pathfinder9

Study ID: NN7088-4029

pathfinder 9

A multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional (NIS) post authorisation safety study (PASS)

.

PASS information

Title	A multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia A
Protocol version identifier	Version 2.0, 17 April 2020
Date of last version of protocol	N/A
EU PAS Register number	Study not yet registered
Active substance	Turoctocog alfa pegol (N8-GP) ATC code: [redacted]
Medicinal product	Esperoct®
Product reference	
Procedure number	
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	This study is designed for the purpose of obtaining safety information from real-world post authorisation use.

Primary objective:

to investigate the long-term safety of N8-GP including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A.

Secondary objective:

to further evaluate the general safety of N8-GP during routine use in patients with haemophilia A under the circumstances in which it was prescribed by the physician. This will include FVIII inhibitors and allergic/hypersensitivity reactions.

Countries of study

Expected countries: Germany, Spain, Italy, Switzerland, Slovenia, Slovakia, Croatia, Portugal, Greece
The list of countries is not complete

Author

[redacted]

Marketing authorisation holder

Marketing authorisation holder (MAH)

Novo Nordisk A/S

Novo Allé

DK-2880 Bagsværd

Denmark

MAH contact person

[redacted]

1 Table of contents

Page

2 List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AR	Adverse Reaction
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGRF	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FVIII	Factor VIII
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practice

ICH-GCP	International Conference on Harmonisation/GCP
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune Tolerance Induction
LAR	Legally Acceptable Representative
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder
N8-GP	Turoctocog alfa pegol
NIS	Non-interventional Study
PASS	Post Authorisation Safety Study
PEG	40 kDa glycoPEGylated
PK	Pharmacokinetics
PTPs	Previously treated patients
rFVIII	Recombinant factor VIII
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SIF	Safety Information sheet
UNL	Upper normal limit
UTN	Universal Trial Number

WHO World Health Organisation

3 Responsible parties

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties. During any period of unavailability, the physician should delegate responsibility for study activities of patients to a specific qualified physician who should be readily available to patients during that time. If the physician is no longer able to fulfil the role of physician (e.g. if he/she retires), a new physician must be appointed in consultation with Novo Nordisk. The physician and site personnel must have sufficient English skills according to their assigned task(s).

The physician must follow the instructions from Novo Nordisk when processing data. The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law. Upon request from Novo Nordisk, the physician must provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that technical and organisational safety measures have been taken.

Please refer to the Stand-alone documents (Annex 1) for additional information about responsible parties. A list of all collaborating institutions and physicians will be made available to authorities upon request.

4 Abstract

4.1 Title

A multinational, prospective, open labelled, non-controlled, non-interventional post-authorisation study (PASS) of turoctocog alfa pegol (N8-GP) during long-term routine prophylaxis and treatment of bleeding episodes in patients with haemophilia. Version 2.0 draft 23 January 2020. Author

4.2 Rationale and background

Novo Nordisk has developed turoctocog alfa pegol (N8-GP), a 40 kDa glycoPEGylated (PEG) human recombinant factor VIII (rFVIII) with an extended half-life, for the treatment and prophylaxis of haemophilia A.

Marketing authorisation applications for Esperoct® (N8-GP) have been submitted globally. Esperoct® was approved in the US in February 2019 followed by EU in June 2019.

As per guideline, it is a request from the European Medicines Agency (EMA) to collect additional clinical safety data and to ensure consistency between the outcome from the pre-authorisation

clinical trials and those from post-approval local clinical practice use of commercially available product.[1]

The general safety profile of N8-GP for the treatment of patients with haemophilia A is well examined in long-term exposure data from the pivotal-phase 3 trial in adolescents and adults, in the paediatric phase 3 trial and the surgery phase 3 trial and is similar to the safety profile of currently approved FVIII products.

Specific pharmacological risks for FVIII replacement products include FVIII inhibitor development and allergic-type hypersensitivity reactions, which were evaluated in all phase 3 trials.

4.3 Research question and objectives

The research question behind the study is to gain additional knowledge on safety in prophylaxis patients and obtain additional clinical data on the use of N8-GP in the setting of local clinical practice.

The primary objective of the study is to investigate the safety of N8-GP including the PEG moiety during prophylaxis and long-term use in patients with haemophilia A as prescribed by the physician.

Secondary objectives are to further evaluate the general safety of N8-GP during routine prophylaxis (including FVIII inhibitors and allergic/hypersensitivity reactions) and long-term use in patients with haemophilia A as prescribed by the physician.

Exploratory objectives are to monitor possible clinical effects of long-term exposure to N8-GP prophylaxis in patients with haemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma level.

The primary endpoint of the study is:

- Number of Adverse Events (AEs) reported during the study period

The secondary endpoint is:

- Number of Serious Adverse Events (SAEs) reported during the study period

The exploratory endpoints are:

- Number of AEs related to hepatic or renal function during the study period
- Number of AEs that are defined within the system organ classes "Nervous system" or significant deviations from expected neurologic function during the study period
- Changes in laboratory parameters during the study period; including the hepatic and renal function parameters
- Changes in PEG-plasma levels from study start to end of study
- Number of FVIII treatment requiring bleeding episodes reported during the study period

4.4 Study design

This is a prospective, multinational, non-interventional PASS in patients with moderate or severe haemophilia A. Patients fulfilling the inclusion criteria can participate in the study regardless of previous treatment regimen, allowing inclusion of patients previously exposed to N8-GP and/or other FVIII products.

Patients will be treated with commercially available N8-GP according to local clinical practice at the discretion of the physician.

The total study duration is estimated to be 7 years with a planned recruitment period of approximately 2 years. The aim is to collect data on 50 patients on prophylaxis with N8-GP for at least, but not limited to 5 years. Patients may continue in the study for the total planned study duration allowing active data collection for up to 7 years.

4.5 Population

Approximately 60 male haemophilia A patients of any age will be enrolled to allow for completion of 50 patients.

Inclusion Criteria:

1. Signed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
2. The decision to initiate treatment with commercially available Esperoct® has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in this study.
3. Male patients of all ages, according to local label, are allowed in this study
4. Diagnosis of severe or moderate Haemophilia A

Exclusion Criteria:

1. Previous participation in this study. Participation is defined as having given informed consent in this study
2. Known or suspected hypersensitivity to N8-GP or related products
3. Mental incapacity, unwillingness or language barriers precluding adequate understanding and cooperation
4. Clinical suspicion or presence of FVIII inhibitors at time of inclusion

4.6 Variables

Data within safety, i.e. number of AEs, will be collected. Data and results from assessments and laboratory analyses performed according to local clinical practice at the participating sites will be recorded upon availability. Consumption of N8-GP will be based on treatment regimen and reported

bleeding episodes and will be reported in the electronic Case Report Form (eCRF) system, based on patients own diary.

