Protocol

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Adverse Event Data Collection from the EUHASS Registry on Turoctocog alfa pegol

Non-Interventional Post-Authorisation Safety Study (PASS)

Protocol originator:
[redacted]
Medical & Science, Biopharm

PASS information

Title	Adverse event data collection from the EUHASS Registry on turoctocog alfa pegol
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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
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Product reference	EU/1/19/1374
Procedure number	EMEA/H/C/004883
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 side effects of longer-term exposure to turoctocog alfa pegol in patients with haemophilia A
Countries of study	The European Region where agreement is obtained with the EUHASS registry
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2 List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
BU	Bethesda Unit
CHMP	Committee for Medicinal Product for Human use
EUHASS	European Haemophilia Safety Surveillance System
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
PK	Pharmacokinetics
PTP	Previously Treated Patients
PSUR	Periodic Safety Update Report
rFVIII	Recombinant Factor VIII
UTN	Universal Trial Number

3 Responsible parties

The present study will utilise third party data from the European Haemophilia Safety Surveillance System (EUHASS).

4 Abstract

This non-interventional study concerns a safety data collection based on adverse event data from a third-party registry that include information about adverse events from patients with haemophilia A treated with turoctocog alfa pegol. The study is intended to address questions related to PEG with special emphasis on the two major excretion organs (liver and kidney) and the neurological system. The primary objective is to investigate possible clinical side effects of long-term exposure to turoctocog alfa pegol and will include all patients treated with turoctocog alfa pegol who reported adverse events to the EUHASS registry. The study is part of the risk management plan for turoctocog alfa.

4.1 Title

Adverse event data collection from the EUHASS registry on Turoctocog alfa pegol.

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	From December 2019
End of data collection	January 2025
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	July 2025

7 Rationale and background

Novo Nordisk has developed turoctocog alfa pegol, a 40-kDaglycoPEGylated human recombinant coagulation Factor FVIII (rFVIII) with an extended half-life for the treatment and prophylaxis of bleeding episodes in patients with haemophilia A. In the "Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products" the Committee for Medicinal Product for Human use (CHMP) indicates that a post-marketing investigation should be performed to collect additional clinical data and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies and routine use.

Turoctocog alfa pegol has improved pharmacokinetic (PK) properties including a 1.6-fold increase in terminal half-life compared with standard FVIII products, which offers the possibility of achieving FVIII levels in the range of moderate haemophilia A with a less-burdensome every fourth day or twice weekly treatment regimen (Tiede 2013, Giangrande 2017 and Meunier 2017).

The relevant clinical trials to apply for the Marketing Authorisation Application (MAA) have been completed and submitted to regulatory agencies for worldwide approval. Turoctocogalfa pegol is approved in United States of America, European Union, Canada, Japan and Switzerland under the tradename Esperoct®.

The turoctocog alfa pegol application was based on the pathfinder™ clinical programme including 270 unique previously-treated patients (PTPs) children, adolescents and adults with severe haemophilia A (FVIII activity ≤1%). The confirmatory phase 3 trials showed that turoctocog alfa pegol is efficacious for prophylaxis, successful treatment of bleeding episodes and in providing effective haemostasis during and after major surgical procedures (Giangrande 2017, Meunier 2017, Hampton 2017).

Specific pharmacological risks for FVIII replacement products include FVIII inhibitor development and allergic-type hypersensitivity reactions, which were evaluated in all clinical studies. Through the clinical development programme, turoctocog alfa pegol was well tolerated and has demonstrated a safety profile in the pivotal-phase 3 trial (NN7088-3859), in the paediatric phase 3 trial (NN7088-3885) and in the surgery phase 3 trial (NN7088-3860) similar to that of currently marketed FVIII products. One instance of development of FVIII inhibitors in PTPs (NN7088-3859) has been reported. An expected rate of allergic reactions, no confirmed thromboembolic events, no systematic changes over time for any laboratory parameters, and no unexpected safety concerns were identified in 270 PTPs with more than 80,000 exposure days (>900 patient years of treatment).

During the Marketing Authorisation Application review, CHMP has raised a theoretical safety concern regarding potential long- term effects of PEG accumulation in organs and other tissues. It should be noted, that based on modelling data and supported by analyses of PEG plasma levels in clinical samples from adolescent/adult and paediatric patients, plasma steady-state PEG concentrations have been reached in the turoctocog alfa pegol clinical programme without any indication of PEG-related adverse effects to date.

