Protocol

Study ID: NN7999-4031

paradigm8

Register No.: EUPAS26592

A Non-Interventional Post-Authorisation Safety Study (PASS) in male haemophilia B patients receiving Nonacog Beta Pegol (N9-GP) prophylaxis treatment

Non-interventional post authorisation safety study (PASS)

Redacted report
includes redaction of personal identifiable information only.

Includes:
Protocol version 1.16 (12 June 2018), global amendment no.1 (07 November 2019)

Protocol originator:

[redacted]

PASS information

Title	A Non-Interventional Post-Authorisation Safety Study (PASS) in male haemophilia B patients receiving Nonacog Beta Pegol (N9-GP) prophylaxis treatment
Protocol version identifier	Version 2.0, 07 November 2019
Date of last version of protocol	Version 1.16, 12 June 2018
EU PASS Register number	EUPAS26592
Active substance	Nonacog beta pegol (N9-GP). ATC code: B02BD04.
Medicinal product	Refixia®, Rebinyn®
Product reference	EU/1/17/1193 (this number covers the three strengths in EU) Drug Identification number Canada: 02470187 for Rebinyn 500 IU 02470268 for Rebinyn 1000 IU 02470276 for Rebinyn 2000 IU .
Procedure number	EMEA/H/C/PSP/S/0059
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:** The primary objective of the study is to investigate safety of N9-GP in prophylaxis and during longterm routine use (Adverse Drug Reaction) in patients with haemophilia B in the manner it is prescribed by physicians. **Secondary objectives:** Secondary objectives are to further evaluate the general safety and clinical effectiveness of N9-GP in prophylaxis and during long-term routine use in patients with haemophilia B in the manner it is prescribed by the physicians.

Countries of study	Expected countries: AT, BE, CA, CH, DE, DK, ES, GR, NL, NO, PT, SE, UK The list of countries is not complete.

Author	[redacted]

Marketing authorisation holder(s)

Marketing authorisation holder (MAH)	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
MAH contact person	[redacted]

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2 List of Abbreviations

ABR	Annualised bleeding rate
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastine time
AsBR	Annual spontaneous bleeding rate
AST	Aspartate aminotransferase
AT	Antithrombin
BU	Bethesda Unit
CD4+	Cluster of Differentiation 4 positive
CHMP	Committee for Medicinal Product for Human use
CNS	Central Neurological System
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
eCRF	Electronic CRF
CRP	C-reactive Protein
DBL	Data Base Lock
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS Register	European Post-Authorisation Study Register
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIX	Factor IX
FPFV	First Patient First Visit
GCP	Good Clinical Practice

GGT	Gamma-glutamyl Transferase
GPP	Good Pharmacoepidemiological Practices
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
IBD	International Birth Date
ICH-GCP	International Conference on Harmonisation / GCP
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune Tolerance Induction
LAR	Legally Authorised Representative
LPLV	Last Patient Last Visit
N9-GP	Nonacog beta pegol
NSR	Non-Interventional Study Report
PASS	Post Authorisation Safety Study
PEG	40 kDa glycoPEGylated
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PTPs	Previously treated patients
rFIX	recombinant factor IX
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SIF	Safety Information Form
SmPC	Summary of product characteristics
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 post authorisation safety study (PASS) 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. The medical care given to, and medical decisions made on behalf of patients should always be the responsibility of a qualified physician.

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.

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).

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 Non-Interventional Post-Authorisation Safety Study (PASS) in male haemophilia B patients receiving Nonacog Beta Pegol (N9-GP) prophylaxis treatment. Version 2.0, 07 November 2019. Author: [redacted].

4.2 Rationale and background

Novo Nordisk has developed N9-GP, a 40-kDa glycoPEGylated (PEG) human recombinant factor IX (rFIX) with an extended half-life, for the treatment and prophylaxis of haemophilia B. The clinical trial programme for the world wide regulatory submission has been completed.

Novo Nordisk has received approval of N9-GP from Food and Drug Administration (FDA), European Medicines Agency (EMA), Swissmedic, and Health Canada for the use in patients with haemophilia B either as prophylaxis or on-demand treatment for control of bleeding episodes as well as control or as prevention of bleeding in the perioperative setting.

In the EMA "Guideline on clinical investigation of recombinant and human plasma-derived factor IX (FIX) products"[1], EMA points to the low number of patients suffering from haemophilia B, and that data from pre-licensing studies are considered insufficient to assess all aspects of therapy with FIX products. Therefore, 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 marked product/commercially available product (Refixia®/REBINYN®), a post-marketing investigation should be performed.

The general safety profile of N9-GP for the treatment of patients with haemophilia B is well-examined in long-term exposure data from the pivotal (NN7999-3747) and the extension (NN7999-3775) phase 3 trials, the paediatric phase 3 trial (NN7999-3774) and the surgery phase 3 trial (NN7999-3773).

Specific pharmacological risks for FIX replacement products include FIX inhibitor development, allergic reactions, and thromboembolic events, which were evaluated in all phase 3 trials. In addition, there exists a theoretical safety concern that there will be clinical effects of longer-term exposure to PEG.

The key purpose of the N9-GP PASS is to gain additional knowledge of safety in prophylaxis patients and effectiveness of N9-GP when used as prophylactic treatment in haemophilia B patients.

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 N9-GP in the setting of local clinical practice.

The primary objective of the study is to investigate safety of N9-GP in prophylaxis and during long-term routine use (Adverse Drug Reaction (ADR)) in patients with haemophilia B in the manner it is prescribed by the physicians.

Secondary objectives are to further evaluate the general safety and clinical effectiveness of N9-GP in prophylaxis and during long-term routine use in patients with haemophilia B in the manner it is prescribed by the physicians.

Exploratory objectives are to monitor possible clinical effects of long-term exposure to N9-GP prophylaxis in patients with haemophilia B, including optional assessments of kidney and liver function parameters, and neurological function, and patients' PEG plasma level – where allowed as part of a non-interventional study. Additional exploratory objectives are to further investigate health economic/patient reported outcomes (PRO)s.

The primary endpoint of the study is:

- Number of Adverse Drug Reactions (ADRs) (FIX inhibitors, allergic reactions, and thromboembolic events) reported during the study period

The secondary endpoints are:

- Number of Serious Adverse Events (SAEs) reported for a period up to 9 years
- Number of bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years
- Number of treatment requiring bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years
- Haemostatic effect of N9-GP when used for treatment of bleeding episodes, assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure for a period up to 9 years
- Haemostatic response of N9-GP when used in perioperative management, assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure for a period up to 9 years

The exploratory endpoints are:

- Number of ADRs that are defined within the system organ classes nervous system and psychiatric disorders for a period up to 9 years
- Number of ADRs related to hepatic or renal function for a period up to 9 years
- Change in estimated Glomerular Filtration Rate (eGFR) from study start to end of study
- Change in alanine aminotransferase (ALT) and bilirubin from study start to end of study
- Change in PEG-plasma levels from study start to end of study
- Number of abnormal findings as assessed by neurological examination across all age groups for a period up to 9 years
- Change in quality of life during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Change in physical activity level or functional abilities during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Consumption of N9-GP used for treatment per year (IU/Kg/year) for a period up to 9 years
- Number of healthcare resources (emergency room, hospitalisation, clinic) utilization due to a treatment requiring bleeding episode or sequelae thereof during follow-up intervals
- Adherence to treatment prescribed by the physician (percent difference prescribed versus utilized dose) during follow-up intervals

4.4 Study design

This is a prospective, multinational, non-interventional PASS in haemophilia B patients without current inhibitors. Patients fulfilling the inclusion criteria can participate in the study regardless of previous treatment regime if any, allowing inclusion of patients previously exposed to N9-GP and/or other FIX products.

Patients will be treated with commercially available N9-GP according to local clinical practice at the discretion of the physician. Patients on prophylaxis regimen with N9-GP can be included in the study.

