Cover Page for Statistical Analysis Plan

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Sponsor trial ID:	NN7088-4410
Official title of study:	Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A
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.Note: The date in the header from Page 2 is the date of compilation of the documents and not of an update to content.

16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN7088-4410

Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

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List of abbreviations

ABR	annualised bleeding rate
AE	adverse event
AESI	adverse event of special interest
eGFR	Estimated glomerular filtration rate
EoT	end-of-trial
FAS	Full Analysis Set
LLOQ	lower limit of quantification
LOCF	last observation carried forward
SAE	serious adverse event
SAP	statistical analysis plan

1 Introduction

1.1 Trial information

In the following, a brief description of the trial is presented. Please go to the protocol for further details.

Rationale:

The rationale for performing this trial is to allow the continued evaluation of the safety and efficacy of turoctocog alfa pegol in order to obtain additional data on long-term use. Introducing a twice or three times weekly prophylactic dosing regimen to the majority of patients is intended to show potential improvement in clinical outcomes by converting patients to a milder bleeding phenotype. Joint health and target joints will be assessed and evaluated at inclusion and at end of trial.

Objectives and endpoints:

Primary objective
To investigate the safety of turoctocog alfa pegol during continuous use for prevention and treatment of bleeding episodes of previously turoctocog alfa pegol treated severe haemophilia A patients.

Secondary objectives
To investigate the following in severe haemophilia A patients previously treated with turoctocog alfa pegol

- Development of FVIII inhibitors
- Efficacy of turoctocog alfa pegol prophylaxis
- Haemostatic efficacy of turoctocog alfa pegol when used for treatment of bleeds

Overall design:

This phase 3 trial is a multi-centre, multi-national, open-label, non-randomised trial evaluating safety and efficacy of turoctocog alfa pegol during prophylaxis treatment and treatment of bleeds. There will be three turoctocog alfa pegol treatment arms (dosing once weekly, twice weekly, and three times weekly) and no comparator.

1.2 Scope of the statistical analysis plan

This SAP is based on the protocol *Safety and Efficacy of turoctocog alfa pegol (N8-GP) in Prophylaxis and Treatment of Bleeds in Previously N8-GP Treated Patients with Severe Haemophilia A*, version 1.0.

2 Statistical considerations

Novo Nordisk will be responsible for the statistical analyses.

2.1 Sample size determination

All patients participating in NN7088-3859 (pathfinder2) or NN7088-3885 (pathfinder5) fulfilling the inclusion and exclusion criteria of this trial will be eligible to participate where continuous safety assessments will be made. Given that at least 150 patients participate in this trial, the background incidence rate could be up to 0.02 for a given adverse event that was not observed, i.e. the 95% upper bound on the rate of occurrence is 0.02.

2.2 Definition of analysis sets

In general, safety endpoints will be reported for Safety Analysis Set while efficacy endpoints will be reported for Full Analysis Set (FAS). These analysis sets are described below.

The patients or observations to be excluded, and the reasons for their exclusion must be documented before database lock. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Safety analysis set
All patients enrolled in the trial have previously been exposed to trial product and therefore all enrolled patients will be included in the Safety Analysis Set. The trial patients will be analysed according to the received treatment.

Full analysis set
All patients exposed to at least one dose of trial product in the current trial will be included in the Full Analysis Set. The trial patients will be analysed according to the received treatment.

Exceptional outlier plasma activities may be excluded when analysing pharmacokinetic-related endpoints based on the FAS. Default rules for exclusion are described in the paragraph on pre-dose FVIII activity level. Decision to exclude additional FVIII activity measurements from analysis based on the FAS may be made during a review prior to database lock according to ICH-E9, and it will be the joint responsibility of the clinical pharmacology scientist and the trial statistician to decide upon this. The observations to be excluded from the FAS and the reason for their exclusion will be documented and signed by the clinical pharmacology scientist and the trial statistician as part of the database lock minutes. This will also be described in the clinical trial report. The documentation will be stored together with the remaining trial documentation.

2.3 Statistical analyses

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

2.3.1 Primary endpoint

Number of adverse events reported
All reported adverse events (AEs) will be considered treatment emergent adverse events since all patients had been treated with N8-GP in other pathfinder trials prior to participation in this trial. All AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) will be summarised by frequency of events and frequency of patients with any event. Furthermore, all AEs will be summarised by severity and causal relation to trial product. In addition, listings will be provided displaying all AEs, SAEs and AESIs.

2.3.2 Secondary endpoints

For all endpoints based on bleeding episode data, only bleeding episodes treated with N8-GP will be included.

