm B [PPX]).

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

FIX activities below lower limit of quantification (LLOQ) will be set to half the value of the LLOQ.

All bleeding endpoints will be evaluated based on bleeding episodes requiring treatment with haemostatic drugs. Non-treatment requiring bleeding episodes will only be listed. Bleeding episodes in relation to surgery will also only be listed, i.e. not included in the analysis of bleeding endpoints.

Multiple bleeding locations occurring from the same event (e.g. due to a bicycle accident) or at the same time point will be counted as one bleeding episode and only one haemostatic response will be considered for the bleeding episode. In case different responses were registered for different bleeding locations in such a bleeding episode, the worst response will be used in the analysis.

A re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after stopping treatment. If a bleed occurs in the same location later than 72 hours after stopping the treatment, it is considered a new bleed. Re-bleeds will only be considered for joint bleeds since the specific location for other bleeds (e.g. subcutaneous) are not captured in the database.

In the sub-analyses of ABR, where there are less than 5 patients in a sub-group, model based estimation will not be done. If no bleedings occur in a sub-group, then the confidence interval will not be calculated.

### 9.4.2 Primary endpoint

| Endpoint title | Time frame | Unit | Details |
|---|---|---|---|
| Haemostatic effect of nonacog beta pegol when used for treatment of bleeding episodes during on-demand and PPX | From start of treatment (week 0) until end of treatment (up to week 50) | Count | Assessed as success/failure based 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' |

This endpoint will be evaluated based on data from both Arm A and Arm B.

The primary endpoint of haemostatic effect of nonacog beta pegol will be summarised by dichotomizing into success/failure based on counting excellent and good as 'success' and moderate and none as 'failure', and based only on reported responses. For the calculation of success rate, the numerator will include all treated bleeding episodes with a reported haemostatic response of good or excellent, while the denominator will include all treated bleeding episodes with a reported haemostatic response. Furthermore, a sensitivity analysis will be conducted, where the denominator also includes treated bleeding episodes with missing response (i.e. missing response is counted as failure).

Haemostatic effect as measured by the four-point scale will also be summarised and listed.

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.

### 9.4.3 Secondary endpoints

#### 9.4.3.1 Confirmatory secondary endpoint(s)

The trial has no confirmatory secondary endpoints.

#### 9.4.3.2 Secondary efficacy endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of treated bleeding episodes during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | Count |
| Consumption of nonacog beta pegol for treatment of bleeding episodes | From start of treatment (week 0) until end of treatment (up to week 50) | IU/kg per bleed |
| Consumption of nonacog beta pegol for PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/kg per year |
| FIX trough levels during PPX treatment (Arm B only) | From start of treatment (week 0) until end of treatment (week 50) | IU/mL |

**Number of treated bleeding episodes during PPX treatment**

This endpoint will be evaluated based on data from Arm B only.

This 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 prophylaxis duration used as offset. Estimates of ABR will be provided with 95% confidence intervals.

Only the observed bleeding episodes will be counted and the offset will be actual PPX duration.

A sensitivity analysis based on a negative binomial regression model with the logarithm of PPX duration used as offset will also be performed.

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

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

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

ABR will also be presented separately for patients coming from an on-demand regimen and a PPX regimen. For both groups, the ABR will be compared descriptively to the ABR immediately prior to initiation of PPX with nonacog beta pegol.

**Consumption of nonacog beta pegol for treatment of bleeding episodes**

This endpoint will be evaluated based on data from both Arm A and Arm B.

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 nonacog beta pegol for PPX treatment**

This endpoint will be evaluated based on data from Arm B only.

The number of injections for PPX treatment (i.e. excluding treatment of breakthrough bleeds) will be summarised and listed.

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

**FIX trough levels during PPX treatment**

This endpoint will be evaluated based on data from Arm B only.