4.7 Data sources

Data and results available in the patients' medical records, from assessments and laboratory analyses performed according to local practice at the participating sites and from patients own diary will be recorded in the eCRF.

4.8 Study size

The study is planned to include safety follow-up assessments at routine care visits for at least, but not limited to 5 years with 50 patients. Patients may continue in the study for the total planned study duration allowing active data collection for up to 7 years.

4.9 Data analysis

No formal testing of statistical hypothesis will be performed. All data will be presented using descriptive statistics. Categorial data will be summarized by frequency tables while continuous data will be summarized by mean, standard deviation, median, minimum and maximum value.

4.10 Milestones

First Patient First Visit (FPFV)	03 June 2020
Planned date for Last Patient Last Visit (LPLV)	03 June 2027
Planned completion of non-interventional study report (NSR)	03 May 2028

5 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
None				

6 Milestones

Milestone	Planned date
Start of data collection Defined as First Patient First Visit (FPFV)	03 June 2020
End of study Defined as Last Patient Last Visit (LPLV)	03 June 2027
End of data collection Defined as Data base Lock (DBL)	28 August 2027
Interim DBL	approximately 2.5 years after FPFV
Registration in the EU PAS Register	Prior to start of data collection, i.e. before FPFV
Final report of study results	03 June 2028
Study progress report	Annual (June 2021-June 2027)

7 Rationale and background

Novo Nordisk has developed turoctocog alfa pegol (also referred to as N8-GP), a 40-kDa glycoPEGylated human recombinant coagulation Factor VIII (rFVIII) with an extended half-life, for the prophylaxis and treatment of bleeding episodes in patients with haemophilia A. N8-GP has improved pharmacokinetik (PK) properties including a 1.6 fold increase in terminal half-life compared with standard FVIII products, which offers the possibility of achieving FVIII levels in the range of moderate haemophilia A with a less burdensome every fourth day or twice weekly treatment regimen.[2-4]

Marketing authorisation applications for Esperoct® have been submitted globally. Esperoct® was approved in the US in February 2019 followed by EU in June 2019, and Canada and Switzerland in July.

The regulatory approval of N8-GP was based on the comprehensive pathfinder™ programme, a phase 1 to 3a clinical programme including 270 unique previously-treated patients (PTPs) children,

adolescents and adults with severe haemophilia A (FVIII activity ≤1%). The phase 3 trials documented that N8-GP is efficacious for prophylaxis and treatment of bleeding episodes across all age groups[2, 3] and in providing effective haemostasis during and after major surgical procedures.[5] The median annualized bleeding rate for adolescents and adults was 1.18 and for children 1.95. In children, 82 % of their target joints did not bleed during the main phase of the trial, and children overall also showed an enhanced quality of life. The overall success rate for the first treatment of a bleeding episode evaluated within 8 hours was 88 %.[2, 3]

The general safety profile of N8-GP for the treatment of patients with haemophilia A is well examined through the clinical development programme, where N8-GP was well tolerated and has demonstrated a safety profile in the pivotal phase 3 trial in adolescents and adults, in the paediatric phase 3 trial and the surgery phase 3 trial similar to that of currently approved FVIII products.

The Committee for Medicinal Product for Human use (CHMP) has raised a theoretical concern regarding potential long-term effects of PEG accumulation in organs and other tissues. Based on modelling data and supported by analyses of PEG plasma levels in clinical samples from adolescent/adult and paediatric patients participating in the N8-GP phase 3 trials, plasma steady-state PEG concentrations have been reached in the clinical trial programme without any indication of PEG-related adverse effects to date. The clinical safety of long-term exposure to N8-GP – including evaluation of potential clinical consequences of exposure to 40 kDa PEG in organs and tissues – is yet to be established.

As per guideline, it is a request from the European Medicines Agency (EMA) to collect additional clinical data and to ensure consistency between the outcome from the pre-authorisation clinical trials and those from post-approval local clinical practice use of commercially available product.[1] Therefore, a post-marketing investigation should be performed. Novo Nordisk has received an obligation to conduct a Post-Authorisation Safety Study (PASS) to investigate the potential effects of PEG accumulation in organs and other tissues.

The purpose of this non-interventional PASS is thus to gain additional knowledge on the safety of N8-GP in patients with haemophilia A after longer-term treatment and to evaluate possible clinical consequences hereof under observational (‘real-world’) conditions of local clinical practice.

8 Research question and objectives

8.1 Primary objective

To investigate long-term safety of N8-GP including the PEG moiety of the substance during routine prophylaxis in patients with haemophilia A.

8.2 Secondary objective

To further evaluate the general safety including FVIII inhibitors and allergic/hypersensitivity reactions of N8-GP during routine use in patients with haemophilia A under the circumstances for which it was prescribed.

8.3 Exploratory objectives

To monitor possible clinical effects of long-term exposure to N8-GP in patients with haemophilia A, including assessments of kidney and liver function parameters, neurologic function and patients' PEG plasma level, besides the number of FVIII treatment requiring bleeding episodes.

9 Research methods

In this document physician refers to the individual overall responsible for the conduct of this non-interventional study at the study site. Tasks can be performed by a health care professional according to qualifications and at the discretion of the responsible physician.

9.1 Study design

This is a prospective, multi-national, non-interventional post-authorisation study in patients with haemophilia A, prescribed prophylaxis with N8-GP by the treating physician prior to and independent of the decision to include the patient in the study. The study is designed to obtain additional real-life exposure and safety information.

The study is planned to include safety follow-up assessments at routine care visits for at least, but not limited to 5 years with 50 patients. Patients may continue in the study for the total planned study duration allowing active data collection for up to 7 years.

This study aims to observe routine use of N8-GP in any eligible patient in accordance with care prescribed by the treating physician, to the extent that enrolment of patients is allowed under local regulatory rules.

Monitoring of safety will be performed from a patient's first exposure to N8-GP after enrolment in this study defined by completion of informed consent through the patient's last visit in the study (defined as end of study or withdrawal of informed consent). Adverse events (AEs) are expected to be captured through the periodic clinical evaluations every 6-12 months that are routinely undertaken in patients with haemophilia A. Follow-up on any AE will be carried out until resolution of the AE, and if the patient discontinues to the extent allowed by IRB/ethics committees following discontinuation of the study. Exploratory assessment of the patients' PEG plasma level as requested by EMA, will be performed at pre-defined time points (see section 9.2.7.4) and if considered clinically warranted by the responsible physician.

