Protocol

Study ID: NN7999-4413

EU PAS Register No: x

Adverse Event Data Collection from External Registries on Nonacog Beta Pegol

Redacted protocol
Includes redaction of personal identifiable information only.

Non-Interventional Post-Authorisation Safety Study (PASS)

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Protocol originator:
[redacted], MD [redacted]
Medical & Science Biopharm

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PASS information

Title	Adverse event data collection from external registries on nonacog beta pegol
Protocol version identifier	0.1
Date of last version of protocol	This is the first version of the protocol
EU PAS Register number	Study will be registered by Novo Nordisk, and the EU PAS Register number added in connection with future amendments
UTN Number	U1111-1212-4050
Active substance	Nonacog beta pegol. ATC code: B02BD
Medicinal product	Rebinyn®, Refixia®
Product reference	EU/1/17/1193
Procedure number	EMEA/H/C/4178
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	The primary objective of this study is to investigate potential clinical effects of longer-term exposure to nonacog beta pegol in patients with haemophilia B
Countries of study	The European Region, Canada and other countries where agreement is obtained with registries

Author	[redacted], [redacted] Novo Nordisk A/S Vandtaarnsvej 108-110 2860 Soeborg Denmark

Marketing authorisation holder (s) (MAH (s))	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	[redacted], [redacted] Novo Nordisk A/S Vandtaarnsvej 108-110 2860 Soeborg Denmark

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2 List of abbreviations

EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practice
ISPE	International Society for Pharmaceutical Engineering
LAR	Legally Acceptable Representative
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
UTN	Universal Trial Number

3 Responsible parties

The present study will collect third party data from the PedNet Haemophilia Registry (PedNet), and from the European Haemophilia Safety Surveillance System (EUHASS).

Data from national and international registries in countries where nonacog beta pegol has been approved and marketed could be included in the data collection.

4 Abstract

This non-interventional study concerns a safety data collection based on adverse event data from third party registries that include information about adverse events from patients with haemophilia B treated with nonacog beta pegol. The study is intended to support addressing questions related to PEG with special emphasis on the two major excretion organs (liver and kidney), and the choroid plexus. The primary objective is to investigate possible clinical effects of long-term exposure to nonacog beta pegol, and will include all patients treated with nonacog beta pegol who reported adverse events to the PedNet and EUHASS and possibly other national or international registries.

4.1 Title

Adverse event data collection from external registries on nonacog beta pegol (PASS), Version updated protocol no. 0.1, August 2018.

5 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason

6 Milestones

Milestone	**Planned date**
Start of data collection	First patient first visit 01-Oct-2018
End of data collection	Q4-2027
Reporting of study results	Data will be reported in PSURs
Registration in the EU PAS Register	Study will be registered by Novo Nordisk, and the EU PAS Register number added in connection with future amendments
Final report of study results	Q2-2028

7 Rationale and background

Novo Nordisk has developed nonacog beta pegol, a 40-kDa glycoPEGylated human recombinant coagulation Factor IX (rFIX) with an extended half-life, for the treatment and prophylaxis of bleeding in patients with haemophilia B. Nonacog beta pegol has improved pharmacokinetic (PK) properties including higher recovery and a 5-fold increase in terminal half-life compared with standard FIX products; thus nonacog beta pegol offers the possibility of achieving high and sustained FIX levels with a less-burdensome once-weekly treatment regimen (1).

Nonacog beta pegol is approved in the USA and Canada as REBINYN®, and in the EU, Switzerland and Japan as Refixia®.

The approval of of nonacog beta pegol was based on the paradigm™ programme, a phase 3 clinical programme including 115 unique previously-treated patients (PTPs) children and adults with severe or moderate haemophilia B (FIX activity ≤2%).

Specific pharmacological risks for FIX replacement products include FIX inhibitors, allergic-type hypersensitivity reactions, and thrombotic events, which were evaluated in all trials. Through the clinical development programme, nonacog beta pegol has demonstrated a safety profile similar to that of currently approved FIX products, and was well tolerated with no development of FIX inhibitors, 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 130 PTPs with a total of 13,063 exposure days (per 30-April-2018).

Although non-clinical data reveal no concern for humans based on conventional safety pharmacology and repeated dose toxicity studies in rats and monkeys, questions have been raised based on the following.