The FIX trough and recovery levels will be analysed by a mixed model on the log-transformed plasma FIX activity with 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 less than 5 days or more than 9 days after last dose will be excluded.
- Pre-dose and post-dose values taken less than twice the PPX treatment interval (14 days) 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.
- FIX 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 recovery will be calculated and presented in summary tables and plots.

### 9.4.3.3 Secondary safety endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Number of patients with inhibitory antibodies against FIX defined as titre ≥0.6 Bethesda units (BU) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of adverse events (AEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |
| Number of serious adverse events (SAEs) | From start of treatment (week 0) until end of treatment (up to week 50) | Count |

The safety endpoints will be evaluated based on data from both Arm A and Arm B.

**Number of patients with inhibitory antibodies against FIX defined as titre ≥0.6 BU**

The rate of neutralising antibodies will be reported and a 1-sided 97.5% upper confidence limit will be provided based on an exact calculation for a binomial distribution. For the calculation of the inhibitor rate, the nominator will include all patients with neutralising antibodies while the denominator will include all patients with a minimum of 10 exposures plus any patients with less than 10 exposures but with neutralising inhibitors.

**AEs and 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.

### 9.4.3.4 Secondary pharmacokinetic endpoints

Pharmacokinetic parameters to be derived in the trial (Arm B only) are listed in Table 9-1.

**Table 9-1 Definition and calculation of pharmacokinetic parameters**

| Title | Time frame | Unit | Details |
|---|---|---|---|
| Incremental recovery (IR) | Single-dose: 30±10 minutes post injection at week 0<br>Steady-state: 30±10 minutes post injection at week 12 | (IU/mL)/(IU/kg) | The increase in plasma FIX activity from pre-dose to 30 min post-dose divided by the dose injected.<br>IR is calculated by subtracting the FIX 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 body weight. |
| FIX activity 30 min post-injection ($C_{30min}$) | Single-dose: 30±10 minutes post injection at week 0<br>Steady-state: 30±10 minutes post injection at week 12 | IU/mL | The FIX activity recorded 30 min after end of injection. Expected to be the maximum FIX activity observed. |
| FIX activity 168 h post-injection ($C_{168h}$) | Single-dose: 168±24 hours post-injection at week 0<br>Steady-state: 168±24 hours post-injection at week 12 | IU/mL | The FIX activity recorded 168 hours after end of injection. Expected to be the minimum FIX activity observed. |
| $AUC_{(0\text{-}inf)}$ | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h·IU/mL | Area under the plasma activity versus time profile from time zero to infinity. Measure of total plasma exposure.<br>$AUC_{(0\text{-}inf)} = AUC_{(0\text{-}t)} + C_{(t)} / \lambda_z$,<br>where $C_{(t)}$ is the last measurable activity. |
| $AUC_{(0\text{-}t)}$ | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | 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. |
| $AUC_{(0\text{-}168h)}$ | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h·IU/mL | $AUC_{(0\text{-}168h)}$ is calculated using the linear trapezoidal method from time 0 to 168 hours. If FIX activities are not available up to 168 hours post-dose, the area under the missing terminal part of the curve will be determined by interpolation or extrapolation using a similar principle as for $AUC_{(0\text{-}inf)}$, where the terminal elimination rate constant, $\lambda_z$, is used given that there are sufficient measurements for the determination of the terminal elimination rate constant. |
| Accumulation ratio | 0-168 hours post-injection at weeks 0 and 12 | | Accumulation ratio is calculated as $AUC_{(0\text{-}168h)}$ at steady state/$AUC_{(0\text{-}168h)}$ after a single dose. |
| Terminal half-life ($t_{½}$) | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h | $t_{½} = \ln(2) / \lambda_z$, where $\lambda_z$ is the 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. |
| Clearance (CL) | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | mL/h/kg | CL= Dose / AUC.<br>Using $AUC_{(0\text{-}inf)}$ for single-dose and $AUC_{(0\text{-}168h)}$ for steady-state. |
| $V_z$ | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | mL/kg | Apparent volume of distribution based on the terminal phase.<br>$V_z = CL/\lambda_z$ |
| $V_{ss}$ | 0-168 hours post-injection at week 12 | mL/kg | Apparent volume of distribution at steady state.<br>$V_{ss} = CL \cdot MRT$ |
| %extrap | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | % | Percentage of $AUC_{(0\text{-}inf)}$ determined by extrapolation.<br>$AUC_{(t\text{-}inf)}/AUC_{(0\text{-}inf)}$ |
| MRT | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | h | Mean residence time.<br>$MRT = AUMC/AUC_{(0\text{-}inf)}$, 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). |

