Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Statistical analysis plan ..... Link

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Statistical Analysis Plan

Trial ID: NN7415-4255

A Multi-Centre Trial Evaluating Efficacy and Safety of Prophylactic Administration of Concizumab in Patients with Severe Haemophilia A without Inhibitors

Author:

[redacted]

Biostatistics LCM Haem, GH & Concizumab

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List of abbreviations

ABR	annualised bleeding rate
AE	adverse event
aPTT	activated partial thromboplastin time
AT	antithrombin
C_{max}	maximum plasma concentration
CPoC	clinical proof of concept
ETP	endogenous thrombin potential
FAS	full analysis set
FIX	coagulation factor IX
FVIII	coagulation factor VIII
H-DAT	Haemophilia Device Assessment Tool
Hemo-TEM	Haemophilia Treatment Experience Measure
LPFT	last patient first treatment
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PGI-C	Patient's Global Impression of Change

PK	pharmacokinetics
PRO	patient reported outcome
PT	prothrombin time
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(-ly)
SDS	Sheehan Disability Scale
SF-36v2	36-Item Short Form Health Survey
SIAQ-ISRQ	Self-Injection Assessment Questionnaire - Injection Site Reaction Questionnaire
TEAE	treatment emergent adverse events
TFPI	tissue factor pathway inhibitor
TSQM	Treatment Satisfaction Questionnaire for Medication
VERITAS-PRN®	Validated Hemophilia Regimen Treatment Adherence Scale
VERITAS-Pro®	Validated Hemophilia Regimen Treatment Adherence Scale – Prophylaxis

1 Introduction

1.1 Trial information

NN7415-4255, explorer™5, multi-centre single arm trial, which aim to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in patients with severe haemophilia A without inhibitors. For further information about the trial please refer to the protocol.

1.2 Scope of the statistical analysis plan

This Statistical Analysis Plan (SAP) is based on the protocol A Multi-Centre Trial Evaluating Efficacy and Safety of Prophylactic Administration of Concizumab in Patients with Severe Haemophilia A without Inhibitors, version 4, and amendments 1 and 2.

The scope of this SAP is to specify some further technical details on matters which have not been adequately described in the protocol. No changes have been made to the analyses specified in the protocol.

2 Statistical considerations

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Please refer to Figure 2–1 for further information.

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. 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. Further, the endpoints will not include re-bleed.

A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping treatment of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping treatment, the bleed is defined as a new bleeding episode.

Clinical proof of concept

The statistical analysis of the collected data aims to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia A patients without inhibitors. Since 36 patients were actually enrolled in the study compared to the planned number of 33 patients, the objective will be assessed when the last of the 36 patients has completed 24 weeks of dosing (or has withdrawn before that).

Two criteria will be evaluated in a hierarchical fashion in support of CPoC comprising a comparison of the ABR of all patients with a threshold of 12, irrespective of individual dose titration. The primary CPoC criterion aims at evaluating the effect of concizumab at the last dose level reached for a patient. Hence, for this evaluation, only observations from the period where patients are on their end dose at time of analysis will contribute to the analysis. Furthermore, observations from the 2 week run-in period will be not be included. Since this evaluation disregards a subset of data collected the result should be viewed taking in to account the potential bias. The second CPoC criterion aims at evaluating the effect of concizumab when given as an escalation regimen. Hence, this will compare the ABR of haemophilia A patients treated with concizumab with the typical historical ABR of haemophilia A patients being treated on-demand using all data after enrolment. The second CPoC criterion will only be evaluated if the first one succeeds.

The referred comparisons will be made using a negative binomial model with log of exposure time in main part as offset. For each criterion, evidence of effect will be concluded if the 95% confidence interval of the estimated ABR is below 12.

Clinical arguments for the hierarchical test approach

Concizumab exhibits non-linear PK due to target mediated drug disposition and it is expected that the dose response curve of the ABR is rather steep. This implies that patients that are on a dose which is not efficacious are likely to bleed as patients that are not treated at all. Subset of data collected from the last dose clinically deemed as efficacious would reflect the efficacy of concizumab in the given patient.