In a repeat dose toxicity study in monkeys, mild and transient body tremors were seen 3 hours post dosing and abated within 1 hour. These body tremors were seen at doses of nonacog beta pegol (3,750 IU/kg), which were more than 90 times higher than the recommended dose for humans (40 IU/kg). No mechanism behind the tremors was identified. Tremors have not been reported in the clinical trials.

In repeat-dose toxicity studies in monkeys and rats, PEG was shown by immunohistochemical staining to be bio-distributed to blood in connective tissue and cytoplasm of epithelial cells of the choroid plexus of the brain in both rats and cynomolgus monkeys. No other brain structures showed presence of PEG. The presence of PEG was not associated with microscopic signs of cellular vacuolation or dysfunction. PEG was found in vesicles (lysosomes) in the epithelial cells of the choroid plexus in high-dose animals from the 26-week Rowett nude rat study, when assessed by

transmission electron microscopy. The PEG stored in lysosomes did not affect normal epithelial cell function as judged from the overall cell ultrastructure, including rough endoplasmatic reticulum and polysomes and was thus not considered adverse.

The distribution and excretion studies in rat and mice show that PEG is cleared from organs/tissues over time (including choroid plexus). Based on these data, estimated elimination half-lives of all organs (15–49 days) were calculated and used to create a model to simulate plasma and tissue concentrations following repeated dosing in rats and in humans. The results indicate that a maximum concentration (steady state) will be reached for most organs within 1 year and for choroid plexus within 2 years in humans. This was substantiated by PEG plasma concentration data in clinical samples from the paediatric trial NN7999-3774 (paradigm™5) documenting that steady-state plasma levels were reached in 3-6 months and were within the predicted range based on the plasma-tissue model.

The clinical safety of long-term dosing of nonacog beta pegol, including evaluation of possible clinical consequences of potential 40 kDa PEG accumulation, is yet to be established; however no unexpected serious adverse safety findings have been reported in the completed or on-going trials.

The main purpose of this registry based non-interventional PASS is to evaluate the long-term safety of nonacog beta pegol in patients with haemophilia B and possible clinical consequences under routine clinical care.

This trial is classified as a Post-Authorisation Safety Study (PASS) not requiring Pharmacovigilance Risk Assessment Committee (PRAC) endorsement (Ref: EMA - Guideline on good pharmacovigilance practice (GVP) Module VIII - Post-authorisation safety studies (rev 2). EMA/813938/2011, 04 August 2016).

8 Research question and objectives

8.1 Primary objective

To investigate the safety of long-term exposure to nonacog beta pegol in patients with haemophilia B.

8.2 Secondary objective

To assess specific pharmacological risks for FIX replacement products including nonacog beta pegol (FIX inhibitors, allergic-type hypersensitivity reactions, and thrombotic events).

9 Research methods

9.1 Study design

This is as registry-based post-authorisation safety study (PASS) collecting data from existing third party databases. The proposed registries are PedNet and EUHASS, and may include other international or national/local registries.

9.1.1 Primary endpoint

Adverse Drug Reactions (ADRs) reported to the registries with suspected relation to nonacog beta pegol in patients with haemophilia B for renal, hepatic, neurodevelopmental, neurocognitive, neurologic or psychiatric events.

9.1.2 Secondary endpoint

Other ADRs reported to the registries during the study period with suspected relation to nonacog beta pegol in patients with haemophilia B, including ADRs of special interest (de novo FIX inhibitors ≥0.6 BU); anaphylaxis and other allergic reactions; thromboembolic events).

9.1.3 Treatment of patients

Patients will be treated with commercially available nonacog beta pegol according to routine clinical practice at the discretion of the treating physician.

9.2 Setting

9.2.1 Study Population

All patients with haemophilia B treated with nonacog beta pegol who reports adverse events to the PedNet and EUHASS, and possibly other national or international registries.

A decision to initiate treatment with commercially available nonacog beta pegol has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in the registries in scope.

9.2.2 Inclusion criteria

Participation in the PedNet Registry and/or the European Haemophilia Safety Surveillance System (EUHASS), or other national and international registries.

9.2.3 Exclusion criteria

As this is a study collecting third-party data from registries, there are no exclusion criteria.

9.2.4 Withdrawal criteria

1. PedNet, any patient will be able to reconsider his/her participation in the registry from the age of 12 years
2. EUHASS, no withdrawal criteria specified

In case of withdrawal, the registry should attempt to collect any outstanding data. The primary reason (adverse reaction or other) for discontinuation should be obtained, if possible.