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 re-bleed is defined as a worsening of symptoms in the same location after an initial period of improvement, either on treatment or within 72 hours after completed treatment. If a bleeding episode occurs in the same location later than 72 hours after completed treatment it is considered a new bleeding episode.

2.3.2.1 Supportive secondary endpoints

Incidence of FVIII inhibitors ≥0.6 BU
The number of inhibitor patients will be reported and all inhibitor data will be presented.

Number of bleeding episodes on prophylaxis
The ABR of treatment requiring bleeding episodes will be estimated by a Poisson regression model with logarithmic prophylaxis duration as offset and allowing for over-dispersion. Over-dispersion will be estimated as Pearson's chi-square statistic divided by the degrees of freedom. The estimated ABR will be presented together with a two-sided 95% confidence interval. For sub-groups with no bleeds or less than 5 patients, the 95% confidence interval will not be presented. A sensitivity analysis based on a negative binomial regression model with number of bleeding episodes requiring treatment as the outcome variable, and adjusting for exposure time will also be performed.

The analysis of ABR will be repeated as a sensitivity analysis to investigate the potential impact of early withdrawals by imputing number of bleeding episodes for withdrawals. For patients withdrawing prematurely, the number of bleeding episodes counting in the analysis will be imputed up to what they could be expected to have had if they had completed the trial. If e.g. a patient withdraws after 12 months with 5 bleeding episodes, but the patient should have been in the trial for 24 months, then this patient will in the sensitivity analysis count as having had 10 bleeding episodes in 24 months. This is similar to LOCF and will prevent a downwards bias in ABR caused patients with many bleeding episodes withdrawing early. If a patient changes from once weekly to one of the more frequent dosing frequencies, then when doing the sensitivity calculation for once weekly, bleeds during time on the more frequent dosing is calculated using LOCF based on the previous period on every seven day dosing. This is also the case if a patient changes from every seven day dosing more than once, i.e. for each period on more frequent dosing the bleeds for every seven day dosing is imputed based on the previous consecutive period on every seven day dosing.

ABR for each treatment regimen (once weekly, twice weekly, and three times weekly) will be estimated by age group (0-5 years, 6-11 years, 12-17 years and 18- years).

ABR will also be estimated by doing the following further sub-groupings:

- Cause of bleed (spontaneous and traumatic)
- Location of bleed. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Country. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Race. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Ethnicity. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Month in trial. No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).
- Time since last dose (0-24 hours, 24-48 hours, 48–72 hours and >72 hours). No sensitivity analyses will be done for this sub-grouping (neither using negative binomial modelling nor using imputation).

Number of spontaneous bleeding episodes on prophylaxis
Included in the above description of ABR by cause of bleed.

Haemostatic effect of N8-GP when used for treatment of bleeding episodes assessed as: Excellent, Good, Moderate, or None
Haemostatic effect will for each treatment regimen (once weekly, twice weekly, and three times

weekly) be summarised by age group (0-5 years, 6-11 years, 12-17 years and ≥18 years). Haemostatic effect will be summarised according to:

- Response expressed as excellent, good, moderate, none.
- Success or failure, where success will be defined as a response of good or excellent and failure will be defined as moderate, none or missing
- Success or failure after exclusion of bleeds with missing evaluation of haemostatic response, i.e. success will be defined as a response of good or excellent and failure will be defined as moderate or none information.

Furthermore, success rates will be estimated with 95% confidence intervals using logistic regression accounting for repeated measures within patient assuming compound symmetry working correlation. Age group will be included as a factor and modelling done separately for each treatment regimen. This estimation will be done both including missing haemostatic evaluations as failures and excluding missing evaluations.

Summaries will also be done for the following further sub-groupings:

- Cause of bleed (spontaneous and traumatic). Estimation of success rates and 95% confidence intervals using above described modelling will also be performed (both including missing as failures and excluding missing).
- Location of bleed.
- Severity.
- Country.
- Race
- Ethnicity

Number of N8-GP injections required per bleeding episode

This endpoint will be summarised and listed.

Pre-dose FVIII activity levels for patients on N8-GP prophylaxis

The following rules will be implemented for FVIII pre-dose and post-dose activity to ensure data representing steady-state on a given treatment regimen:

- FVIII activity data prior to the 4th prophylaxis dose will be excluded for each switch in treatment regimen
- FVIII activity data will be excluded if post-dose activity is ≤ pre-dose FVIII activity
- FVIII activity data will be excluded if post-dose sample is taken more than 90 minutes after dosing
- FVIII activity results will be excluded for plasma samples defrosted during transit.