2.1 Sample size calculation

The sample size calculation has been determined taking the small patient population into account, while also aiming for an acceptably narrow 95% confidence interval for the ABR.

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 30 patients.

It is expected that the treatment duration of the main part allowing for escalation time for some patients is on average 6 months in the below calculations.

When evaluating the power of the negative binomial analysis referred above, an annual bleeding rate of 4 is assumed for the end dose concizumab regimen, respectively in combination with an over-dispersion of 6. The power for concluding a bleeding rate lower than 12 then becomes approximately 95%. The power under varying values of true ABR and over-dispersion for the primary CPoC criterion are shown below in Table 2–1.

Table 2–1 Power in comparison between concizumab prophylaxis treatment and an ABR threshold of 12 under different assumptions of ABR and over-dispersion.

Power	Over-dispersion		
ABR	**5**	**6**	**7**
4	99%	95%	92%
5	95%	90%	86%
6	87%	81%	72%

For the secondary CPoC criterion that includes data prior to potential dose escalation, it is expected that the treatment duration of the main part is on average 8 months with an average ABR of 5.4 for the concizumab treated patients. This yields a marginal power of approximately 87% for the secondary CPoC criterion.

In prior Novo Nordisk trials conducted in haemophilia patients, the typical 1-year over-dispersion for non-inhibitor patients on prophylaxis with FVIII or FIX has been in the range 4-8, implying 24 weeks over-dispersion of 3-5 (e.g. in NN7008-3543, NN7088-3859 and NN7999-3747). On that background, an over-dispersion of 6 over the 24 weeks in the main part of the current trial is deemed realistic.

2.2 Definition of analysis sets

All dosed patients will be included in the Full Analysis Set (FAS) as well as in Safety Analysis Set (SAS).

2.3 Primary endpoint

The primary endpoint is the number of bleeding episodes during at least 24 weeks from treatment onset. All treated bleeding episodes will be considered for this endpoint, including bleeding episodes recorded as post-surgical or caused by surgery or other medical or dental procedures.

The primary endpoint will be estimated using negative binomial regression with log of exposure time in the included observational period of the main phase as offset, providing an actual estimate of the ABR as well as a corresponding 95% confidence interval. The offset for first CPoC criterion is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for subjects on 0.15 mg/kg. The offset for the second criterion is the log of the individual exposure time in the main part.

This analysis has the underlying assumption that the missing data mechanism is “missing at random”, i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The endpoint will be estimated based on the full analysis set (FAS) and only data collected

prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

2.3.1 Sensitivity analysis

To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis will be performed where patients having discontinued before finalization of the main part are assumed to have a worse outcome compared to what was observed during the main part of the trial. This will be done by adding a value Δ_i to the observed bleeding episodes in the main part of the trial before analysing the data. The offset is maintained as being the exposure during the main phase since it is not possible to identify the amount of missing observation time. The degree of worsening, Δ_i, will gradually be increased to evaluate at which point the upper 95% confidence limit of the prophylactic concizumab ABR is no longer below a threshold of 12. The results of the primary analysis will be considered robust if the tipping point is above what is considered clinical plausible.

The second CPoC criterion evaluating the effect of concizumab when given as an escalation regimen includes observations from the 2 week run-in period. In the 2 week run-in period some patients have been allowed to continue on pre-trial prophylaxis treatment and so including this period in the analysis may result in some patients having fewer bleeds in the run-in period. Since this can affect the ABR, an additional sensitivity analysis will be performed where the second CPoC criterion will be evaluated as described for the primary endpoint but without including observations from the 2 week run-in period.

The primary endpoint is assessed using all treated bleeding episodes including those recorded as post-surgery or caused by surgical or other medical or dental procedures. Since the inclusion of bleeding episodes recorded as post-surgery or caused by surgical or other medical or dental procedures can affect the ABR, an additional sensitivity analysis will be performed excluding these bleeding episodes from the primary and secondary CPoC criteria.