The total study duration is estimated to be 9 years with a planned recruitment period of at least 4 years. The patients will be in the study between 5 and 9 years.

4.5 Population

Approximately 70 male haemophilia B patients of any age will be screened to allow for at least, but not limited to 50 patients to complete at least 4 years on prophylaxis with N9-GP. Patients prescribed to prophylaxis treatment can participate in the study.

Key inclusion criteria

1. Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
2. Male patients at any age with haemophilia B assigned to N9-GP prophylaxis treatment.
3. Decision to initiate treatment with commercially available N9-GP has been made by the patient(s)/Legally Authorised Representative(s) (LAR(s)) and the treating physician before and independently from the decision to include the patient in this study.

Key exclusion criteria

1. Previous participation in this study. Participation is defined as signed informed consent.
2. Known or suspected hypersensitivity to N9-GP or related products.
3. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
4. Clinical suspicion or presence of FIX inhibitor at time of inclusion.

Withdrawal criteria

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

4.6 Variables

Key variables are assessment of:

Safety: Number of ADRs and adverse events (AEs) will be assessed by monitoring patients following AEs, perform physical and neurological examinations as well as take blood samples including measurement of renal and kidney parameters and PEG plasma levels.

Clinical effectiveness: ABR assessed by number of treatment requiring bleeding episodes for patients with long-term routine treatment with N9-GP. Success or failure of treatment of bleeding episodes reported by the patient or the physician. The assessment of bleeding episodes provides an overall assessment of a patient's response to N9-GP using the following 4-point scale with the following scores: Excellent, Good, Moderate, and Poor.

Health Economics: Consumption of N9-GP and use of healthcare resources will be monitored by reporting of treatment and use of resources by the physician in the electronic Case Report Form (eCRF) system, based on patients own diary when possible.

PRO: Age specific questionnaires will be completed by the patients and/or parent(s)/LAR(s) at the baseline visit and preferably yearly hereafter until the end of study visit.

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

4.7 Data sources

It is the intention of this non-interventional study to observe long-term routine treatment with N9-GP in the individual patient. Data and results available in the patient's medical record, patients own diary and from assessments and laboratory sampling performed according to local clinical practice, or at the discretion of the physician, at the participating sites will be recorded in the eCRF. In addition, available information in the patient's medical record or patients own diary related to treatment, bleeding events and in case a patient is hospitalised should be reported in the eCRF by the physician.

4.8 Study size

The sample size for this study will be at least but not limited to 50 patients (expected to complete at least 4 years treatment in the study) to obtain additional real-world post-authorisation exposure and safety information. The study is intended to reflect the population in the countries where N9-GP is marketed. Study participants can be recruited regardless of their age, hereby aiming to include all age groups as per approved labelling.

4.9 Data analysis

No formal testing of statistical hypotheses will be performed. Evaluation of data will be based upon descriptive statistics, i.e. summary tables, listings and figures. Categorical data will be summarised by frequency tables while continuous data will be summarized by mean, standard deviation, median, minimum and maximum value separated into age groups.

At least 2 interims will be conducted (see section 4.10).

4.10 Milestones

First Patient First Visit (FPFV):	1st April 2019
Planned date for Last Patient Last Visit (LPLV):	15th December 2027
Planned completion of non-interventional study report (NSR):	7th June 2028

Interim reports are planned when ten patients have had their first visit after one year of inclusion and when twenty five patients have had their first visit after one year of inclusion in the study.

Additional interims may be conducted to collect safety data for submission to authorities or publications.

5 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1 (Global)	07 November 2019	4, 9, 11	Amendment	- Ensure reporting of specific bleeding events as SAEs - Clarification of endpoints related to treatment requiring bleeding events - Update inclusion/ exclusion criteria to reflect routine practice. - Simplification of data collected for haemophilia treatment and removal of study diary - Specify process for safety forms related to immunogenicity and hypersensitivity events - Removing screening failure

6 Milestones

Planned duration of the enrolment period is 4 years.

Milestone	**Planned date**
Start of data collection Defined as first entry of patient data	1st April 2019
End of study Defined as Last Patient Last Visit (LPLV)	15th December 2027
End of data collection Defined as Data base lock (DBL)	2nd February 2028
Registration in the EU PAS Register	Obtained on 20 November 2018; EUPAS26592
Study progress report 1	December 2019
Study progress report 2	December 2020
Study progress report 3	After 31st May 2021 (aligned with International Birth Date (IBD) for Refixia)

Milestone	Planned date
Interim DBL	When ten patients have had their first visit after one year of inclusion
Interim DBL	When twenty five patients have had their first visit after one year of inclusion
Final report of study results	7th June 2028

7 Rationale and background

Novo Nordisk has developed nonacog beta pegol (N9-GP), a 40-kDa glycoPEGylated (PEG) human recombinant coagulation Factor IX (rFIX) with an extended half-life, for the treatment and prophylaxis of bleeding episodes in patients with haemophilia B. N9-GP has improved pharmacokinetic (PK) properties including higher recovery and a 5-fold increase in terminal half-life compared with standard FIX products, which offer the possibility of achieving high and sustained FIX levels with a less-burdensome once-weekly treatment regimen[2-4].

Novo Nordisk has received the US FDA approval of N9-GP (REBINYN®), indicated for on-demand treatment and control of bleeding episodes and the perioperative management of bleeding in adults and children with haemophilia B. REBINYN® is not indicated for routine prophylaxis in the treatment of patients with haemophilia B or for immune tolerance induction in patients with haemophilia B in US.

Novo Nordisk has received the EU approval of N9-GP (Refixia®) from EMA, indicated for treatment and prophylaxis of bleeding in patients 12 years and above with Haemophilia B.

Swissmedic approved N9-GP (Refixia®) for treatment and prophylaxis of bleeding in previously treated patients (PTPs) with haemophilia B.

Health Canada approved N9-GP (REBINYN®) for control and prevention of bleeding episodes, control and prevention of bleeding in the perioperative setting as well as routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 18 years and above with haemophilia B.

The review of N9-GP was based on the paradigm™ programme, a phase 1 and 3 clinical programme including 115 unique PTPs, children, adolescents and adults with severe or moderate haemophilia B (FIX activity ≤2%). The confirmatory phase 3 trials showed an efficacious weekly prophylaxis regimen, successful treatment of bleeding episodes and haemostasis during and after major surgical procedures[4-7]. The sustained high FIX levels ≥15% obtained with N9-GP 40 IU/kg once-weekly prophylaxis across all age groups resulted in: reduced ABR in adolescents and adults

with median ABR 1.04 bleeding episodes/patient/year and children with median ABR 1.00 bleeding episodes/patient/year ; reduced annualised spontaneous bleeding rates (AsBR) in adolescents and adults with median AsBR 0.0 bleeding episodes/patient/year and in children median AsBR 0.0 bleeding episodes/patient/year ; resolution of 90% of target joints in adolescents and adults and 100% in children, and enhanced quality of life[5-8]. The overall success rate for the treatment of bleeds was 93%.

Specific pharmacological risks for FIX replacement products include FIX inhibitor development, allergic reactions, and thromboembolic events, which were evaluated in all clinical studies. Through the clinical development programme, N9-GP has demonstrated a safety profile similar to that of currently approved FIX products. N9-GP was well tolerated with no development of FIX inhibitors in PTPs, no thromboembolic events, no systemic changes over time for any laboratory parameters, an expected rate of allergic reactions, and no unexpected safety concerns identified in 115 PTPs with 8801 total exposure days (170 patient years of exposure).