| | | | |
|---|---|---|---|
| $\lambda_z$ | Single-dose: 0-168 hours post-injection at week 0<br>Steady-state: 0-168 hours post-injection at week 12 | 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 pharmacokinetics will be based on the pharmacokinetic session at Visit 2, and steady-state pharmacokinetics will be based on the pharmacokinetic session at Visit 5.

The pharmacokinetic parameters will be calculated using plasma FIX activity obtained from one-stage clotting assay. The pharmacokinetic 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 FIX 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 FAS excluding outliers.

Which specific pharmacokinetic data points and profiles that will be excluded will be defined prior to database lock. Profiles with pre-dose FIX activity >5% at Visit 2 (possibly indicating inadequate wash out) and profiles that are not indicative of a normal i.v. injection (i.e. clearly increasing plasma FIX activity initially) should be excluded. If a patient is treated with an additional dose during the pharmacokinetic session, the plasma concentrations after the occurrence will then be excluded. Furthermore, if the pharmacokinetic profile shows indications of an additional dose (e.g. clearly increased plasma FIX activity), the plasma concentrations after the occurrence will then also be excluded.

Individual and mean pharmacokinetic profiles will be presented graphically.

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

### 9.4.4 Other safety analyses

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

To analyse the trajectories of neurological examination over time, shift plots will also be presented by examining the proportion of neurological examination items which shift between every two consecutive examinations.[30] For each item, the shift will be categorised into one of the three following groups:

- Shift up (improved): from abnormal to normal findings
- Shift down (worsening): from normal to abnormal findings
- No change: from abnormal to abnormal findings; or from normal to normal findings

### 9.4.5 Other analyses

**Surgery**

Surgery information (surgery details, haemostatic response, consumption of nonacog beta pegol, blood loss, etc) will be listed.

## 9.5 Interim analyses

No interim analysis is planned.

# 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[31] and applicable ICH Good Clinical Practice (GCP) Guideline.[32]
- 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. For China, an international cooperative relevant report of related China's Human Genetic Resources will be submitted based on local regulation requirement.
- 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, the patient's LAR 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 LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines,[32] Declaration of Helsinki[31] 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 or their LAR 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 LAR.
- If the minor reaches legal age while participating in the trial and has only signed an age specific informed assent form, the patient has to re-consent to an informed consent form for patients reaching legal age.

### 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 and/or the patient's LAR must be informed about the patient's privacy rights, including that his 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 and/or the patient's LAR.

- The patient and/or the patient's LAR must be informed that the patient's medical records may be examined by auditors or other authorised personnel 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.

If anaphylactic reactions occur in 2 patients after trial product administration, enrolment of additional patients will be put on hold. All investigators will be informed in writing. An urgent Novo Nordisk safety committee meeting will be called for to decide whether or not the trial can continue with or without modifications. During this evaluation, the trial will be on hold meaning no new patients will be recruited. Dosing of patients on treatment may continue while further evaluation of the anaphylactic reactions is made by the Novo Nordisk safety committee unless otherwise decided by the Novo Nordisk safety committee.

### 10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at chinadrugtrials.org.cn, clinicaltrials.gov, www.clinicaltrialsregister.eu, and 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)[33], the Food and Drug Administration Amendment Act (FDAAA)[34], European Commission Requirements[35-37] 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 + 50 weeks corresponding to visit 10 (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 10. 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:

- AE forms
- Safety information forms
- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a subject)

- 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 personnel 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.