2.3.2 Additional analysis

An additional evaluation of the primary endpoint will be made, including actual concizumab dose level (interpreted as the patient's last dose level) as additional factor in the primary analysis model specified above. Point estimates and 95% confidence interval will be provided for the ABR at the different dose levels of concizumab (0.15, 0.20 and 0.25 mg/kg). Furthermore, a series of analyses with individual steady state PK/PD assessments included as log-transformed covariates in the negative binomial regression model as specified for the primary analysis will be performed in order to evaluate possible associations between PK/PD and ABR that potentially could guide dose-selection. The referred steady-state PK/PD assessments comprise the concizumab trough level, maximum plasma concentration (C_{max}) of concizumab, TFPI value prior to the last s.c. dose

administration, peak thrombin generation (nM), Endogenous thrombin potential (nM*min) and velocity index (nM/min) prior to the last dose administration at 24 weeks.

2.4 Supportive secondary endpoints

2.4.1 Supportive secondary efficacy endpoints

- The number of bleeding episodes during 76 weeks from treatment onset
- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset
- The number of spontaneous bleeding episodes during 76 weeks from treatment onset

The supportive secondary endpoints will be analysed using the same two analyses as for the primary endpoint; one only including observations from the period on the last dose level and one including the entire escalation regimen.

2.4.2 Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from
- treatment onset
- Number of TEAEs during 76 weeks from treatment onset.
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset.
- Occurrence of anti-concizumab antibodies during 76 weeks from treatment onset.
- Change from baseline of fibrinogen during 24 weeks from treatment onset.
- Change from baseline of fibrinogen during 76 weeks from treatment onset.
- Change from baseline of D-dimer during 24 weeks from treatment onset.
- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset.
- Change from baseline of F1 + 2 during 76 weeks from treatment onset.
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset.
- Change from baseline of PT during 76 weeks from treatment onset.
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset.
- Change from baseline of APTT during 76 weeks from treatment onset.
- Change from baseline of antithrombin (AT) during 24 weeks from treatment onset.
- Change from baseline of AT 76 weeks from treatment onset.

Adverse Events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding.

A Treatment Emergent Adverse Event (TEAE) is defined as an event that has onset from the first exposure to treatment until the last visit in the trial. Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All Adverse events will further be listed. Relations to Novo Nordisk products used by patients in the trial, such as turoctocog alfa/NovoEight®, is reported as described in section 12.2 of the protocol and will be transferred to the Argus safety system and not reported in the report of the trial.

Frequency of binding anti-concizumab antibodies will by listed and summarised by time frame according to the two endpoint definitions.

All laboratory safety endpoints will be plotted by time, both as absolute values and change from baseline. Laboratory safety endpoints will further be summarised and listed.

2.4.3 Supportive secondary pharmacokinetic endpoints

- Concentration of concizumab prior to the last dose administration at 24 weeks
- Concentration of concizumab prior to the last dose administration at 76 weeks

The pharmacokinetic endpoints will be summarised and listed.

2.4.4 Supportive secondary pharmacodynamic endpoints

- *Free TFPI concentration*
  - Value prior to the last dose administration at 24 weeks
  - Value prior to the last dose administration at 76 weeks
- *Thrombin generation*
  - Peak thrombin generation (nM) prior to the last dose administration at 24 weeks
  - Peak thrombin generation (nM) prior to the last dose administration at 76 weeks
  - Endogenous thrombin potential (nM*min) prior to the last dose administration at 24 weeks
  - Endogenous thrombin potential (nM*min) prior to the last dose administration at 76 weeks
  - Velocity index (nM/min) prior to the last dose administration at 24 weeks
  - Velocity index (nM/min) prior to the last dose administration at 76 weeks

The PD endpoints will be summarized and listed.

2.4.5 Exploratory endpoints

2.4.5.1 Exploratory safety endpoints

- Number of adverse events related to technical complaints during at least 24 weeks from treatment onset
- Number of adverse events related to technical complaints during at least 76 weeks from treatment onset

Adverse events related to technical complaints will be listed and summarised

2.4.5.2 Exploratory patient reported outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset
- Change in Hemo-TEM after 76 weeks from treatment onset
- Change in SF-36v2 after 24 weeks from treatment onset
- Change in SF-36v2 after 76 weeks from treatment onset
- Change in SDS after 24 weeks from treatment onset
- Change in SDS after 76 weeks from treatment onset
- Change in TSQM after 24 weeks from treatment onset
- Change in TSQM after 76 weeks from treatment onset
- Change in SIAQ-ISRQ after 24 weeks from treatment onset
- Change in SIAQ-ISRQ after 76 weeks from treatment onset
- Status of PGI-C after 24 weeks from treatment onset

Patient reported outcomes (PROs) will be collected using questionnaires at visits 1, 2, 4, 5, 6, 7, 8, 9, 10 and 16.