Due to a theoretical safety concern regarding PEG, Committee for Medicinal Product for Human use (CHMP) requested that potential clinical effects of longer-term exposure to N9-GP should be investigated. Based on modelling data and supported by PEG plasma analyses in clinical samples from paediatric patients, steady-state PEG concentrations in plasma and all tissues have been reached in the N9-GP clinical programme without any indication of PEG-related adverse effects to date. The clinical safety of long-term exposure to N9-GP – including evaluation of possible clinical consequences of potential 40 kDa PEG accumulation in target organs of specific interest (liver, kidney, choroid plexus) – is yet to be established.

Novo Nordisk has received an obligation from the CHMP to conduct a PASS to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs. Thus, the main purpose of this non-interventional PASS is to evaluate the long-term safety using N9-GP in patients with haemophilia B after ongoing treatment and possible clinical consequences hereof under observational (‘real-world’) conditions of local clinical practice.

8 Research question and objectives

8.1 Primary objective

The primary objective of the study is to investigate the safety of N9-GP in prophylaxis and during long-term routine use (Adverse Drug Reactions) in patients with haemophilia B in the manner it is prescribed by physicians. This will include assessment of specific pharmacological risks for FIX replacement products (FIX inhibitors, allergic reactions, and thromboembolic events).

8.2 Secondary objective(s)

Secondary objectives are to further evaluate the general safety and clinical effectiveness of N9-GP in prophylaxis and during long-term routine use in patients with haemophilia B in the manner it is prescribed by the physicians.

8.3 Exploratory objectives

Exploratory objectives are to monitor possible clinical effects of long-term exposure to N9-GP prophylaxis in patients with haemophilia B, including optional assessments of kidney and liver function parameters, and neurological function, and patients' PEG plasma level – where allowed as part of a non-interventional study. Additional exploratory objectives are to further investigate health economic/PROs.

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's.

9.1 Study design

This is a prospective, multinational, non-interventional PASS in male haemophilia B patients without current inhibitors. Patients fulfilling the inclusion criteria can participate in the study regardless of previous treatment regime if any, allowing inclusion of patients previously exposed to N9-GP in the paradigm™ programme, but also patients exposed to other FIX products.

Patients will be treated with commercially available N9-GP according to local clinical practice at the discretion of the physician. Patients on any treatment regimen with N9-GP and patients undergoing surgical procedures receiving N9-GP for perioperative haemostasis can be included in the study.

This study has been designed for the purpose of obtaining additional real-world post-authorisation exposure and safety information.

A baseline visit (V1) will be documented for all patients after informed consent is signed. When all inclusion and exclusion criteria have been confirmed baseline data can be obtained and recorded. As illustrated in Table 9–1 assessments will be documented (e.g. visit 2, 3, 4 etc.) when a patient visits the clinic according to local clinical practice until end of study visit. Patients are expected to be in the study between 5 and 9 years.

It is expected that patients will have visits to the clinic as of local clinical practice at which the study visits will take place. Data and results from assessments and laboratory sampling performed according to local clinical practice or upon physician's discretion will be recorded upon availability.

An overall monitoring of the effectiveness and safety will be performed by the physician based on patient's record data and patient interview at the site visit. The relevant data recorded by the site during a patient's participation in the study will be captured in the eCRF.

9.1.1 Primary endpoint

- Number of Adverse Drug Reactions (ADRs) (FIX inhibitors, allergic reactions, and thromboembolic events) reported during the study period

9.1.2 Secondary endpoints

- Number of Serious Adverse Events (SAEs) reported for a period up to 9 years
- Number of bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years
- Number of treatment requiring bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years
- Haemostatic effect of N9-GP when used for treatment of bleeding episodes, assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure for a period up to 9 years
- Haemostatic response of N9-GP when used in perioperative management, assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure for a period up to 9 years

9.1.3 Exploratory Endpoints

9.1.3.1 Exploratory Safety Endpoints

- Number of ADRs that are defined within the system organ classes nervous system and psychiatric disorders for a period up to 9 years
- Number of ADRs related to hepatic or renal function for a period up to 9 years
- Change in eGFR from study start to end of study
- Change in ALT and bilirubin from study start to end of study
- Change in PEG-plasma levels from study start to end of study

9.1.3.2 Exploratory Endpoints within Neurological Development

- Number of abnormal findings as assessed by neurological examination across all age groups for a period up to 9 years

9.1.3.3 Exploratory Health Economics/patient reported outcome Endpoints

- Change in quality of life during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Change in physical activity level or functional abilities during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Consumption of N9-GP used for treatment per year (IU/Kg/year) for a period up to 9 years
- Number of healthcare resources (emergency room, hospitalisation, clinic) utilization due to a treatment requiring bleeding episode or sequelae thereof during follow-up intervals
- Adherence to treatment prescribed by the physician (percent difference prescribed versus utilized dose) during follow-up intervals

9.1.4 Treatment of patients

Patients will be treated with commercially available N9-GP according to local clinical practice at the discretion of the treating physician. Patients may undergo surgical procedures while participating in the study.

As a non-interventional study, there is no prohibited concomitant medication during participation. If the treating physician decides to use other FIX replacement therapy products or in hybrid therapy with N9-GP or additional haemostatic agents, any concurrent medications (including other FIX products, anti-fibrinolytics, topic haemostatic products or sealants) should be documented by the study site.

If a patient is suspected or considered to develop inhibitory antibodies to FIX a positive local laboratory inhibitor test should preferably be confirmed by the central laboratory. Patients who develop FIX inhibitors can continue treatment with N9-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 (baseline screening):	70
Planned number of patients to be included in the study:	60
Planned number of patients to complete 4 years treatment:	50
Anticipated number of patients to be included in each country:	Depending on availability in relevant countries

Time period for the study: Estimated to 9 years

9.2.2 Inclusion criteria

1 Signed informed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol)

2 Male patients at any age with haemophilia B assigned to N9-GP prophylaxis treatment

3 Decision to initiate treatment with commercially available N9-GP has been made by the patient(s)/LAR(s) and the treating physician before and independently from the decision to include the patient in this study

9.2.3 Exclusion criteria

1 Previous participation in this study. Participation is defined as signed informed consent

2 Known or suspected hypersensitivity to N9-GP or related products

3 Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation

4 Clinical suspicion or presence of FIX inhibitor at time of inclusion

9.2.4 Withdrawal criteria

- The patient may withdraw- or the parent(s)/Legally Authorised Representative(s) 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 (e.g. adverse event or other) for discontinuation should be specified in the eCRF.

9.2.5 Rationale for selection criteria

The study is intended to reflect the population for which N9-GP is approved and marketed in the various countries, therefore study participants can be recruited regardless of their age as long as N9-GP is prescribed by the physician. In general, all patients from pre-authorisation clinical studies could be enrolled in post-marketing investigations.

Patients with severe haemophilia B after successful ITI can be included, in order to obtain valuable information in this patient cohort. The proportion of these ITI patients should not be more than 25% of the whole cohort.

The study population are the patients who based on the indication will benefit from treatment with N9-GP.

The very 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.

All exclusion criteria are generic and not specific to treatment with N9-GP, thus no impact on the number of patients available for analysis is expected.