9.2.5 Visit procedures

As this study will collect data that have already been collected by the registries, and as the study is strictly non-interventional, Novo Nordisk will have no influence over visit procedures. Visit procedures will be as defined by the treating physician.

9.2.6 Assessments for safety and effectiveness

Assessments for safety and effectiveness will be performed according to routine clinical practice at the participating sites.

9.3 Variables

The variables to be collected in this study will be restricted to the variables that are collected by the registries. All patient visits will be performed according to normal local clinical practice. No additional visits will be conducted due to the participation in this study.

9.4 Data sources

Currently, the PedNet and EUHASS Registries are in scope for the data collection; however other national or international registries could be added.

Data on ADRs related to nonacog beta pegol will be reported from the registries to Novo Nordisk via annual reports.

9.4.1 PedNet Registry

PedNet is an observational prospective cohort of patients with mild, moderate or severe haemophilia A and B with FVIII/IX levels of <1-25% born between 01-Dec-2000 and 01-Dec-2020.

Data that can be provided by the PedNet Registry are as follows.

<u>Baseline</u>

- Year of birth
- Ethnicity (Caucasian/non Caucasian)
- Mutation type

- Haemophilia Type (A/B)
- Severity (Mild/Moderate/Severe)
- Age at diagnosis
- Reason of diagnosis
- Family history of haemophilia at time of diagnosis
- Family history of inhibitor at time of diagnosis

Inhibitor status

- Inhibitor (yes/no; high/low)
- Number of exposure days (ED) till inhibitor development

First exposure days

- Number of ED
- Age at ED
- Reason of treatment
- Location (in case of bleed)
- Side (in case of bleed)
- Severity (in case of bleed)
- Number of units given
- Product
- Remarks

9.4.2 European Haemophilia Safety Surveillance System, EUHASS

EUHASS is a pharmacovigilance programme to monitor the safety of treatments for people with inherited bleeding disorders in Europe. Haemophilia treatment centres report adverse events directly to the EUHASS website and regular surveillance reports are produced.

The EUHASS collects the following types of adverse event data.

- Allergic and other acute reactions
- Transfusion transmitted infections
- Inhibitors – first occurrence
- Inhibitors – recurrence
- Thrombosis – within 30 days of concentrate
- Thrombosis – no concentrate in the last 30 days
- Malignancies
- Neurological adverse events
- Deaths

The EMA has disclosed that they are in contact with the PedNet Registry and EUHASS to advise on the requirements to follow-up more specifically for PEGylated products, thus it may be expected that the data collection from PedNet and EUHASS will change going forward.

9.5 Study size

All patients with haemophilia B treated with nonacog beta pegol who reports adverse events to the PedNet and EUHASS, and possibly other national or international registries will be included. However, it should be noted that not all eligible haemophilia treatment centres are contributing to the PedNet and EUHASS data collections, as participation is voluntary.

These data are judged to facilitate an expansion to the safety experience of long-term treatment with nonacog beta pegol that will be able to complement other safety data collections described in section 9.9.

9.6 Data management

Data on ADRs related to nonacog beta pegol will be reported from the registries to Novo Nordisk via annual reports.

9.7 Data analysis

Novo Nordisk will be responsible for all statistical analyses.

9.7.1 Statistical methods

This is a purely descriptive study and the statistical analyses and presentations do not include any testing of pre-specified hypotheses.

9.7.1.1 Primary Endpoint

The referred ADRs of the primary endpoint (renal, hepatic, neurodevelopmental, neurocognitive, neurologic or psychiatric events) will be summarised, displaying the nature, number and seriousness of reactions.

9.7.1.2 Secondary Endpoint

Other ADRs of the secondary endpoint, including ADRs of special interest (de novo FIX inhibitors ≥0.6 BU); anaphylaxis and other allergic reactions; thromboembolic events) will be summarised, displaying the nature, number and seriousness of reactions.

9.7.2 Interim analysis

The registries will provide data to Novo Nordisk once per year in the form of annual reports. Interim results will be provided by Novo Nordisk within PSURs and 5-year renewal.