The clinical safety of long-term dosing of turoctocog alfa 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 EUHASS registry based non-interventional PASS is to evaluate the long-term safety of turoctocog alfa pegol in patients with haemophilia A and possible clinical consequences under observational ("real world") conditions of 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 (revision 3). EMA/813938/2011, 9 October 2017).

8 Research question and objectives

8.1 Primary objective

To investigate the safety of long-term exposure to turoctocog alfa pegol in patients with haemophilia A.

8.2 Secondary objective

To assess specific pharmacological risks for FVIII replacement products including turoctocog alfa pegol (FVIII 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) using data from the EUHASS registry.

9.1.1 Primary endpoint

Adverse events reported to the registry with suspected relation to turoctocog alfa pegol, Adverse Drug Reactions (ADRs), in patients with haemophilia A for renal, hepatic and neurological events.

9.1.2 Secondary endpoint

Other AEs reported to the registry during the study period with suspected relation to turoctocog alfa pegol in patients with haemophilia A, including ADRs of special interest (de novo FVIII inhibitors ≥0.6 BU); anaphylaxis and other allergic reactions; thromboembolic events).

9.1.3 Treatment of patients

Patients will be treated with commercially available turoctocog alfa 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 A treated with turoctocog alfa pegol and reporting adverse events to EUHASS.

A decision to initiate treatment with commercially available turoctocog alfa 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 registry in scope.

9.2.2 Inclusion criteria

Participation in the European Haemophilia Safety Surveillance System (EUHASS).

9.2.3 Exclusion criteria

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

9.2.4 Withdrawal criteria

Not applicable, as data is collected from a registry.

9.2.5 Visit procedures

As this study will collect data that have already been collected by the EUHASS registry, 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 EUHASS registry. 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

The EUHASS registry is in scope for data collection.

Data on ADRs related to turoctocog alfa pegol will be reported from the EUHASS registry to Novo Nordisk via annual reports.

9.4.1 European Haemophilia Safety Surveillance System, EUHASS

EUHASS is a pharmacovigilance programme that monitors 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 EUHASS to advise on the requirements to follow-up more specifically for PEGylated products, thus it may be expected that the data collection from the EUHASS could include more specific ADRs going forward.

9.5 Study size

All patients with haemophilia A treated with turoctocog alfa pegol that report adverse events to EUHASS will be included. However, it should be noted that not all eligible haemophilia treatment centres are contributing to EUHASS data collection, as participation is voluntary.

These data will contribute to the safety information regarding long-term treatment with turoctocog alfa pegol that will complement other safety data collections described in section 9.9.

9.6 Data management

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

9.7 Data analysis

Novo Nordisk will be responsible for all potential additional 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 and neurological) will be summarised, displaying the type, number and seriousness of reactions.

9.7.1.2 Secondary Endpoint

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

9.7.2 Interim analysis

The EUHASS registry 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 EUHASS registry will be responsible for the data that they submit in their annual reports.

9.8.1 Retention of study documentation

Novo Nordisk will comply with Good Pharmaco-epidemiological 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.

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

The EUHASS is concentrating on pre-specified groups of adverse events relevant for people with inherited bleeding disorders, thus it does not specifically collect information regarding renal or hepatic function, however EUHASS does collect neurologic adverse events.

The quality of the data in the EUHASS depends upon the willingness and possibility for the investigators / sites to report good quality adverse event data to the EUHASS. It is well known that in busy daily clinical practice adverse event reporting can be de-prioritised, thus leading to under-reporting (Alatawi 2017); hence, collected data 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 turoctocog alfa pegol via the EUHASS registry will require that a meaningful number of patients will be prescribed turoctocog alfa 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 turoctocog alfa pegol. In case of adverse events reported within the special areas of interest (renal, hepatic and neurological) 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 such as routine pharmacovigilance, aggregate analyses of safety data, a prospective non-interventional PASS, as well as analyses from on-going clinical trials, registry data will 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 3, June 2015).

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 turoctocog alfa pegol, which could have an impact on current and future generations of haemophilia A patients.

10.1 Informed consent form for study patients

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 turoctocog alfa pegol reported from the EUHASS. Thus, Novo Nordisk A/S is not involved

in the data collection as such, it is merely receiving data from the EUHASS registry. 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.

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

It will probably not be feasible to perform any follow-up as EUHASS is merely a safety surveillance system.

11.3 Turoctocog alfa pegol safety committee

Novo Nordisk has an internal safety committee that performs ongoing safety surveillance of turoctocog alfa 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 turoctocog alfa 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 EUHASS database 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 EUHASS 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 regarding 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

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