The study population is characterized through the inclusion criteria:

- Criterion no. 1 is included in accordance with Good Pharmacoepidemiology Practices (GPP)[9]
- Criterion no. 2 is based on the EMA guideline concerning post-marketing investigation and expanded for the purpose of reflecting local clinical practice[1]
- Criterion no. 3 is derived from Good Pharmacovigilance Practices (GVP)[10, 11]

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)[12]
- Criterion no. 3 serves to protect patient safety by eliminating the risk of not following prescribed dosing of N9-GP.
- Criterion no. 4 is derived from the EMA guideline concerning post-marketing investigation[1]

9.2.6 Visit procedures

Flowchart

Table 9–1 Flow Chart

	Baseline	Treatment	Follow-Up
Visit	Screening, Visit 1	Visit 2,3,4 etc	End of Study
PATIENT RELATED INFORMATION AND ASSESSMENTS			
Informed Consent	X		
In/exclusion Criteria	X		
Medical history	X		
Haemophilia treatment and bleed history	X		
Details of Haemophilia	X		
Demography	X		
Concomitant illness	X		
Concomitant medication	X	X	X
Withdrawal criteria		X	X
Genotype[a]	X	X	X
EFFECTIVENESS			
Bleeding event[b]	X	X	X
Body measurements	X	X	X
SAFETY			
FIX inhibitor	X	X	X
Factor IX Activity	X	X	X
PEG concentration	X	X	X
Coagulation Parameters	X	X	X
Biochemistry	X	X	X
Haematology	X	X	X
HIV	X	X	X
Hepatitis	X	X	X
Urinalysis	X	X	X
Physical examination	X	X	X
Neurological examination	X	X	X
Vital signs	X	X	X
Adverse event		X	X
OTHER ASSESSMENTS			
Surgery related information	X	X	X
PRO questionnaires[c] (prior to other assessments)	X	X	X
REMINDERS			
Discuss content and use of patients own diary	X	X	

End of study			X

a) Genotype consent if and whenever the patient is willing to share already obtained result or take a sample for analysis.
b) Ensure to evaluate the severity of the bleeding events.
c) Depending on age group. Preferably performed yearly, but not more often.

Informed consent when entering the study is required as is filling in the questionnaires. The rest of the assessments listed in the flow chart are not mandatory but it is recommended to monitor safety and effectiveness of N9-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, including data from patients own diary 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 can be 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.

In the protocol the references to patient activities during and between visits may, when relevant, be performed by a parent/LAR. Questionnaires must be filled in by the relevant part (patient and/or parent/LAR).

Patients enrolled in the study should be provided with contact address(es) and telephone number(s) of the physician site and/or staff. During a patient's participation in the study, all relevant data should be entered in the eCRF based on patients own diary. 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. The primary reason (e.g. adverse event or other) for discontinuation should be specified in the eCRF and as much data as possible from the patients own diary should be recorded into the eCRF.

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. All relevant data necessary for evaluating whether or not a patient can be enrolled in the study e.g. inclusion/exclusion criteria must be available prior to enrolling a patient.

The following must be recorded in the eCRF after having obtained informed consent:

- Date of informed consent, see section 10.1
- Confirmation on inclusion and exclusion criteria, see section 9.2.2 and 9.2.3

After having obtained informed consent the following must be performed and recorded in the eCRF:

- N9-GP treatment regimen at study entry, see section 9.2.6.14
- PRO questionnaire dispensing, training and completion, see section 9.2.6.13

If available in the patient's medical record or collected if relevant, the following must be recorded in the eCRF after having obtained informed consent:

- Details of haemophilia, see section 9.2.6.8
- Medical history, see section 9.2.6.8
- Demography, see section 9.2.6.5
- Concomitant illness, see section 9.2.6.6
- Concomitant medication, see section 9.2.6.7

If performed, the following should be recorded in the patient's record and the eCRF after having obtained informed consent:

- Body measurement, see section 9.2.6.10
- Physical examination, see section 9.2.6.11
- Neurological examination, see section 9.2.6.11
- Vital signs, see section 9.2.6.12
- Ongoing bleeding episodes (incl. severity), see section 9.2.6.16
- Surgery related information, see section 9.2.6.17

The following laboratory results should be recorded in the eCRF, if available:

- FIX inhibitor, see section 9.2.6.18
- Factor IX activity, see section 9.2.6.18
- Coagulation parameters, see section 9.2.6.18
- Lupus anticoagulant, see section 9.2.6.18
- Biochemistry, see section 9.2.6.18
- Haematology, see section 9.2.6.18
- HIV and hepatitis (viral antibody status or test) , see section 9.2.6.18
- Urinalysis, see section 9.2.6.18

The following laboratory samples are recommended to take and send to central laboratory:

- FIX inhibitor (if not available from local lab), see section 9.2.6.18
- PEG plasma level, see section 9.2.6.18
- Genotyping if not available and consent is given, see section 9.2.6.18

9.2.6.2 Assessment visits (Visits 2, 3, 4 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?".

The patient should be encouraged to bring his own personal notes/diary to each visit to enable the physician to discuss content and use and enter the relevant data into the eCRF.

The most recent of the below specified data/blood sample results since the previous visit should be recorded in the eCRF.

The following must be performed and recorded in the eCRF:

- Withdrawal criteria, see section 9.2.4
- Change in haemophilia treatment regimen, see section 9.2.6.14
- PRO questionnaire completion, see section 9.2.6.13

The following should be recorded in the patient´s record and the eCRF, if available:

- Body measurement, see section 9.2.6.10
- Physical examination, see section 9.2.6.11
- Neurological examination, see section 9.2.6.11
- Vital signs, see section 9.2.6.12
- Concomitant medication, see section 9.2.6.7
- Adverse events, see section 9.2.6.15
- Bleeding events (incl. severity), see section 9.2.6.16
- Surgery related information, see section 9.2.6.17

The following laboratory results must be recorded in the eCRF, if available:

- FIX inhibitor, see section 9.2.6.18
- Factor IX activity, see section 9.2.6.12
- Coagulation parameters, see section 9.2.6.18
- Lupus anticoagulant, see section 9.2.6.18
- Biochemistry, see section 9.2.6.18
- Haematology, see section 9.2.6.18

- HIV and hepatitis (viral antibody test), see section 9.2.6.18
- Urinalysis, see section 9.2.6.18

The following laboratory samples are recommended to take and send to central laboratory:

- PEG plasma level, see section 9.2.6.18
- Genotyping if not available and consent is given, (only to be taken once during the study), see section 9.2.6.18

9.2.6.3 Phone contacts

In case a patient calls the site during his participation in the study all relevant study information should be entered in the patients' medical record and subsequently in the eCRF.

9.2.6.4 End of study visit

This visit will take place within 6 months before the study LPLV. If the patient does not visit the site during that period, as of local clinical practice, phone contact should be attempted to collect the study relevant information, based on patients own diary and enter this into the patient's medical records and in the eCRF.

If possible this visit should be performed for all patients ending in the study also for withdrawals.

The following must be reviewed and recorded:

- Withdrawal criteria, see section 9.2.4
- End of study form
- PRO questionnaire completion, see section 9.2.6.13
- Change in haemophilia treatment regimen, see section 9.2.6.14

The following should be recorded in the patient's record and the eCRF, if available:

- Body measurement, see section 9.2.6.10
- Physical examination, see section 9.2.6.11
- Neurological examination, see section 9.2.6.11
- Vital signs, see section 9.2.6.12
- Concomitant medication, see section 9.2.6.7
- Adverse events, see section 9.2.6.15
- Bleeding events (incl. severity), see section 9.2.6.16
- Surgery related information, see section 9.2.6.17

The following laboratory results should be recorded in the eCRF, if available:

- FIX inhibitor, see section 9.2.6.18
- Factor IX activity, see section 9.2.6.18

- Coagulation parameters, see section 9.2.6.18
- Lupus anticoagulants, see section 9.2.6.18
- Biochemistry, see section 9.2.6.18
- Haematology, see section 9.2.6.18
- HIV and hepatitis (viral antibody test), see section 9.2.6.18
- Urinalysis, see section 9.2.6.18

The following laboratory samples are recommended to take and send to central laboratory:

- PEG plasma level, see section 9.2.6.18
- Genotyping if not available and consent is given, (only to be taken once during the study), see section 9.2.6.18

9.2.6.5 Demography

Collected as allowed by local law:

- Date of birth, year or age
- Ethnicity
- Race

9.2.6.6 Concomitant illness

Definition of concomitant illness: any clinically significant illness that is present at study entry (i.e., at visit 1) or emerges during the study.

Any changes from visit 1 in concomitant illnesses must be recorded at each visit in the eCRF.