The follow up period after discontinuation of study drug should be as long as possible, preferably until end of study.

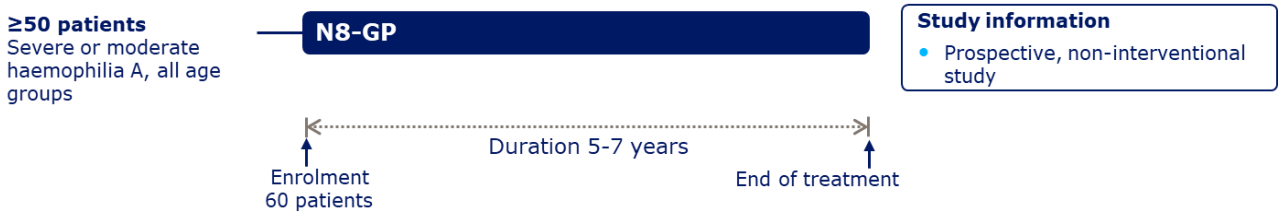

Figure 9-1 Study Design

9.1.1 Primary endpoint

Endpoint	Time frame	Unit
Number of Adverse Events (AEs) reported during the study period	From inclusion of the patient until end of study	Count of events

9.1.2 Secondary endpoint

Endpoint	Time frame	Unit
Number of Serious Adverse Events (SAEs) reported during the study period	From inclusion of the patient until end of study	Count of events

9.1.3 Exploratory endpoints

Endpoint	Time frame	Unit
Number of AEs related to hepatic or renal function during the study period	From inclusion of the patient until end of study	Count of events
Number of physician-identified AEs related to the system organ class “Nervous system” or significant	From inclusion of the patient until end of study	Count of events

deviations from expected neurologic function during the study period		
Changes in laboratory parameters during the study period, including hepatic and renal function parameters	From inclusion of the patient until end of study visit	Count of events
PEG-plasma levels	At entry, after 2 years, and at the end of study	ng/mL
Number of FVIII treatment requiring bleeding episodes reported during the study period	As described in section 9.2.7.1	Count of events

9.1.4 Treatment of patients

Patients will be treated with commercially available N8-GP for prophylaxis and treatment of bleeding episodes according to routine clinical practice at the discretion of the treating physician. Patients may undergo surgical procedures while participating in the study.

As this is a non-interventional study, there is no prohibited concomitant medication during participation. If the treating physician decides to use other FVIII replacement therapy products or combination therapy with N8-GP or additional haemostatic agents, any concurrent medications (including other FVIII products, anti-fibrinolytics, topic haemostatic products or sealants) should be documented by the study site.

Patients who develop FVIII inhibitors can continue treatment with N8-GP at the discretion of the physician. If this is decided, the dosing and dosing frequency will be decided by the treating physician based on the clinical evaluation.

9.2 Setting

9.2.1 Study Population

Planned number of patients to be included: 60

Planned number of patients to complete the study: 50

Anticipated number of patients to be included in each country: Depending on availability in relevant countries

Time period for the study: Estimated to 7 years

9.2.2 Inclusion criteria

1. Signed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
2. The decision to initiate treatment with commercially available Esperoct® has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in this study.
3. Male patients of all ages, according to local label, are allowed in this study
4. Diagnosis of severe or moderate Haemophilia A

9.2.3 Exclusion criteria

1. Previous participation in this study. Participation is defined as having given informed consent in this study
2. Known or suspected hypersensitivity to N8-GP or related products
3. Mental incapacity, unwillingness or language barriers precluding adequate understanding and cooperation
4. Clinical suspicion or presence of FVIII inhibitors at time of inclusion

9.2.4 Rationale for selection criteria

The study is intended to reflect the population for which N8-GP is approved and marketed in the various countries, therefore study participants can be recruited regardless of their age as long as N8-GP is prescribed by the physician according to local label. In general, all patients from pre-authorisation clinical studies could be enrolled in post-marketing investigations.

Patients who previously developed inhibitors can be included after successful ITI. The proportion of ITI patients should not be more than 25% of the whole cohort.

The few inclusion and exclusion criteria will reduce selection bias. As a multicentre, multinational population has been selected the generalizability of the study is evaluated as high. The study is global and can include all ethnic groups.

The study population is characterized through the inclusion criteria:

Criterion no. 1 is included in accordance with Good Pharmacoepidemiology Practices (GPP)[6]

Criterion no. 2 is included in accordance with Good Pharmacovigilance Practice (GVP) and based on the EMA guideline concerning post-marketing investigation and expanded for the purpose of reflecting local clinical practice[1]

Criterion no. 3 is included to reflect the population for which N8-GP is approved and marketed in the respective countries.

Criterion no. 4 is included based on the EMA guideline concerning post-marketing investigation and expanded for the purpose of reflecting local clinical practice[1]

The study population is characterized through the exclusion criteria:

Criterion no. 1 is to ensure that a patient only counts once in the data analyses

Criterion no. 2 is included in accordance with International Conference on Harmonisation/Good Clinical Practice (ICH-GCP)[7]

Criterion no. 3 serves to protect patient safety by eliminating the risk of not following prescribed dosing of N8-GP.

Criterion no.4 is derived from the EMA guideline concerning post-marketing investigation[1]

9.2.5 Withdrawal criteria

The patient may withdraw - or the parent(s)/LAR may withdraw the patient - at will at any time.

In case of withdrawal, the physician should attempt to collect any outstanding data. The primary reason (adverse event or other) for discontinuation should be specified in the Case Report Form (CRF).