- 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, eCRF and other subject 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 patient's 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 and/or the patient's LAR 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. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g. by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). 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 personnel 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.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators.

#### 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.[38]

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.

## 10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory unless otherwise stated (except for urinalysis; see below).
- 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.
- At visits where it is not possible to perform the required blood sampling, re-scheduling of the visit within the visit window (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 laboratory 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 laboratory 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.
- 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.

### Blood sampling volume

The investigator should follow local guidelines such as the European guideline for blood sampling and volume of blood at each visit in relation to the patient's body weight and age.

**Table 10-1 Protocol-required efficacy laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| FIX activity | FIX activity |

**Table 10-2 Protocol-required safety laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| Antibody assessments | • Anti-N9-GP antibodies (including indirect detection of anti-PEG antibodies)<br>• FIX inhibitors<br>• Anti-HCP antibodies |
| Haematology | • Erythrocytes<br>• Haemoglobin<br>• Leukocytes<br>• Thrombocytes<br>• Differential count (lymphocytes, monocytes, neutrophils, eosinophils, basophils) |

| | |
|---|---|
| Biochemistry | • Alanine Aminotransferase (ALT)<br>• Albumin<br>• Alkaline phosphatase<br>• Aspartate Aminotransferase (AST)<br>• Creatinine<br>• Bilirubin, total<br>• C-reactive protein (CRP)<br>• Urea |
| Virology | • Hepatitis B surface antigen (HBsAg)<br>• Hepatitis C virus antibody<br>• 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)<br>• CD4+ T cell count (only at screening) |
| Coagulation parameters | • Activated partial thromboplastin time (aPTT)<br>• International normalised ratio (INR)<br>• Prothrombin time (PT)<br>• Lupus anticoagulant |
| Urinalysis | • pH<br>• Protein<br>• Erythrocytes<br>• Leukocytes<br>• Glucose<br>• Albumin/creatinine ratio |
| Other tests | • eGFR calculated by the central laboratory based on the creatinine value using the MDRD equation<br>• PEG plasma concentration |
| Notes:<br>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.<br>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<br>• Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected<br>• Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition<br>• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction<br>• Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent<br><br>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.<br>Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.<br>• Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE.<br>• 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**<br>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**<br>• 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 patient 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 AEs 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**

An AESI is an event which, in the evaluation of safety, has a special focus due to requirements from regulatory authorities.

A serious AESI should be reported following the same reporting requirements and timelines as for SAEs (see Section 10.3.5).

The following are defined as AESIs in this trial:

- **Inhibitor formation against FIX** is always considered a serious AESI. If an investigator obtains any indication of inhibitor formation by clinical signs or central laboratory results, this should be reported as a serious AESI. Please update the reported serious AESI with inhibitor tests results, when these are available.

- **Allergic reaction** including, but not limited to, any acute IgE mediated reaction or delayed type hypersensitivity (clinical signs may include various types of skin rashes) that does not meet the definition of anaphylaxis as described by Sampson et al.[23] (see below).
- **Anaphylactic reaction** as defined by Sampson et al.[23] (see below).
- **CNS-related AEs** including, but not limited to, any learning and behavioural deficits. Examples include but are not limited to:
  - Headache
  - Seizures
  - Vision problems
  - Acute changes in mental status
  - Developmental, cognitive or behavioural issues.
- **Thromboembolic events** (clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion, see definitions below).
- **Renal AEs** including new onset of renal disorder or renal impairment or acute and chronic renal failure.

AESIs must always be reported on an AE form and safety information form in the eCRF.

**Clinical criteria for diagnosing anaphylaxis according to Sampson et al.:**[23]
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).

**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 intravenous.
- 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.

### 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.
- 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 AE 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 subject, 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[22] 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 and Hy's law). 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 CRF 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.