In case a concomitant illness deteriorates during the study, and the physician evaluates this to be related to the study product, an adverse event must be recorded and reported according to section 11.3. If the change influences the patient's eligibility to continue in the study, the sponsor must be informed.

9.2.6.7 Concomitant medication

Definition of concomitant medication: any medication other than N9-GP that is taken during the study, including reported at baseline, visit 1.

Details of all concomitant medication must be recorded at study entry (i.e., at baseline, visit 1). Any changes in medication must be recorded at each visit (assessment visits and end of study visit) in the eCRF.

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

9.2.6.8 Medical history

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable and be recorded at the baseline based on discussion with the patient or based on the medical records. In the event that a diagnosis is unknown, the description of symptoms should be recorded.

Details of haemophilia

- Diagnosis of haemophilia B (date, if known)
- Classification of haemophilia B and FIX level from medical history
- Underlying gene defect, i.e. result from previous test if available
- Clinical suspicion of inhibitors, including transient inhibitors, from medical history

Family history of haemophilia: If possible, information about relatives with haemophilia B and inhibitors should be obtained.

Haemophilia treatment and bleed history

- Prophylaxis/preventive regimen within the last two years
  - Number of months on prophylaxis
  - Current dose and frequency of dosing
  - Recombinant or plasma derived FIX product (brand name if possible)
  - Bleeding episodes within regimen
- On-demand regimen within the last two years
  - Number of months with on-demand regimen
  - Recombinant or plasma derived FIX product (brand name if possible)
  - Bleeding episodes within regimen
- Previous exposure to N9-GP
  - Doses on prophylaxis and on-demand treatment, within clinical trial or as standard care
  - Dose level and frequency
  - Treatment during bleeding episodes, ITI and surgeries
- Surgeries within the last 5 years
  - Date of surgery
  - Indication
  - Recombinant or plasma derived FIX product (brand name if possible)
  - Surgical procedure

9.2.6.9 HIV and anti-HCV antibodies status

HIV and anti-HCV status should be recorded, if available (HBsAg and/or anti-HCV antibodies, HIV 1 & 2 antibodies, HIV viral load, CD4+ count).

If the patient is HIV and/or HCV and/or HBV positive it is recommended to make an analysis for antibodies and viral count regularly during the study.

9.2.6.10 Body measurements

- Body weight
- Height, without shoes

It is recommended to weigh the patient at every visit and measure the height if the patient is in the age of growing in height. For visit 1, details in the medical records for the last measurement can be used if evaluated still to be valid.

9.2.6.11 Physical examination

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

- General appearance
- Head, ears, eyes, nose, throat and neck
- Lymph node palpation
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Genito-urinary system
- Musculo-skeletal system
- Central and peripheral nervous system (general evaluation)
    - Elaborated neurological examination, see below
- Skin
- Signs and symptoms of vascular thrombosis (e.g. but not limited to swelling, tenderness and leg pain)

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).

Neurological examination

It is highly recommended to perform neurological examination yearly. The neurological examination can be done by any physician, but can also be performed by a neurologist upon preference at site. The examination may include:

For all age groups evaluate:

- Level of consciousness

For children evaluate the child's general appearance according to his age group in regards to:
- Appearance
- Language
- Social interactions
- Developmental milestones
- Fontanelle assessments (for children <18 months)

For adults:
- Mental state

For all age groups:
- Cranial Nerves
- Body tone
- Strength (of the four extremities)
- Reflexes
- Sensory aspects
- Gait
- Coordination and fine motor function

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

9.2.6.12 Vital signs

- Pulse
- Blood pressure (diastolic and systolic)

Blood pressure and pulse rate will be measured according to local clinical practice; preferably after the patient has rested comfortably for 3 minutes. Measurements of each individual patient should, if possible, be performed using the same method and position (e.g. sitting) throughout the study.

9.2.6.13 Patient reported outcomes

In this study, patient reported outcomes (PRO) questionnaires will be used to assess patient's health-related quality of life and ability to be physically active.

The questionnaires in Table 9–2 should be completed preferably at baseline visit, thereafter yearly and at the end of study visit. PRO questionnaires should preferably be completed at a visit before any other study-related activities.

Table 9–2 Questionnaires

Age group in years	0 -< 5	5 -< 8	8 -< 15	15 -< 18	18 -< 70	≥ 70
Questionnaire to be filled in	No questionnaires	• SF-10 (filled in by parent/LAR) • Ped-HAL Parent's version (filled in by parent/LAR)	• SF-10 (filled in by parent/LAR) • Ped-HAL Children's version	• SF-36 v2 • Ped-HAL Children's version • IPAQ	• SF-36 v2 • HAL • IPAQ	• SF-36 v2 • HAL

• HAL = Haemophilia Activity List, Ped-HAL = Paediatric HAL, IPAQ = International Physical Activity Questionnaire (long last 7 days self-administered format), SF = Short Form healthy survey

Each questionnaire takes approximately 5-10 minutes to complete.

The same PRO questionnaires should be applied throughout the study according to the patient's age at visit 1. Thus, the patient and parent/LAR should complete the same questionnaires at subsequent assessment visits as he/they did at visit 1, regardless of change in the patient's age.

Questionnaires to patients and parents/LARs will be provided in the local language. If no validated translated version of a questionnaire exists it will not be provided.

9.2.6.14 Haemophilia treatment regimen

Haemophilia treatment regimen at study entry, and any changes in regimen during the study, must be recorded in the eCRF, *including, product, type, dosage, frequency and start date*. This will be recorded for both N9-GP and other haemophilia related treatment.

The physician should at each visit discuss the haemophilia treatment with the patient. The patient should be asked if the prophylaxis doses of N9-GP were taken as prescribed since last visit, and any deviations from the prescription must be recorded in the eCRF. The physician should encourage the patient to note down in his own personal notes/diary any treatment relevant details between the visits, which can be used as basis in the discussions during the routine visits to the clinic. The relevant data will be recorded in the eCRF by the physician.

9.2.6.15 Adverse events

All AEs, either observed by the physician or reported by the patient must be recorded and evaluated by the physician. At each contact with the site during the study, the patient should be asked about AEs since the last contact. Please refer to section 11 for AE definitions, collection, recording, and reporting. AE monitoring must be performed from a patient's first exposure to N9-GP after having signed the informed consent and until a patient's last visit in the study.

Bleeding events are considered adverse events, but should only be reported as such if the bleeding event is either fatal, life threatening, or evaluated by the investigator as possibly caused by the study products. Causes to a bleeding event may be considered as an AE e.g. an injury.

9.2.6.16 Assessment of bleeding events and treatment responses

The physician should at each visit ask the patient if he experienced any bleeding events since last visit and record the relevant bleed details in the eCRF. The physician should encourage the patient to note down in his own personal notes/diary any details related to bleeding events (including heamostatic effect) between the visits, which can be used as basis for the discussion with the physician during the routine visits in the clinic.

Information to be collected in the eCRF from bleeding events is:

- Date for when the bleeding event started and stopped
- Cause of the bleeding event
  - i.e. spontaneous, traumatic or due to surgery
- Anatomical location of bleeding event
- Treatment of bleeding event
  - amount and date of each dose of FIX or other product
- Date for last dose of haemophilia medication taken prior to start of the bleeding event
- Severity of bleeding event
  - mild/moderate, severe
- Haemostatic response assessed by the 4-point scale defined in the below
- Symptoms during bleeding event
  - i.e. pain, swelling, warmth, redness, motion restriction

A bleeding event will per default be considered as mild/moderate unless evaluated as severe by the physician. Rating of the bleeding event should follow the World Haemophilia Federation guidelines[13].

The severity of bleeding events is defined as:

- Mild/Moderate: Bleeding events that are uncomplicated joint bleeds, muscular bleeds without compartment syndrome, mucosal- or subcutaneous bleeds.
- Severe: All intracranial, retroperitoneal, iliopsoas and neck bleeds must be categorised as severe. Muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) should also be reported as severe.