9.2.6 Visit procedures

Table 9-1 Flow Chart

	Section	Baseline	Visits	Follow-Up
Visit		Visit 1	Visit 2.1, 2.2, 2.3 etc	Visit 3 (End of Study)
PATIENT RELATED INFORMATION AND ASSESSMENTS				
Informed Consent	9.2.8.1	X		
In/exclusion Criteria	9.2.2 9.2.3	X		
Medical history	9.2.8.2	X		
Haemophilia treatment and bleed history	9.2.8.3	X		
Details of Haemophilia	9.2.8.4	X		
Demography	9.2.8.5	X		
Concomitant illness	9.2.8.6	X		
Concomitant medication	9.2.8.7	X	X	X
Withdrawal criteria	9.2.5		X	X
Genotype[a]	9.2.8.8	X		
Dosing regimen	9.2.8.9	X	X	X
Body measurements	9.2.8.10	X	X	X
EFFECTIVENESS				
Bleeding episode[b]	9.2.7.1	X	X	X
SAFETY				
FVIII inhibitor	9.2.7.2	X	X	X
Factor VIII Activity	9.2.7.3	X	X	X
PEG plasma level[c]	9.2.7.4	X	X[c]	X
Biochemistry	9.2.7.5	X	X	X
Urinalysis	9.2.7.6	X	X	X
Physical examination	9.2.7.7	X	X	X
Adverse event	9.2.7.8		X	X
OTHER ASSESSMENTS				
Surgery	9.2.8.11		X	X
REMINDERS				
Discuss content and use of patients own diary	9.2.7.1, 9.2.8.9	X	X	
End of study	9.2.6.4			X

a) Only the FVIII genotype should be captured if available as existing result in medical records.

b) Only FVIII requiring bleeding episodes must be captured including bleed details and severity rating where available.
c) One measurement two years after enrolment and if considered clinically warranted by the responsible physician.

Informed consent is required when entering the study. The rest of the assessments listed in the flow chart are not mandatory, but it is recommended to monitor safety of N8-GP in participating patients. Information from assessments performed during the patient's participation in the study should be recorded in the eCRF from the time informed consent has been obtained. For each visit the site personnel should enter all available information in the eCRF as specified in the below sections.

Patients should receive care at their respective clinic in accordance with local clinical practices. All study visits should be performed according to local clinical practice. The physician should keep a patient enrolment log and a log of patients evaluated for, but not included in the study, throughout the enrolment period. These logs may be separate or combined in one document. Patient identification is to be accomplished via allocation of a six-digit number which consists of a three-digit site code and a three-digit patient ID. A range of numbers will be provided by Novo Nordisk.

Signed informed consent must be obtained from the patient or, for patients under legal age, from the parent(s) or LARs prior to any study related activities.

Patients enrolled in the study should be provided with contact address(es) and telephone number(s) of the physician site and/or staff. In case a patient is being prematurely withdrawn from the study the physician should ensure that the procedures for the last visit are recorded, if possible.

9.2.6.1 Baseline (Visit 1)

Relevant data available in the patient's medical record at the time of the baseline visit may be used as baseline data and should be entered in the eCRF after having obtained informed consent. All relevant data necessary for evaluating whether a patient can be enrolled in the study e.g. inclusion/exclusion criteria, see section 9.2.2 and 9.2.3, must be available prior to enrolling a patient. Relevant data regarding the assessments listed in the flow chart for visit 1 must be entered in the eCRF, if available.

9.2.6.2 Visits 2.1, 2.2, 2.3, etc.

At each contact with the site during the study, the patient should be asked about possible adverse events since the last contact. This may be done by posing a simple question such as "have you experienced any problems since the last contact?".

Relevant data regarding the assessments listed in the flow chart must be entered in the eCRF, if available.

9.2.6.3 Phone contacts

In case a patient calls the site during his participation in the study all relevant study information, i.e. reported AEs, should be entered in the patients' medical records and subsequently in the eCRF.

9.2.6.4 End of study visit

This visit will take place just prior to the planned study LPLV date. In case a patient withdraws his consent, the physician should encourage the patient to come in for an end of study visit. Relevant data regarding the assessments listed in the flow chart must be entered in the eCRF, if available.

The end of study visit may, if not possible to be conducted as an on-site visit, be performed as a phone contact. This should only be done in case a patient does not visit the site as part of his routine care.

The following must be reviewed and recorded:

- End of study form
- Withdrawal criteria, in case a patient has withdrawn, section 9.2.5

9.2.7 Assessments for safety and effectiveness

9.2.7.1 Bleeding episodes

The physician should at each visit ask the patient if he has experienced any FVIII treatment requiring bleeding episodes since his last visit. The physician should encourage the patient to note down the date, cause and anatomical location of each FVIII treatment requiring bleeding episodes between the visits in his own personal notes/diary. This information should be entered into the eCRF.

9.2.7.2 FVIII inhibitor

In case a FVIII inhibitor test is performed as part of the local clinical practice the result should be recorded in the eCRF. A patient has confirmed inhibitor if the patient has been tested positive for inhibitors at two consecutive tests 1-4 weeks apart. Even if the second inhibitor test is positive, the patient may continue treatment with N8-GP.

A positive inhibitor test considered related to N8-GP should be reported as a serious adverse event (SAE) regardless of confirmation, see section 11. Any potential follow-up inhibitor testing should be reported as a follow-up to the reported SAE, see section 11.

9.2.7.3 FVIII activity

In case FVIII activity is determined as part of the local clinical practice, the result(s) should be recorded in the eCRF.

9.2.7.4 PEG plasma level

PEG plasma levels should be determined three times during the course of the study. This should preferably be done at baseline (visit 1), after two years of participation in the study and at the 'End of study visit'. Additionally, the responsible physician can request additional analyses if considered clinically warranted. The sample will be analysed at a special laboratory, contracted by sponsor, to determine the concentration of PEG in the patients' blood.

9.2.7.5 Biochemistry

If below biochemistry analyses are performed as a part of the local clinical practice, they should be recorded in the eCRF.

- Aspartate aminotransferase (AST)
- Bilirubin
- Creatinine
- Alanine Aminotransferase (ALT)
- Estimated Glomerular Filtration Rate (eGFR)

9.2.7.6 Urinalysis

If urine dipsticks are used in local clinical practice, the test result for proteins in urine should be recorded in the eCRF.

9.2.7.7 Physical examination

It is recommended to perform physical examination at every visit. The examination may include:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Genito-urinary system
- Musculo-skeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

Findings that exist at the time of enrolment in the study should be reported as medical history, new abnormal findings should be reported as adverse events (AE).

9.2.7.8 Adverse event, serious adverse events and adverse events of special interest

All adverse events (AEs), including serious adverse events (SAEs), either observed by the physician or reported by the patient must be recorded and evaluated by the physician. Adverse events of special interest (AESI), which in the evaluation of safety have a special focus, are listed in section 11.1 and appendix A.

At each contact with the site during the study, the patient should be asked about AEs since the last contact. Please refer to appendix A and section 11 for AE, SAE and AESI definitions, collection, recording, and reporting times. AE collection and reporting must be performed after signed informed consent and until a patient's last visit in the study.

Bleeding episodes are not considered adverse events unless the bleeding episode is fatal, life threatening or evaluated by the investigator as possibly caused by the study product. Causes to a bleeding episode may be considered as an AE e.g. an injury.