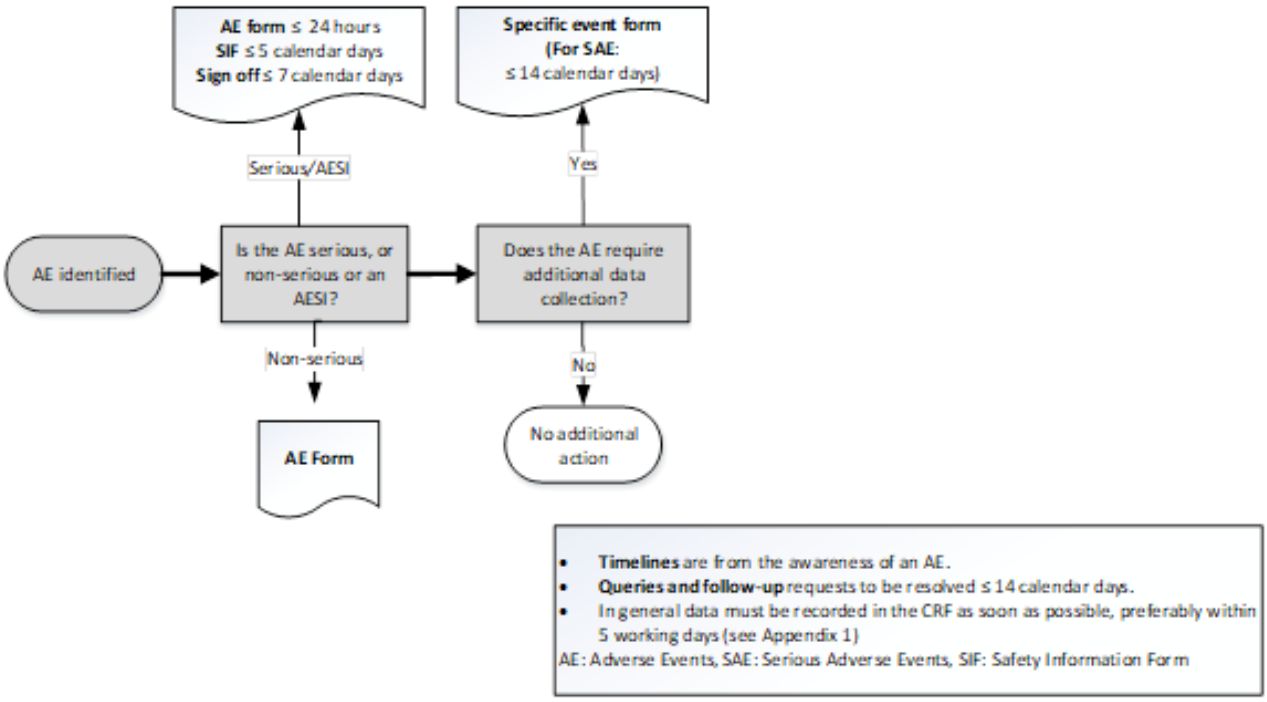



**Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines**

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.