Patient reported outcome questionnaires to be analysed:

- Haemophilia Treatment Experience Measure (Hemo-TEM)
- Validated Hemophilia Regimen Treatment Adherence Scale – Prophylaxis (VERITAS-Pro®) or Validated Hemophilia Regimen Treatment Scale (/ VERITAS-PRN®)
- 36-Item Short Form Health Survey (SF-36v2) (4 week recall)
- Patient Global Impression of Change (PGI-C)
- Sheehan Disability Scale (SDS)
- Treatment Satisfaction Questionnaire for Medication (TSQM, version II)
- Haemophilia - Device Assessment Tool (H-DAT)
- Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)

VERITAS-Pro® or VERITAS-PRN®, SF-36v2, SDS, TSQM, H-DAT and SIAQ-ISRQ will be scored according to their respective scoring algorithms. Change after 24 weeks from treatment onset and after 76 weeks from treatment onset will be described.

2.4.5.3 Exploratory pharmacokinetic and pharmacodynamic endpoints

- Concentration of concizumab over time during 24 hours PK assessment
- Concentration of free TFPI over time during 24 hours PD assessment
- Thrombin generation over time during 24 hours PD assessment
    - Peak of thrombin generation time during 24 hours PD assessment
    - ETP time during 24 hours PD assessment
    - Velocity index time during 24 hours PD assessment

Individual "concentration over time" curves will be presented in a plot. A mean plot including error bars will also be presented. For thrombin generation the endpoints will be summarized and listed.

2.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual clinical study reports might in such case be issued. A final clinical study report describing results from the main and extension part will be written when the last patient has either completed or withdrawn from the trial.

All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 2–1.

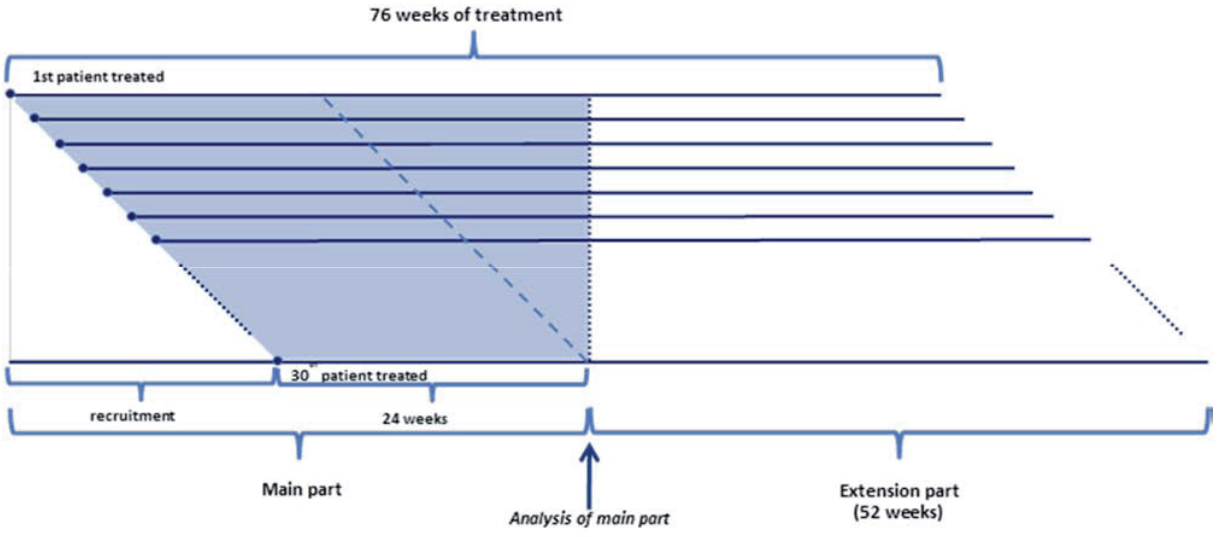

Figure 2–1 Definition of main and extension part

3 Changes to the statistical analyses planned in the protocol

As described in section 1.2 of this document, the scope of this SAP is to specify some further technical details on matters which have not been adequately described in the protocol. No changes have been made to the analyses specified in the protocol.