Upon discussion with the patient and based on the patients own diary, the physician must consider the severity of the bleeding event. It is the responsibility of the physician to assess the severity of a bleeding event. Traumatic bleeding events at other locations than described above can always be considered severe at the physician's discretion.

Table 9–3 4-point scale used for evaluation of the haemostatic effect

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

If a patient has an ongoing bleeding event when coming for visit or a bleeding event begins during the visit all relevant information as above listed must be reported in the eCRF.

9.2.6.17 Surgery

Patients undergoing surgery will be managed according to local clinical practice, and any visits should be documented in the eCRF.

For surgery, the following data if available should be recorded in the patient's record and the eCRF:

- Surgery due to (elective or emergency)
- Date and time of surgery
- Days in hospital
- Drug consumption (pre-, during and post-operative)
- Surgery intervention:
    - Indication
    - Location
    - Procedure

Clinical evaluation of haemostatic response during surgery based on experience as follows:

- Excellent: Better than expected/predicted in this type of procedure
- Good: As expected in this type of procedure

- Moderate: Less than optimal for the type of procedure but haemostatic response maintained without change of treatment regimen
- Poor: Bleeding due to inadequate therapeutic response with adequate dosing, change of regimen required

9.2.6.18 Laboratory results

FIX inhibitor

It is recommended to perform a FIX inhibitor test at visit 1 at either central or local lab. The physician is encouraged to test for FIX inhibitors according to local clinical practice. A positive inhibitor test is defined as above the specific local laboratory assay threshold and for central lab the threshold is defined as ≥ 0.6 BU.

A patient has a confirmed inhibitor if the patient has been tested positive for inhibitors at two consecutive tests 1-4 weeks apart (either by local and/or central laboratory). Even if the second inhibitor test is positive, the patient may continue treatment with N9-GP.

A positive inhibitor test considered related to N9-GP should be reported as a serious adverse event of special interest (AESI), see section 11. If the second inhibitor test is negative this should be reported as a follow-up to the reported AESI, see section 11.

***F9* genotype**

If consent is given and a result from a previous test is available, or if a test is taken locally during the study, the data should be entered in the "Genotype" section of the eCRF.

Central laboratory

Novo Nordisk will appoint one or more laboratories to perform analyses for the samples being sent to the central laboratory. Laboratory kits for blood sampling of analyses to be performed by the central laboratory will be provided to the sites and to be used as preferred.

FIX inhibitor

To ensure consistent and accurate reporting, it is highly recommended to perform a confirmatory FIX inhibitor test at the central laboratory on any suspected inhibitor patient, regardless of causality. It is also recommended to perform a lupus anticoagulant test together with the confirmatory sample.

PEG plasma levels

It is highly recommended at every visit, also at baseline, to take a PEG plasma sample and send it to central laboratory for monitoring the patient's blood level of PEG.

Genotype

If genotyping result is not available a sample can be taken and sent to central laboratory for analyses. Genotype result or sample may only be collected upon consent given.

Other

Lupus anticoagulant samples can be sent to central laboratory for analyses.
Dipsticks for urinalysis can be requested from the central laboratory.

Local laboratory

It is recommended to follow the FIX activity, inhibitors as well as kidney and renal parameters regularly.

Applicable local reference ranges must be collected. Blood samples should only be taken according to local clinical practice or if considered relevant and be recorded in the eCRF.

Haematology

- Haemoglobin
- Haematocrit
- Leucocytes
- Thrombocytes

Coagulation factor IX activity and inhibitors

- Factor IX activity
- FIX inhibitors

Coagulation parameters

- Prothrombin time (PT)
- Activated partial thromboplastine time (aPTT)
- Fibrinogen
- Antithrombin (AT)
- D-dimer

Biochemistry

- Sodium
- Potassium
- Albumin
- Creatinine
- Bilirubin

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl Transferase (GGT)
- Alkaline phosphatase
- C-reactive protein (CRP)
- Urea

Lupus anticoagulant

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

Viral antibody information (should not be more than 1 year old)

- HBsAg and/or anti-HCV antibodies
- HIV 1 & 2 antibodies
- HIV viral load
- CD4+ count

Urinalysis (to be analysed as a laboratory analyses or with dipsticks)

- Spot urine albumin/creatinine ratio
- Spot urine dipstick test (blood (erythrocytes), glucose, leucocytes, protein, pH)

9.2.7 Other assessments

9.2.7.1 Health economics

To characterise the impact of treatment on health economics aspects the following data should be collected in the eCRF, based on the patients own diary when possible:

- Number of hospital admissions and days per admission (length of stay) related to a bleeding event
- Number of hospital admissions and days per admission (length of stay) due to a surgery event if related to the haemophilia condition
- Number of visits to an Emergency room related to a bleeding event
- Number of missed work/school days because of a bleeding event

9.3 Variables

Data within safety, clinical effectiveness, health economics and PROs will be collected. Data and results from assessments and laboratory sampling performed according to local clinical practice at the participating sites will be recorded upon availability.

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

9.4 Data sources

It is the intention of this non-interventional PASS to observe long-term routine treatment of the individual patient. Data and results available in the patient's medical record and from assessments and laboratory sampling performed according to local clinical practice at the participating sites will be recorded in the eCRF. In addition, available information from patients own diary related to treatment, bleeding events and in case a patient is hospitalised should be reported in the patient's record and subsequently in the eCRF by the physician.

Data sources are eCRF, paper PROs, paper CRF form (pregnancy in patients female partner) and laboratory data – both local and central. The systems used for this is validated according to internal Novo Nordisk procedures.

9.5 Study size

Given the rarity of the disease a sample size of at least but not limited to 50 patients will allow for a reasonable evaluation of ADRs of special interest (including inhibitor formation). The sample size is based on the regulatory (EMA) requirements[1]. According to an obligation received from the CHMP data from 50 patients treated for at least 4 years are required in a post-marketing study with a FIX product to cover especially ADRs with special focus on FIX inhibitors, allergic reactions and thromboembolic events.

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 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.

CRF Paper forms (all other forms are by eCRF):

- Pregnancy in patient's female partners

Follow up questions to central nervous system (CNS) related adverse events as well as selected other adverse events will be send by email.

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 3-5 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.

CRF data can be corrected only by the physician or the physician's authorised staff. For PRO questionnaires only the patient/parent(s)/LAR(s) can correct the answers to the questions whereas the site staff can correct administrative information as patient number, visit number, dates etc.

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

An audit trail will be maintained in the Electronic Data Capture (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. If corrections are made by the physician's authorised staff after the date of the physician's signature on the case book, this must be signed again by the physician.

The paper CRFs will be source data verified, as applicable, by Novo Nordisk.

The system for EDC and support services for the system will be supplied by a vendor. The activities of the vendor will be under the direction and supervision of Novo Nordisk.

The patient and the biological material obtained from the patient will be identified by a patient number, study site, and study ID number. Appropriate measures such as encryption or deletion must be enforced to protect the identity of human patients in all presentations and publications as required by local/regional/national requirements. Further, appropriate measures such as encryption of data files must be used to assure confidentiality of patient data when it is transmitted over open networks.

Laboratory data will be transferred electronically from the central laboratory performing clinical analyses. The electronic laboratory data will be considered as source data. In cases where laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer. Available local laboratory data will be entered in the eCRF by the physician/site staff. Results from central laboratory analysing patient blood samples will be part of the dataflow into the clinical database for the study.

Site specific eCRF data must after the study database is released be downloaded by site in an electronic readable format of site's choice. Hereafter access to the study specific EDC will be removed.

9.7 Data analysis

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

All summaries will show results by regimen (prophylaxis, on-demand and perioperative management) for the full group of patients. In addition, subgroup analysis will be presented if data allows:

- By age groups: (<6 yrs; ≥6 yrs <12 yrs; ≥12yrs <18yrs; ≥ 18 yrs) .
- By severity of disease (mild/moderate vs severe)

Data analysis may be delegated under an agreement of transfer of responsibilities to external CRO.