9.2.8 Other assessments

9.2.8.1 Informed consent

The date of informed consent must be recorded in the eCRF after having obtained patient's, parent's or LAR's, informed consent, as applicable.

9.2.8.2 Medical history

The information collected for medical history should include diagnosis and resolution date and be recorded at the baseline visit based on discussion with the patient and/or based on medical records. If a diagnosis is unknown, the description of symptoms should be recorded.

9.2.8.3 Haemophilia treatment and bleed history

Haemophilia treatment history should be recorded including the number of months on prophylactic/on demand regimen and the used dosing regimen for the preceding 12 months. In case of an emerging inhibitor the brand name of the FVIII product used for prophylaxis and/or episodic treatment should be recorded in the eCRF.

9.2.8.4 Details of Haemophilia

Details of Haemophilia should be collected with FVIII level from medical history. Previous positive inhibitor status, including transient inhibitors or successful Immune Tolerance Induction (ITI) therapy should be recorded in the eCRF. Known family history of haemophilia should be recorded in the eCRF with "yes" or "no".

9.2.8.5 Demography

Collected as allowed by local law:

- Date of birth
- Ethnicity
- Race

9.2.8.6 Concomitant illness

Definition of concomitant illness: any clinically significant illness that is present at study entry (i.e. at baseline visit/visit 1) including viral infections e.g. human immunodefiency virus (HIV) and should include diagnosis. If a diagnosis is unknown, the description of symptoms should be recorded.

Any changes from visit 1 in concomitant illness must be recorded at each visit in the eCRF. In case a concomitant illness deteriorates during the study, an adverse event must be recorded and reported according to section 11 and appendix A. If the change influences the patient's eligibility to continue the study, the sponsor must be informed.

9.2.8.7 Concomitant medication

Definition of concomitant mediation: any medication other than N8-GP that is taken during the study, including medication reported at baseline visit (visit 1). Any changes in medication must be recorded at each visit in the eCRF.

The information collected for each concomitant medication should preferably include trade name or generic name, indication, start and stop date or continuation. If concomitant medication is taken due to an adverse event this must be listed in the eCRF.

9.2.8.8 Genotype

If a FVIII genotyping result is available this should be recorded in the eCRF. Genotype result may only be collected upon consent given.

9.2.8.9 Dosing regimen

The N8-GP dosing regimen at study entry and any changes in regimen during the study, must be recorded in the eCRF, including dosing regimen and date.

The physician should at each visit discuss the haemophilia treatment with the patient. The patient should be asked if the prophylaxis doses of N8-GP were taken as prescribed since last visit, and any deviations from the prescription must be recorded in the eCRF.

The physician should ensure that the patient notes down any treatment relevant details between the visits in his own personal notes/diary. The patient diary (for example national mobile application or personal paper diaries) must be used as a basis in the discussion during the routine visits to the clinic.

9.2.8.10 Body measurements

It is recommended to weigh the patient at each visit and measure the height if the patient is in the age of growing height. The height should be measured without shoes.

9.2.8.11 Surgery

Patients undergoing surgery will be managed according to local clinical practice. For surgery the following data should be recorded in the patient's eCRF, if available:

- Date of surgery
- Indication

9.3 Variables

Data within safety (AEs) will be collected. Data and results from assessments and laboratory analyses according to flow chart will be recorded if performed as part of the routine clinical practice. Consumption of N8-GP will be based on treatment regimen and reported bleeding episodes and will be reported in the electronic Case Report Form (eCRF) system, based on patients own diary.

Ongoing monitoring will ensure that all collected data will be transferred to the eCRF as relevant.

9.4 Data sources

Data and results available in the patients' medical record and from assessments and laboratory analyses performed according to local practice at the participating sites will be recorded in the eCRF. In addition, available information from patients own diary related to treatment, FVIII treatment requiring bleeding episodes and in case a patient is hospitalized should be reported in the patient's record and subsequently in the eCRF by the health care professional. Data sources are eCRFs, paper CRF form (pregnancy in patient's female partner), medical record and laboratory data.

9.5 Study size

The study is planned to include safety follow-up assessments at routine care visits for at least 5 years with 50 patients. The sample size is based on a regulatory request from EMA and no formal sample size calculation was performed.

9.6 Data management

Data management is the responsibility of Data Management at Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to another data management unit within Novo Nordisk or a Contract Research Organisation (CRO).

Novo Nordisk will provide electronic Case Report Forms (eCRFs) for capture of study specific patient data. Instructions for completion and correction of eCRF will be provided.

The only CRF Paper form included in the study is "pregnancy in patient's female partner".

The physician must ensure that study specific patient data is entered in the eCRF as soon as possible after the visit and no later than 5 days after.

The physician should ensure that all available data present is registered, and all possible questions answered. If a test/assessment has not been done and will not be available, or if the question is not applicable, it must be indicated according to the instructions for completing eCRFs.

Appropriate measures such as encryption or deletion must be enforced to protect the identity of patients when transmitting data, in all presentations and publications as required by local/regional/national requirements.

The system for Electronic Data Capture (EDC) and support services for the system will be supplied by [redacted] The activities of [redacted] will be under the direction and supervision of Novo Nordisk.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry and the corrected entry.

By signing the affirmation statement/casebook the physician confirms that the information in the eCRF is complete and correct.

If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement/casebook, this must be signed again by the physician.

After the study database is released, site specific eCRF data must be downloaded by site in an electronic readable format of site's choice. The access to the study specific EDC may subsequently be revoked.

9.7 Data analysis

Novo Nordisk will be responsible for the statistical analyses but may contract a CRO to perform the task.

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

9.7.1 Definition of analysis sets

All safety analyses will be based on the safety analysis set (SAS) where all patients exposed to N8-GP during study period will be included.

9.7.2 Statistical methods

No formal testing of statistical hypothesis will be performed. All data will be presented using descriptive statistics. Categorial data will be summarized by frequency tables while continuous data will be summarized by mean, standard deviation, median, minimum and maximum value.

Subgroup analysis will be presented:

- By age groups (< 6 years, 6 to < 12 years, 12 to < 18 years, 18 to < 65 years, ≥ 65 years)
- By severity of disease (moderate and severe)

Patients who previously developed inhibitors before entering this study might be presented separately if deemed necessary.

9.7.2.1 Primary endpoint

- Number of Adverse Events (AEs) reported during the study period

The number of AEs reported during the study period will be summarised together with the number of patients with any AE. Furthermore, listings will be provided displaying all AEs.