The pre-dose FVIII activity levels will be modelled to get an estimate of the pre-dose level for N8-GP at steady-state. The model will be a mixed model on the logarithmic plasma activity levels with age as a factor and patient as a random effect. Separate modelling will be performed for each treatment regimen. Plasma concentrations below lower limit of quantification (LLOQ) will be set to half the value of the LLOQ. The estimated pre-dose FVIII level will be presented together with the 95% confidence intervals.

A sensitivity analysis will be performed including all activity results except activities measured in relation to the first 4 prophylaxis doses after switch of treatment regimen.

Pre-dose activity will furthermore be summarised by visit and treatment regimen.

Change in joint health status from start to end of trial
Target joint status is assessed at inclusion in trial. For intervals of 12 months, the number of baseline target joints with 0, 1, 2,… number of bleeds is presented.

Haemostatic response during major surgical interventions
The endpoint of assessment of haemostatic effect during major surgical intervention (excellent, good, moderate or none) will be summarised and listed.

Change from baseline till end of trial in treatment satisfaction (Hemo-SAT)
Data will be scored according to established scoring algorithms (where applicable) and changes from first assessment (at screening/V1) to last assessment (at EoT visit) will be summarised and listed using descriptive statistics. Further analysis will be performed separately by Novo Nordisk Health Economics Department.

2.3.3 Exploratory endpoint

Incidence of anti-N8-GP binding antibodies
Number of positive/negative samples will be summarised by visit and listed.

Incidence of anti-PEG binding antibodies
Number of positive/negative samples will be summarised by visit and listed. Furthermore, plots will be created of incremental recovery in relation to PEG antibody status at baseline and during the trial. Rules for exclusion of FVIII activity measurements are defined in the paragraph: “Pre-dose FVIII activity levels for patients on N8-GP prophylaxis”.

2.3.4 Interim analyses

Interim analysis may be performed, if deemed appropriate.

2.4 Pharmacokinetic and/or pharmacodynamic modelling

Data from the trial may be used for exploratory pharmacokinetic and/or pharmacodynamic analysis as needed.

2.5 Additional efficacy related tables/figures/listings

Post-dose activity measurements will be modelled and presented in the same forms as pre-dose activity measurements, see section on "Pre-dose FVIII activity levels on N8-GP prophylaxis".

Incremental recovery is defined as post-dose FVIII activity minus pre-dose FVIII activity and divided by the administered dose. Incremental recovery will be summarised by visit and listed.

2.6 Additional safety related tables/figures/listings

All safety parameters not addressed above such as laboratory parameters, vital signs and physical examinations will be summarised by visit.

Laboratory reference ranges and abnormal laboratory values will be listed.

Furthermore, the following safety related output will be created.

Frequency of adverse events that are reported within the system organ classes nervous system, psychiatric, hepatic and renal disorders
Will be summarised and listed.

Changes in laboratory assessments, including hepatic and renal function parameters
Individual profiles of laboratory parameters will be created by age group as plots of parameter values vs. time since first dose in trial.

Estimated glomerular filtration rate (eGFR) in ml/min per 1.73 m^2 will be calculated e.g. using following formula:

For ≥ 18 years of age: Constant * s-cr $^{-1.154}$ * age$^{-0.203}$ * [1.212 if black or African American] *[0.742 if female], where constant=175*(88.4$^{1.154}$) (1)

For <18 years of age: Constant* height (cm)/s-cr, where constant=0.413*88.4 (2)

eGFR will also be plotted vs. baseline value.

Polyethylene glycol (PEG) concentration in plasma
There is no evidence from our data of any clinical consequences due to long-term exposure to PEG. However, to accommodate a general concern from the authorities regarding systemic accumulation of PEG, concentration of PEG in plasma will be measured at visit 3 plus at the end-of-trial visit, and summarised for each visit.

3 Changes to the statistical analyses planned in the protocol

There are no changes to the statistical analyses described in the protocol. The text in Section 2 "Statistical Considerations" of this SAP is identical to the text in the "Statistical Considerations" section in the protocol.

4 References

1. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation for the Modification of Diet in Renal Disease Study Group Andrew S. Levey, MD; Juan P. Bosch, MD; Julia Breyer Lewis, MD; Tom Greene, PhD; Nancy Rogers, MS; and David Roth, MD, Annals of Internal Medicine March 1999; 130: 461

2. New Equations to Estimate GFR in Children with CKD Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. J Am Soc Nephrol. 2009 Mar;20(3):629