9.7.1 Definition of analysis sets

Descriptions and analysis of effectiveness will be based on the Full Analysis Set (FAS), as defined in ICH E9 guidelines[14] (Statistical Principles for Clinical Trials). The FAS includes all patients with post-dosing data, where data from patients with pre-existing inhibitor will be presented separately. In the rare case where a patient developed inhibitor towards FIX after the exposure to N9-GP, the data from this patient after development of inhibitor will be presented together with those who has pre-existing inhibitors. The definition for SAS that will be used for presenting safety data is the same as FAS.

The patients or observations to be excluded, and the reasons for their exclusion must be documented and signed by those responsible before database lock. The patients and observations excluded from analysis sets, and the reason for this, will be described in the non-interventional study report (NSR).

For patients with severe haemophilia B after successful ITI a separate analysis might be presented if deemed necessary.

9.7.2 Statistical methods

No formal testing of statistical hypotheses will be performed. All data will be presented using descriptive statistics and additional analyses for the specific endpoints are described in the subsequent sections. Categorical data will be summarized by frequency tables while continuous data will be summarized by mean, standard deviation, median, minimum and maximum value.

Primary Endpoint

- Number of Adverse Drug Reactions (ADRs) (FIX inhibitors, allergic reactions, and thromboembolic events) reported during the study period

Number of the Adverse Drug Reactions (ADRs) as defined in section 11.2 during the study period will be summarised together with the incidence of patients with any reaction. Furthermore, listings will be provided displaying all reactions.

Secondary Safety Endpoint

- Number of Serious Adverse Events (SAEs) reported for a period up to 9 years

Number of Serious Adverse Events (SAEs) reported for a period up to 9 years will be summarised. Furthermore, listings will be provided displaying all adverse events.

Secondary Effectiveness Endpoints

- Number of bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years.

- Number of treatment requiring bleeding episodes during long-term routine use of N9-GP (prophylaxis) as assessed by annualised bleeding rate (ABR) for a period up to 9 years.

Definition of bleeding episode: 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. A bleeding event which occurs within 72 hours after stopping treatment of a previous bleeding event at the same or a subset of the same anatomical locations 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.

Number of treatment requiring bleeding episodes during prophylaxis will be presented by type (spontaneous, traumatic or other origin). ABR rate will be summarised and a 95% two-sided confidence interval will be provided based on a Poisson regression model adjusting for exposure time and allowing for over-dispersion.

Treatment requiring bleeding episodes occurring in the time period between the patient stops weekly prophylaxis to go to surgery and to the date and time when patient resumes weekly prophylaxis treatment will be presented in a listing and will not be included in the estimation of the ABR during prophylaxis treatment.

- Haemostatic response of N9-GP when used for prophylaxis of bleeding episodes, assessed as success/failure based on a four-point scale for haemostatic response (excellent, good, moderate and poor) by counting excellent and good as success and moderate and poor as failure for a period up to 9 years

Haemostatic response of N9-GP in treatment of bleeding episodes and in perioperative management assessed as success or failure of overall treatment regimen. Description of the haemostatic response of N9-GP when used for treatment of bleeding episodes will be measured and listed according to the four point scale for haemostatic response (excellent, good, moderate or poor).

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

Exploratory Safety Endpoints

- Number of ADRs that are defined within the system organ classes nervous system and psychiatric disorders for a period up to 9 years
- Number of ADRs related to hepatic or renal function for a period up to 9 years

ADRs/AEs will be summarized by number of reactions/events and number of patients with any reactions/events. Since patients will have different durations in the study rates (reactions/events per 100 patient years of exposure) will also be calculated and presented. Summary tables will be created. Furthermore, listings will be provided displaying all ADRs and AEs reported during the study.

- Change in eGFR from study start to end of study
- Change in ALT and bilirubin from study start to end of study
- Change in PEG-plasma levels from study start to end of study

Summary tables for baseline and change (from baseline visit) in laboratory parameters will be created. Furthermore, listings and individual over time profile plots (where deemed relevant) will be provided displaying laboratory parameters reported during the study.

Exploratory Endpoints Neurological Development

- Number of abnormal findings as assessed by neurological examination across all age groups for a period up to 9 years

Abnormal findings will be summarized by number of findings and number of patients with any findings. Summary tables for baseline and (where possible) change (from baseline visit) for available parameters (see section 9.2.6.11 for more details) may be created. Furthermore, listings will be provided displaying all available neurological parameters reported during the study.

Exploratory Health Economics/patient reported outcome Endpoints

- Change in quality of life during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Change in physical activity level or functional abilities during long-term routine use of N9-GP (prophylaxis) from study start to end of study
- Consumption of N9-GP used for treatment per year (IU/Kg/year) for a period up to 9 years
- Number of healthcare resources (emergency room, hospitalisation, clinic) utilization due to a treatment requiring bleeding episode or sequelae thereof during follow-up intervals

- Adherence to treatment prescribed by the physician (percent difference prescribed versus utilized dose) during follow-up intervals

Health economic data and (where applicable) changes in PRO data from study start to end of study will be summarised and listed using descriptive statistics.

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

Additional Assessments

- Incidence of inhibitory antibodies against FIX

Incidence of inhibitory antibodies will be summarized by number of patients with inhibitors.

9.7.3 Interim analysis

Two interim reports are planned. The first interim report will be generated once ten patients have had their first visit after one year of inclusion in the study and the second interim report when twenty five patients have had their first visit after one year of inclusion in the study.

Additional interims may be conducted to collect safety data for submission to authorities or publications.

9.7.4 Sequential safety analysis/safety monitoring

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

9.7.5 Patients Reported Outcome

Changes in PROs will be summarised and listed using descriptive statistics. Changes in PRO scores from visit 1 to the subsequent assessment approximately one year later as described in section 9.2.6.13 and from visit 1 to end of study will be calculated and listed.

Scoring algorithms for the PRO instruments are available and will be used to generate the PRO scores.

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 paper CRFs/eCRFs are completed.

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 (i.e. obtains informed consent from the first patient), the following documents must be available at Novo Nordisk:

- Regulatory approval and/or notification as required
- Documentation of the physician's qualifications as medically qualified (for instance a short Curriculum Vitae (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
- Non-interventional study agreement

9.8.3 Retention of study documentation

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

Novo Nordisk will comply with all the requirements of Good Pharmacoepidemiological Practice[9] (GPP) and relevant national legislation related to archiving of study documentation. Records containing patient sensitive data must not be archived by Novo Nordisk, but must be kept with physician and patient and according to local regulations pertaining to personal data protection.

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, which ever 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 local 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

Not applicable section, as all aspects of the research method is covered by the previous sections.

10 Protection of human subjects

The study will be conducted in accordance with GPP[9], applicable regulatory requirements, and in accordance with the Declaration of Helsinki[15].

There is no burden added to the patient's life by participating in this study. The potential benefit for the patient is the systematic assessments of safety. There are no additional risks associated with this activity. For information on AEs, see the approved labelling.

10.1 Informed consent form for study patients

Prior to any study-related activity, the physician must give the patient and/or the patient's parent(s)/LAR(s) oral and written 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[15].

A voluntary, signed and personally dated, informed consent form will be obtained from the patient and/or the patient's parent(s)/LAR(s) prior to any study-related activity. 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 parent(s)/LAR(s)) 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 Novo Nordisk and regulatory authorities as applicable

Data will be collected and handled in accordance with local law and IEC/IRB 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 accordance with regulatory requirements, including GVP, the sponsor will inform the health authorities of N9-GP related ADRs. In certain situations other 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 N9-GP related serious ADRs, 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 procedure. If after the termination of the study the risk/benefit analysis has changed, the new evaluation should be provided to the IEC/IRB in case it will have an impact on the planned follow-up of the patients who have participated in the study. If so, the actions needed to protect the patients should be described.