9.7.2.2 Secondary Endpoint

- Number of Serious Adverse Events (SAEs) during the study period

Number of Serious Adverse Events (SAEs) reported during the study period will be summarised together with the number of patients with any SAE. Furthermore, listings will be provided displaying all SAEs.

9.7.2.3 Exploratory Endpoints

- Number of AEs related to hepatic or renal function during the study period
- Number of AEs that are defined within the system organ class nervous system during the study period and/or Number of physician-identified AEs related to significant deviations from expected neurologic function during the study period

Number of these specific AEs during study period will be summarised together with the number of patients with any of these AEs. Furthermore, listings will be provided displaying all these specific AEs.

- Changes in laboratory parameters during the study period, including hepatic and renal function parameters.

Laboratory parameters will be summarised by visit. Furthermore, change from baseline (visit 1) will be summarised. Listings and individual over time profile plots (where deemed relevant) will be provided displaying laboratory parameters reported during the study period.

- PEG-plasma levels at study entry, after two years and at the end of study

PEG plasma level will be summarised by visit. Listings and individual over time profile plots will be provided displaying PEG plasma level reported during the study period.

- Number of FVIII treatment requiring bleeding episodes reported during the study period

Number of FVIII treatment requiring bleeding episodes reported during the study period will be summarised. Furthermore, listings will be provided displaying all FVIII requiring bleeding episodes.

Definition of a bleeding episode: Multiple bleeding locations occurring during the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. A bleeding which occurs within 72 hours after stopping treatment of a previous bleeding event at the same or a subset of the same anatomical location(s) is considered a re-bleed, and is not a new bleeding episode. If a bleeding event occurs in the same location later than 72 hours after stopping treatment of a previous bleeding event it is considered a new bleeding episode.

9.7.3 Interim analysis

Interim results will be provided within N8-GP Periodic Safety Update Report (PSUR) and at 5-year renewal. An additional interim analysis will be performed approximately 2.5 years after first patient first visit. Additional interims may be done to report safety data for publications.

9.7.4 Sequential safety analysis/safety monitoring

Events listed in the endpoints will be reported as SAEs, AESIs, ARs and AEs, and summarized separately by statistical analysis.

9.8 Quality control

9.8.1 Monitoring procedures

During the course of the study, the monitor should visit the study site regularly to ensure that the protocol has been adhered to and that relevant data have been recorded. The extent of source data verification and validation of endpoints will be described in the monitoring guideline for the study. The monitor must also ensure that the eCRFs and paper CRF are completed as applicable.

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

- Ethnicity
- Race

9.8.2 Critical documents

Before the physician starts the study (which is when informed consent is obtained from the first patient at the respective site), the following documents must be available to Novo Nordisk:

- Regulatory approval and/or notification as required
- Documentation of the physician's qualifications as medically qualified (for instance a short CV or authorisation)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol, any amendments, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement (or document of waiver by IEC/IRB of informed consent)
- Non-interventional study agreement

9.8.3 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiological Practice (GPP)[6] and relevant national legislation related to archiving of study documentation.

The physician must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

9.9 Limitations of the research methods

As this is a non-interventional study, potential confounding factors cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation.

9.10 Other aspects

N/A

10 Protection of human subjects

The study will be conducted in accordance with GPP, applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[6, 8]

10.1 Informed consent form for study patients

A voluntary, signed and personally dated, informed consent form will be obtained from the patient and/or the patient's parent(s)/LAR prior to any study-related activity. The physician must give the patient and/or the patient's parent(s)/LAR(s) information in a form that the patient or the patient's parent(s)/LAR(s) can read and understand. This includes the use of impartial witness where required.

In obtaining and documenting informed consent, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki.[8]

If a patient is under age, the physician and the parent(s)/LAR(s) will evaluate if the patient is at a level of maturity whereby the patient can sign the informed assent form. National regulation on obtaining informed consent from patients under age must be observed. This signature does not substitute the signature of the parent(s)/LAR(s). The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form.

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

10.2 Data handling

If the patient (or the patient's LAR) withdraws the previously given informed consent, the patient's data will be handled as follows:

- Data collected will be used as part of the statistical analysis
- Safety events will be reported to Global Safety, Novo Nordisk/health authorities.

Data will be collected and handled in accordance with local law and IRB/IEC procedures.

10.3 Institutional Review Boards/Independent Ethics Committee, health authorities and other relevant national institutions/bodies

Study specific documentation (for example study protocol, amendments, Patient Information/Informed Consent Form, patient materials) must be submitted to the relevant national bodies as required by national regulation and procedures in the participating countries.

The study must be approved by the IEC/IRB for each participating country (in France by equivalent authorities).

In accordance with regulatory requirements, including GVP, the sponsor will inform the health authorities of N8-GP related adverse reactions. In certain situations, other adverse events may be subject to expedited reporting, if required by health authorities. In addition, Novo Nordisk will inform the IECs/IRBs (or other appropriate bodies as required locally) of N8-GP related serious adverse reactions, in accordance with the local requirements in force.

10.4 Premature termination of the study

The sponsor may decide to stop the study or part of the study at any time.

If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedures.

10.5 Responsibilities

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom she/he has delegated specified significant study-related duties. The medical care given to, and medical decisions made on behalf of, a patient, should always be the responsibility of a qualified physician.

11 Collection and reporting of safety information

11.1 Collection of adverse events

Safety definitions and a guideline for evaluation of outcome, severity and causality can be found in appendix A.

All adverse events including all fatal outcomes on N8-GP which occur after informed consent is obtained and until the follow-up visit/end of study visit must be collected and reported to Novo Nordisk.

Adverse events must be reported by the physician on the adverse event form (AE form).

In addition, for serious adverse events and adverse events of special interest (AESIs) further information must be reported by the physician on the safety information form (SIF). A serious AESI should be reported following the same reporting requirements and timelines as for SAEs (see Section 11.2).

The following are defined as AESIs in this study:

1. 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.[9]

2. Anaphylactic reaction as defined by Sampson et al (as defined in appendix A).[9]

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

4. Thromboembolic events (clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion, see definitions in appendix A).

5. Medication errors concerning N8-GP. The following should be reported:

    - Administration of wrong drug.

    - Wrong route of administration, such as intramuscular instead of intravenous.

    - Administration of an accidental over- or underdose: The administered dose must deviate from the intended dose to an extent where clinical consequences for the patient were likely to happen as judged by the investigator, although they did not necessarily occur.

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

7. Adverse events of special interest must always be reported to Novo Nordisk. So the AE form and safety information form (SIF) in the eCRF and/or on paper should be filled in.