3.1 Clarification of bleeding episodes for primary endpoint

Section 17.3 of the protocol defines the primary endpoint as the number of bleeding episodes during at least 24 weeks from treatment onset. As specified in section 2.3 of this document, the bleeding episodes considered for the primary endpoint also includes bleeding episodes recorded as post-surgical or caused by surgery or other medical or dental procedures.

3.2 Offset definition for negative binomial regression for primary endpoint

Section 17.3 of the protocol defines the offset of the negative binomial regression as log of exposure time in the main period. This definition only accounts for the second CPoC criterion. The offset should reflect the observation period which differs for the first CPoC which has been further clarified in section 2.3 of this document. This clarification is in line with the beginning of section 17 as described below.

Section 17 of the protocol describes that the CPoC will be evaluated in a hierarchical fashion using two criteria to evaluate the effect of concizumab. The first CPoC criterion is evaluated using only a subset of observations where concizumab patients are at the last dose level reached at the time of analysis and excluding observations from the 2 weeks run-in period with 0.15 mg/kg. The second CPoC criterion is evaluated using all observations in the main part.

The offset for first CPoC criterion is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for subjects on 0.15 mg/kg. The offset for the second criterion is the log of the individual exposure time in the main part.

3.3 Additional sensitivity analysis for second CPoC

Section 17 of the protocol describes how the second CPoC criteria uses all data after enrolment. Section 2.3.1 of this document describes how this may affect the ABR and how an additional sensitivity analysis will be performed.

3.4 Additional sensitivity analysis for primary endpoint

Section 2.3 of this document specifies how the bleeding episodes considered for the primary endpoint includes bleeding episodes recorded as post-surgical or caused by surgery or other medical or dental procedures. Since the inclusion of bleeding episodes recorded as post-surgical or caused by surgery or other medical or dental procedure may affect the ABR, an additional sensitivity

analysis excluding these bleeding episodes will be performed as described in section 2.3.1 of this document.

3.5 Clarification of additional analyses

Section 17.5 of the protocol describes the additional analyses of the primary endpoint. Section 2.3.2 of this document clarifies how the additional analysis including actual concizumab dose level as factor in the primary analysis model should be interpreted as including the patient's last dose level as factor in the primary analysis.

Further, section 2.3.2 of this document clarifies that a series of additional analyses will be performed with each of the PK/PD variables taken prior to last dose at 24 weeks. Each of these PK/PD variables will be included as log-transformed covariates in the negative binomial regression model.

3.6 Clarification of analyses for supportive secondary endpoints

In section 17.6.1 of the protocol the analyses for the supportive secondary efficacy endpoints are defined. In section 2.4.1 of this document it is further clarified that the analyses are performed using observations from patients at the last dose level as well as throughout the escalation regimen.

3.7 Omission of endpoint including H-DAT

In section 17.7.2 of the protocol the last exploratory patient reported outcome endpoint to be summarised is the change in H-DAT after 76 weeks from treatment onset. However, it will not be possible to determine this change since the patients are not asked to complete the ePRO questionnaire H-DAT at treatment onset. In section 2.4.5 of this document the exploratory patient reported outcome endpoint related to change in H-DAT since treatment onset is not included.

3.8 Causal relation between turoctocog alfa/NovoEight® and AE

On the AE case report form for the trial it is not possible to fill in causality to turoctocog alfa/NovoEight®. As mentioned in section 12.2 in the protocol, an AE that is considered to have a causal relationship with a Novo Nordisk marketed product can be reported in the alternative aetiology section on the safety information form and will not be part of the report for this trial as described in section 2.4.2 of this document.