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 he/she has delegated specified significant study-related duties. The medical care given to, and medical decisions made on behalf of, patients should always be the responsibility of a qualified physician.

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 such technical and organisational safety measures have been taken.

11 Managing and reporting of adverse events/adverse drug reactions

11.1 Safety information to be collected

The main scope of the study is to investigate the safety and tolerability of N9-GP.

The following safety information will be **systematically collected**:

- All adverse events (AEs), including serious adverse events (SAEs)
- Safety information required by local laws and/or IECs/IRBs
- Information on pregnancies in female partners of male patients and AEs, and any SAEs experienced by the foetus or new-born infant
- Adverse events of special interest (AESI)

Voluntary reporting of other safety information by the physician should follow the same reporting process flow as for systematic collection.

11.2 Safety definitions

Adverse event

An adverse event is any untoward medical occurrence in a patient administered a product, which does not necessarily have a causal relationship with the product.

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

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

This includes adverse events which arise from:

- a worsening of a concomitant illness
- occupational exposure to a product

Pre-existing conditions and procedures where the reason for the procedure is known should not be reported as adverse events. Worsening of pre-existing conditions should be considered as AEs.

Bleeding events are considered adverse events, but should only be reported as such if the bleeding event is either fatal, life threatening, or evaluated by the investigator as possibly caused by the study products. Causes to a bleeding event may be considered as an AE e.g. an injury

Adverse drug reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended with a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event.

Terms used to describe causal relationship to the study product

- Probable: good reasons and sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed
- Unlikely: the event is most likely related to an aetiology other than the study product

Seriousness criteria

An AE is a **serious adverse event (SAE)** if the event results in any of the following seriousness criteria:

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

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

[b] The term "hospitalisation" is used when a patient is: admitted to a hospital/inpatient (irrespective of the duration of physical stay), or not admitted to a hospital/not inpatient, but stays at the hospital for treatment or observation for more than 24 hours. Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, study related and social purposes do not constitute AEs and should therefore not be

reported as AEs including SAEs. Likewise, hospital admissions for surgical procedures planned prior to study inclusion are not considered AEs including serious adverse events.

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

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

The following AEs must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:

- development of all FIX inhibitor either based on local laboratory tests or clinical suspicion, regardless of confirmation
- 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).

Non-serious adverse event

An AE that does not meet a seriousness criterion is considered to be non-serious.

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.

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 condition/event.
- 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 the sequelae meet a seriousness 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 at the time of reporting.
- Fatal – (only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An AE with fatal outcome must be reported as a SAE).
- Unknown – This term should only be used in cases where the patient is lost to follow-up.

Adverse event of special interest (AESI)

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 11.3).

The following are defined as AESIs in this study:

1. Inhibitor formation against FIX is always considered a serious AESI. If an investigator obtains any indication of inhibitor formation by clinical signs or local laboratory results, this should be reported as a serious AESI. Blood samples for measurement of FIX inhibitors can be analysed at a central laboratory selected by Novo Nordisk.
2. 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[16].
3. Anaphylactic reaction as defined by Sampson et al 2006[16] (see below).
4. CNS-related adverse events, including but not limited to any learning and behavioural deficits. Examples include but are not limited to:
    - Headache
    - Seizures
    - Vision problems
    - Acute changes in mental status
    - Developmental, cognitive or behavioural issues.
5. 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).
6. Medication errors concerning study products. 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: more than 20% from the intended dose. 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.

7. Renal adverse events including new onset of renal disorder or renal impairment or acute and chronic renal failure.

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

Definition of an acute, evolving, or recent myocardial infarction

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

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

Definition of pulmonary embolism

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

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

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

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

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

Definition of other clinically significant thromboembolic events
Sign or suspicion of clinically significant thromboembolic event, eg visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis.

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

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

Clinical criteria for diagnosing anaphylaxis (Sampson et al. 2006[16])
Anaphylaxis is highly likely when two or more of the following occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

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

11.3 Collection and reporting of safety information

At each contact with the site during the study, the patient should be asked about possible experienced AEs since the last contact. Adverse events must be reported by the physician on the adverse event form.

In addition to this, for all SAEs and AESIs, further information must be reported by the physician on the safety information form, and the relevant follow up form (if applicable), respectively.

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

For serious adverse events

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

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

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

Medication errors:

- Further information must be reported on the medication error form **within 14 calendar days** of the physician's first knowledge of the event.

CNS related adverse events (and other relevant events such as hypersensitivity and immunogenicity events):

- Follow up questions will be sent to sites which must be answered **within 14 days**. If serious, the timelines for SAEs apply.

The physician must complete the forms in the eCRF application and / or in the paper format within the above specified timelines of obtaining knowledge about the event(s). For SAEs the physician must sign the form within 7 days after completing the form. Paper forms must be forwarded electronically, fax or courier copies.

The physician should record the diagnosis, if available. If no diagnosis is available, the physician should record each sign and symptom as individual AEs. 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, use a separate form for each sign and symptom. However, if several symptoms or diagnoses occur as part of the same clinical picture, only one safety information form or adverse event form can be used to describe all the events.

The investigator should use the local product information 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 or AESI data. The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. In accordance with regulatory requirements, including GVP[10, 11], the sponsor will inform the regulatory authorities of study product related Serious Adverse Reactions (SARs). In addition, the sponsor will inform the IECs/IRBs (or other appropriate bodies as required locally) of study product related SARs, in accordance with the local requirements in force.

For collection and reporting of pregnancies in male patients' female partners, see section 11.5

11.4 Follow-up on safety information

Follow-up information concerning previously reported serious adverse events including serious AESIs 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 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 (updated and/or additional) information that reflects the situation at the time of the physician's signature.

All SAEs, SARs, AESIs as well as non-serious ADRs 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 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 post-study follow-up period (as stated in this protocol) 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 the 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".

11.5 Collection and reporting of pregnancies in male patients' female partners

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. ADRs and SAEs experienced by the foetus or newborn infant should be collected and reported.

An ad-hoc informed consent form should be signed by the pregnant partner before collecting any ADRs and SAEs in the foetus or new born infant; that is to say from birth to 1 month of age.

Reporting of ADRs or SAEs in foetus, newborn infant must be done on the same forms as described for reporting of AEs. It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the partner, foetus or newborn infant. The reporting timelines are as described for other ADRs and other SAEs.

11.6 Precautions/Over-dosage

Please refer to the summery of product characteristics (SmPC) or corresponding local product labelling texts.

11.7 Safety committee

11.7.1 Internal Novo Nordisk N9-GP Safety Committee

Novo Nordisk has an internal Safety Committee to perform on-going safety surveillance of N9-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 N9-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 will be designated with the responsibility to review and sign the NSR (Signatory Physician).
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

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. All study sites will be registered. This non-interventional PASS must be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by EMA and accessible through EMA's web portal. The EU PAS Register is currently and temporarily hosted on the ENcEPP website http://encepp.eu/. Note: Study registration is regarded as the publication of an internationally-agreed set of information (which can be found at the WHO homepage) about the design, conduct and administration of non-interventional studies. These details are published on a publicly accessible website managed by a registry conforming to WHO standards (also found at the WHO homepage); for example, www.clinicaltrials.gov.

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 public disclosures for publication 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 NSR 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 abstract 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.

This study will be registered by Novo Nordisk at www.clinicaltrials.gov and www.novonordisk-trials.com in accordance with Novo Nordisk Clinical Trials Disclosure Code of Conduct for Clinical Trials Disclosure.

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 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[10, 11]. This is to allow national competent authorities to review in advance the results and interpretations to be published.

For PASS studies in Europe, the study information should be available in the EU PAS Register, see section 6.

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

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