The physician should record the diagnosis, if available. If no diagnosis is available, the physician should record each sign and symptom as individual adverse events. When a diagnosis becomes available, the diagnosis should be reported, and the signs and symptoms covered by the diagnosis should be described.

If more than one sign or symptom is to be reported, a separate adverse event form for each sign and symptom must be used. However, if several symptoms or diagnoses occur as part of the same clinical picture, only one SIF can be used to describe all the adverse events/reactions.

Reports of overdose, abuse, misuse, medication errors, off label use, lack of therapeutic effect or occupational exposure with no associated suspected adverse reaction should be collected when made aware of them and summarised in interim and final study reports.

11.2 Reporting of adverse events

The physician must report adverse events to Novo Nordisk within the following timelines:

Serious adverse events (including serious AESIs)

- Initial information must be reported on the AE form **within 24 hours** of the physician's knowledge of the event.
- Further information must be reported on the SIF **within 5 calendar days** of the physician's knowledge of the event.
- If the initial reporting was made by any other means (for example phone call within 24 hours), initial and further safety information must be provided on the AE form and SIF **within 5 calendar days** of the physician's knowledge of the event on the forms, as described above.

For EU and non-EU countries, Novo Nordisk will follow the reporting obligations as per standard Pharmacovigilance timelines.

Non-serious adverse events (including non-serious AESIs)

- Initial and further information must be reported on the AE form (and SIF for AESIs) within **14 calendar days** of the physician's knowledge of the event.

The physician must complete the forms in the EDC system within the above specified timelines of obtaining knowledge about the event(s). For SAEs, the physician must sign the forms within 7 days after completing the forms.

If for any reason eCRF is unavailable, then fax, telephone or encrypted email the filled in provided paper AE/SIF forms to Novo Nordisk.

11.3 Follow-up on safety information

All serious adverse events, adverse events of special interest and non-serious adverse reactions must be followed until the outcome of the event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse events or non-serious adverse reactions ongoing at the time of the death (that is, the patient dies from another serious adverse event) can be closed with the outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the study and is expected by the physician to recover.

All other non-serious adverse events must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of study, whichever comes first, and until all queries related to these adverse events have been resolved. Adverse events ongoing at time of death (that is, patient dies from another adverse event) can be closed with an outcome of "recovering" or "not recovered".

Follow-up information concerning previously reported serious adverse events, including serious adverse events fulfilling the adverse event of special interest criterion must be reported by the physician **within 24 hours,** of the physician's knowledge of the follow-up information.

Follow-up information concerning previously reported non-serious adverse events, and non-serious adverse events fulfilling the adverse event of special interest criterion must be reported by the physician **within 14 calendar days** of the physician's knowledge of the event.

All follow-up information requested by Novo Nordisk must be forwarded to Novo Nordisk within **14 calendar days** from the date specified on the request, unless otherwise specified in the follow-up information request.

The physician must ensure that the worst-case severity and seriousness is kept consistent through the series of forms used for safety reporting. The follow-up information should only include new (update and/or additional) information that reflects the situation at the time of the physician's signature.

11.4 Regulatory reporting requirements for adverse events

Novo Nordisk will comply with country-specific regulatory requirements for safety reporting to the concerned competent authorities and IRB/IEC.

Sponsor's assessment of expectedness is done according to the following reference documents:

- Company Core Data sheet for N8-GP

11.5 Collection and reporting of technical complaints

Technical complaints can be reported spontaneously to Novo Nordisk affiliate.

11.6 Collection, storage and shipment of technical complaint samples

Technical complaint samples can be returned to Novo Nordisk affiliate.

11.7 Collection and reporting of pregnancies in female patients or male patients' female partners and collection of ARs in infants exposed via breastfeeding

In male patients' pregnant partners, the pregnancy must be reported **within 14 calendar days of the physician's first knowledge of the pregnancy or as soon as possible after receipt of informed consent**. However, no specific timeline applies for collecting follow-up information. Adverse reactions and any serious adverse events experienced by the foetus or newborn infant should be collected and reported.

Reporting of adverse reactions occuring in infants following exposure to a medicinal product from breast milk and other adverse reactions or adverse events in foetus, newborn infant or in connection with the pregnancy must be done on the same forms and within the same reporting timelines as described for reporting of adverse reactions and events. It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant.

11.8 Precautions/Over-dosage

Please refer to the summary of product characteristics (SmPC) or corresponding local product labelling text.

11.9 Novo Nordisk safety committee(s)

Novo Nordisk has an internal safety committee that performs ongoing safety surveillance of N8-GP.

12 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of N8-GP. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk. A physician (Signatory Physician) will be designated with the responsibility to review and sign the non-interventional study report (NSR).

If required by national law, physicians' identity and contact information will be made publicly available, and by signing the protocol the physician commits to this.

12.1 Registration of study information

In accordance with Novo Nordisk commitment to transparency in clinical activities, this study will be registered on www.clinicalTrials.gov and www.novonordisk-trials.com no later than at enrolment of the first study participant. All study sites will be included in the study registration.

This study is subject to registration no later than at enrolment of the first study participant according to Novo Nordisk requirement on non-interventional study disclosure. For studies that include data collected retrospectively, the study is to be registered prior to the first capture of the data. All study sites will be registered.

This non-interventional PASS must, prior to enrolment of first study participant, be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines Agency and accessible through the European Medicines Agency's web portal.

In addition, this study will be registered in the individual country's local study registry(ies) according to local legislation.

12.2 Communication and publication

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

At the end of the study, one or more publication(s) may be prepared by physician(s) in collaboration with Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property and reserves the right not to release interim results or data until a study report is available. The results of this study will be subject to public disclosure on external web sites according to international regulations, as reflected in the Novo Nordisk Commitment to share information about clinical studies.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

The physician must ensure submission of the results of the study (either abstracts or full NSR) to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication. For PASS studies in Europe, an advance agreement on publication policy between Novo Nordisk and physician allows the latter to independently prepare publications based on the study results. Also PASS studies in Europe require Novo Nordisk to communicate to the EMA and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication. This is to allow national competent authorities to review in advance the results and interpretations to be published.

12.3 Physician access to data and review of results

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

Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or product studied in this study.

13 References

1. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (EMA/813938/2011 Rev 3). 2017.

2. Giangrande P, Andreeva T, Chowdary P, Ehrenforth S, Hanabusa H, Leebeek FW, et al. Clinical evaluation of glycoPEGylated recombinant FVIII: Efficacy and safety in severe haemophilia A. Thromb Haemost. 2017;117(2):252-61.