9.8 Quality control

The registries will be responsible for the data that they submit in the annual reports. For Monitoring and Quality Assurance in the PedNet Registry, please refer to enclosed protocol section 7.2

9.8.1 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiological Practice (GPP) and will retain the documentation pertaining to the study according to company procedure.

9.9 Limitations of the research methods

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

Currently, the PedNet is collecting data about inhibitor development, and the EUHASS is concentrating on pre-specified groups of adverse events relevant for people with inherited bleeding disorders, thus neither database collects information regarding renal or hepatic function, and only the EUHASS will be implementing the collection of neurologic adverse events.

It is worth noticing that EUHASS, rather than a registry, is a safety surveillance system for pre-specified categories of adverse events relevant for factor replacement products.

The quality of the data in the registries depends upon the willingness and possibility for the investigators / sites to report good quality adverse event data to the registries. It is well known that in busy daily clinical practice adverse event reporting can be de-prioritised, thus leading to under-reporting (2); hence, data from the registries cannot be expected to be complete. Further, there is a risk of reporting bias in the reporting of safety issues due to increased focus on the potential PEG-associated risks. This would lead to a false positive safety signal for PEG, which should be taken into careful consideration when interpreting the data.

The strength of the study design to answer the research question will depend on several factors. Collecting adverse events related to nonacog beta pegol via the registries will require that a meaningful amount of patients will be prescribed nonacog beta pegol. Further, it will require commitment from health care providers to participate in the data collection, in addition to careful and unbiased reporting of adverse events related to nonacog beta pegol. In case of adverse events reported within the special areas of interest (renal, hepatic and neuropsychological) it would be preferable to be able to follow-up on the events, which might be difficult or not feasible. In conclusion, a registry based study is limited in the ability to answer the question whether the presence of PEG will lead to any hitherto undiscovered long-term safety issues; however in combination with other safety measures, as routine pharmacovigilance, aggregate analyses of safety data, a prospective non-interventional PASS, as well as implementation of additional analyses and

clinical examinations in the on-going clinical trials in paediatric patients, registry data might be able to complement the data collection on PEG safety.

10 Protection of human subjects

The study will be conducted in accordance with GPP (ref ISPE (International Society for Pharmacoepidemiology), Guidelines for Good Pharmacoepidemiology Practices (GPP). Revision 2, April, 2007).

There is no extra burden to the patients by participating in this registry-based data collection. Potential benefits are increased knowledge about the safety profile of nonacog beta pegol, which could have an impact on current and future generations of haemophilia B patients.

10.1 Informed consent form for study patients

PedNet obtains written informed consent of the parents/caregivers.

EUHASS does not obtain consent from the patients before registering of the adverse event data.

11 Managing and reporting of adverse events/adverse reactions

This PASS is based on secondary use of data, and data will consist of safety data reported from the use of nonacog beta pegol reported from pre-defined registries (PedNet and EUHASS). Thus, Novo Nordisk A/S is not involved in the data collection as such, but is merely receiving data from the registries. Data will be received as yearly reports as described in section 9.6.

11.1 Safety information to be collected

Please refer to section 9.4.1 and 9.4.2.

This study is based on secondary use of data and therefore Individual Case Safety Reports will not be performed.

11.2 Follow-up on safety information

For the PedNet, as an observational prospective cohort registry study, it might be possible to follow-up on reported ADRs; however for the EUHASS, which is merely a safety surveillance system for pre-specified categories of adverse events it will probably not be feasible to perform any follow-up.

11.3 Nonacog beta pegol safety committee

Novo Nordisk has an internal safety committee that performs ongoing safety surveillance of nonacog beta pegol.

The safety committee works according to a written guideline, and is responsible for reviewing any safety concern, signal or alert, and determining actions to be taken according to the guidelines for the safety committee.

12 Plans for disseminating and communicating study results

The information obtained during the conduct of this study can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of nonacog beta pegol.

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.

Non-interventional PASS must be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the European Medicines Agency and accessible through the European Medicines Agency's web portal.

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.

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) of the registry database (EUHASS/PedNet) in collaboration with Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property, and reserves the right not to release interim results or data until a study report is available. Following agreement with registry data providers, 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 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 registry owners and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

13 References

1. Negrier C, Knobe K, Tiede A, Giangrande P, Moss J. Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B. Blood. 2011;118(10):2695-701.

2. Alatawi YM, Hansen RA. Empirical estimation of under-reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). Expert Opin Drug Saf. 2017;16(7):761-7.