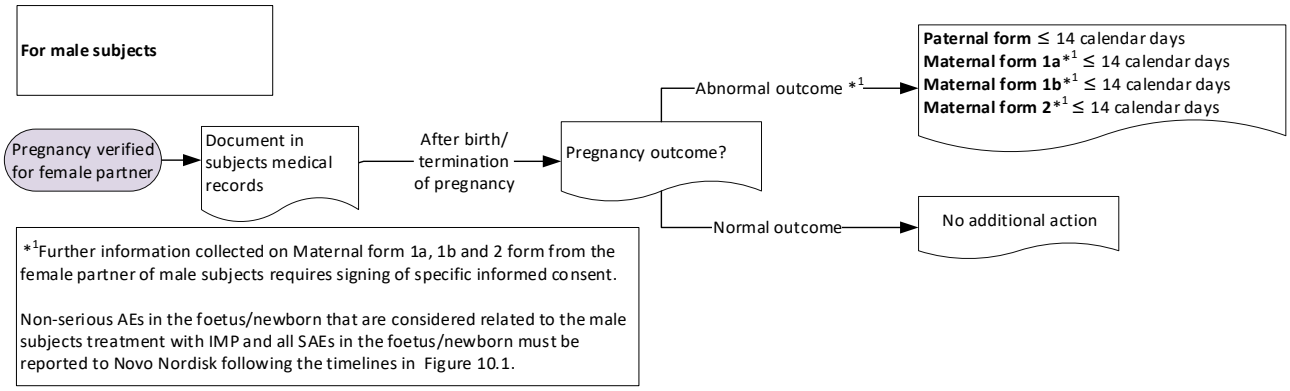



**Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy**

## 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.<br><br>Technical complaints must be reported on a separate technical complaint form:<br>One technical complaint form must be completed for each affected DUN.<br>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:<br>• 24 hours if related to an SAE<br>• 5 calendar days for all other technical complaints<br><br>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.<br>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

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

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

**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 Pediatric Stroke Outcome Measure (PSOM)[39]

## 10.7 Appendix 7: Country-specific requirements

The following items are applicable for China:

| Item | Section | Section title | Local requirement |
|---|---|---|---|
| 1 | 5.1 and 5.2 | Inclusion criteria and 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. |
| 3 | 10.1.10 | Retention of clinical trial documentation | Site specific data should only be stored at site.<br><br>Long-term storage of Chinese patients' trial data is not allowed in other entities. |
| 4 | 10.7 | Appendix 7: Country-specific requirements | The samples which are tested at the central laboratory will be destroyed as biological waste according to local regulation and laboratory manual. The laboratory samples for Chinese patients will be destroyed no later than the finalisation of the clinical trial report, or according to local regulatory requirement. |

## 10.8 Appendix 8: Abbreviations

| | |
|---|---|
| ABR | annualised bleeding rate |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| AUMC | area under the first moment curve |
| BP | blood pressure |
| BU | Bethesda unit(s) |
| C | concentration |
| CDE | Center for Drug Evaluation |
| CL | clearance |
| CNS | central nervous system |
| COVID-19 | coronavirus disease of 2019 |
| CRF | case report form |
| CRP | C-reactive protein |
| CTR | clinical trial report |
| CV% | coefficient of variation in percent |
| DRE | disease-related event |
| DUN | dispensing unit number |
| ED | exposure day |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| ELISA | enzyme-linked immunosorbent assay |
| FAS | full analysis set |
| FDAAA | U.S. Food and Drug Administration Amendments Act |
| FIX | factor IX |
| FVII | factor VII |
| FVIII | factor VIII |
| GCP | Good Clinical Practice |
| HBsAg | hepatitis B surface antigen |
| HCP | host cell protein |
| HIV | human immunodeficiency virus |

| | |
|---|---|
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| inf | infinity |
| IR | incremental recovery |
| IRB | institutional review board |
| IU | international unit(s) |
| i.v. | intravenous(ly) |
| IWRS | interactive web response system |
| $\lambda_z$ | terminal elimination rate constant |
| LAR | legally authorised representative |
| LLOQ | lower limit of quantification |
| LOCF | last observation carried forward |
| MDRD | Modification of Diet in Renal Disease |
| MRT | mean residence time |
| N | number of patients |
| N9-GP | nonacog beta pegol |
| NE | not evaluated |
| PCD | primary completion date |
| PEF | peak expiratory flow |
| PEG | polyethylene glycol |
| PK | pharmacokinetic(s) |
| PPX | prophylaxis |
| rFIX | recombinant FIX |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| SD | single-dose |
| SIF | safety information form |
| SOP | standard operating procedure |
| SS | steady-state |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{½}$ | half-life |
| TEAE | treatment emergent adverse event |

| | |
|---|---|
| TESAE | treatment emergent serious adverse event |
| TMM | trial materials manual |
| UNL | upper normal limit |
| $V_z$ | apparent volume of distribution |
| $V_{ss}$ | apparent volume of distribution at steady state |
| WFH | World Federation of Hemophilia |

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