3. Meunier S, Alamelu J, Ehrenforth S, Hanabusa H, Abdul Karim F, Kavakli K, et al. Safety and efficacy of a glycoPEGylated rFVIII (turoctocog alpha pegol, N8-GP) in paediatric patients with severe haemophilia A. Thromb Haemost. 2017;117(9):1705-13.

4. Tiede A, Brand B, Fischer R, Kavakli K, Lentz SR, Matsushita T, et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A. J Thromb Haemost. 2013;11(4):670-8.

5. Hampton K, Chowdary P, Dunkley S, Ehrenforth S, Jacobsen L, Neff A, et al. First report on the safety and efficacy of an extended half-life glycoPEGylated recombinant FVIII for major surgery in severe haemophilia A. Haemophilia. 2017;23(5):689-96.

6. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). 2011 2011.

7. ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016.

8. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.

9. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second Symposium on the Definition and Management of Anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine. 2006;47(4):373-80.

Appendix A Safety definition and evaluation of outcome, severity and causality

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered/using a product and which does not necessarily have a causal relationship with this treatment.

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

AE Severity assessment definitions:

Mild – No or transient symptoms, no interference with the patient's daily activities.

Moderate – Marked symptoms, moderate interference with the patient's daily activities.

Severe – Considerable interference with the patient's daily activities, unacceptable.

Adverse events of special interest (AESI)

An event which in the evaluation of safety has a special focus.

A serious AESI should be reported following the same reporting requirements and timelines as for SAEs (see Section 11.2).

The following are defined as AESIs in this study:

1. 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.[10]
2. Anaphylactic reaction as defined by Sampson et al (see below).[10]
3. CNS-related adverse events, including but not limited to any learning and behavioural deficits.
4. Thromboembolic events (clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral

infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion, see definitions below).

5. Medication errors concerning N8-GP. The following should be reported:
    - Administration of wrong drug.
    - Wrong route of administration, such as intramuscular instead of intravenous.
    - Administration of an accidental over- or underdose: The administered dose must deviate from the intended dose to an extent where clinical consequences for the patient were likely to happen as judged by the investigator, although they did not necessarily occur.
6. Renal or hepatic adverse events including new onset of renal or hepatic disorder or impairment.

Adverse events of special interest must always be reported to Novo Nordisk. So the AE form and safety information form (SIF) in the eCRF and/or on paper should be filled in.

Definition of an acute, evolving, or recent myocardial infarction

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

1. Typical rise and gradual fall in troponin T or more rapid rise and fall in creatine kinase, muscle and brain or biochemical markers of myocardial necrosis with at least one of the following:

a. Ischaemic symptoms

b. Subsequent development of pathologic Q waves on the ECG

c. ECG changes indicative of ischaemia (ST segment elevation or depression)

d. Coronary artery intervention (e.g. angioplasty)

2. Pathologic findings of an acute myocardial infarction (i.e., pathologic findings of an acute myocardial infarction will be defined when criteria a and b below are fulfilled):

a. Increase in troponin T above the "diagnostic" limit: i.e. > 0.03 µg/L

b. Patients with:

- ST-segment elevation: New ST-segment elevation at the J point in two or more contiguous leads with the cut-off points >= 0.2mV in leads V1, V2 or V3 and 0,1 mV in other leads (contiguity in the frontal plane is defined by the lead sequence aVL, I inverted aVR, II, aVF, III)

- No ST-segment elevation: ST-segment depression and or T-wave inversion in two or more contiguous leads >= 0.1 mV

Definition of pulmonary embolism

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

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

Definition of cerebral thrombosis/infarction

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

1. Computerised tomography
2. Magnetic resonance scan
3. Magnetic resonance angiogram
4. Cerebral angiography

Deep vein thrombosis

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

Definition of other clinically significant thromboembolic events

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

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

Peripheral artery occlusion

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

Clinical criteria for diagnosing anaphylaxis (Sampson et al. 2006)[10]

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

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

Adverse reaction (AR)

An Adverse reaction (AR) is a response to a medicinal product which is noxious and unintended. This includes AR which arises from:

- The use of a product within the terms of the marketing authorisation
- The use of a product outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors.
- Occupational exposure

An AR may be associated with the use of a drug, a medical device or both.

For solicited cases: An AR is an AE for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk or the reporter.

For spontaneous cases: Even if the relationship is unknown or unstated, it meets the definition of an AR. Therefore, all spontaneous reports are considered ARs, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

Causality assessment

- 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 an aetiology other than the N8-GP

Hospitalisation

When a patient stays at the hospital for treatment or observation for more than 24 hours. However, medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Planned procedures, e.g. planned surgery, should not be reported.

Medication error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failure.

Medication errors can therefore be:

- Associated with an AR
- Not associated with an AR
- An intercepted medication error (‘near miss’) is when an intervention caused a break in the chain of events in the treatment process before reaching the patient which would have resulted in a ‘potential’ adverse drug reaction. This intervention has prevented actual harm being caused to the patient; for example a wrongly prepared medicine was actually not administered to the patient because the error was noticed by the nurse.
- A potential medication error which is recognition of circumstances that could lead to a medication error, and may or may not involve a patient. The term potential medication error refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process. An example is a pharmacist who noticed that the names of two medicines are similar and could clearly lead to product name confusion, but no patient was actually involved or has taken the medicine.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used in a manner not in accordance with the authorised product information.

Non-serious

An AE or AR that does not fulfil the requirement for being an SAE or SAR.

Occupational Exposure

An exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release of a finished product.

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Example include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (for example, a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

Outcome categories and definitions

- Recovered/resolved – The patient has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient has signed the informed consent.

- Recovering/resolving – The condition is improving, and the patient is expected to recover from the event. This term is only applicable if the patient has completed the study or has died from another AE.

- Recovered/resolved with sequelae – The patient has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If a sequela meets a SAE criterion, the AE must be reported as a SAE.

- Not recovered/not resolved – The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.

- Fatal – (only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AE in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.

- Unknown – This term should only be used in cases where the patient is lost to follow-up.

Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Serious Adverse Event (SAE)

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

- Death
- Life-threatening experience (actual risk not hypothetically)
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity or is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered an SAE, when based upon appropriate medical judgement - they may jeopardise the patient or subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suspicion of transmission of infectious agents must always be considered an SAE.

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 trial product.
- risk of liver injury defined as ALT or AST >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).
- development of FVIII inhibitor either based on local laboratory tests or clinical suspicion, regardless of confirmation

List of figures and tables

Table of Figures

Page

Table of Tables

Page