Cover Page for Statistical Analysis Plan

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16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

Trial ID: NN7415-4310

A Multi-Centre, Randomised, Open-Label, Controlled Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients with Inhibitors

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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
eptacog alfa	the name 'eptacog alfa (rFVIIa)' will be used throughout the document and the product is identical to rFVIIa,'NovoSeven®, and 'NiaStaseRT®'
FAS	full analysis set
FVIIa	activated coagulation factor VII
Hemo-TEM	Hemophilia Treatment Experience Measure
i.v.	intravenous(-ly)
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
s.c.	subcutaneous(-ly)
SAS	safety analysis set
SDS	Sheehan Disability Scale
SF-36v2	36-Item Short Form Health Survey
SIAQ-ISRQ	Injection Site Reaction Questionnaire domain of Self-Injection Assessment 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

1 Introduction

1.1 Trial information

NN7415-4310, explorer™4, is a multicentre, randomised, open-label, controlled trial where daily treatment with concizumab is evaluated against on-demand treatment in a population of Haemophilia A and B patients with 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, Randomised, Open-Label, Controlled Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients with Inhibitors, version 3, 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.

Data from when the on-demand treated patients are transferred to concizumab subcutaneous (s.c.) prophylaxis will not be included in this evaluation. Observations from the extension part in the on-demand arm will be summarised separately as well as combined with observations from the main part when reporting the extension part data.

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-bleeds.

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 clinical proof of concept (CPoC) that concizumab is efficacious in preventing bleeding episodes in haemophilia patients with inhibitors. The objective will be assessed when the last of the 24 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 annualised bleeding rate (ABR) of all patients in the concizumab group, irrespective of individual dose titration, with the ABR of the patients in the on-demand arm using different sets of observations. The primary CPoC criterion aims at evaluating the effect of concizumab when given at the last dose level reached for the 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 not be included. Since this evaluation disregards a subset of data collected post randomisation, the result should be viewed taking into 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 patients in the concizumab arm with the ABR of the patients in the on-demand arm using all data collected after randomisation. 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 and regimen as factor (concizumab vs. on-demand). For each criterion, evidence of effect will be concluded if the 95% confidence interval of the treatment ratio is below 1.

Clinical arguments for the hierarchical test approach

Concizumab exhibits non-linear pharmacokinetics (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. The 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 estimand will be defined as the “if all patients had adhered” estimand.

The treatment ratio between prophylactic s.c. concizumab and on-demand intravenous (i.v.) eptacog alfa (rFVIIa) during at least 24 weeks for all randomised patients if all patients adhered to trial drug and did not initiate alternative treatment options.

This estimand is a de jure estimand assessing the expected added benefit a patient can achieve if continuing treatment with prophylactic s.c. concizumab as compared to on-demand i.v. eptacog alfa (rFVIIa) under similar conditions as observed in this trial.

The sample size calculation has been determined based on this estimand and the CPoC criteria taking the small patient population into account, while also aiming for an acceptably narrow 95% confidence interval for the rate ratio.

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm. 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, annual bleeding rates of 24 and 6 are assumed for the on-demand patients and the end dose concizumab regimen, respectively. Assuming further over-dispersion of 7, the power for concluding superiority of the concizumab regimen becomes approximately 80%. 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 superiority comparison between concizumab prophylaxis and on-demand treatment under different assumptions of ABR for concizumab and over-dispersion (assuming on-demand ABR=24).

Power	**Over-dispersion (over 6 months)**		
ABR (concizumab)	**6**	**7**	**8**
6	89%	82%	75%
7	84%	75%	70%
8	77%	69%	66%

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 7.6 for the concizumab regimen. This yields a marginal power of approximately 70% 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 coagulation factor FVIII or coagulation factor IX 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). In the NN7128-1907 trial in inhibitor patients, larger 1-year over-dispersion values of approximately 21 and 18, respectively, were observed during an initial 3-month on-demand period and a subsequent 3-month prophylaxis period. It is expected that the variation in the current trial will be smaller, partly due to the longer duration of the trial and partly due to an expected more homogenous patient population. Another published trial including inhibitor patients,

comparing prophylaxis using FEIBA® with on-demand treatment, showed 6-month over-dispersion of 4-5 [32]. On that background, an over-dispersion of 7 over the 24 weeks in 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 endpoint will be analysed when the main part of trial has been completed.

2.3.1 Estimand and primary statistical analysis

The estimand for the primary endpoint is the "if all patients had adhered" estimand.

The treatment ratio between prophylaxis s.c. concizumab and on-demand i.v. eptacog alfa (rFVIIa) during at least 24 weeks for all randomised patients if all patients adhered to trial drug and did not initiate alternative treatment options. To initiate alternative treatment options in this respect is defined as stopping concizumab or eptacog alfa on-demand treatment and initiating alternative treatment options.

This estimand is a de jure estimand assessing the expected added benefit a patient can achieve if continuing treatment with prophylactic s.c. concizumab as compared to on-demand i.v. eptacog alfa (rFVIIa) under similar conditions as observed in this trial.

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time in the included observational period of the main part as offset and regimen as factor. The offset for first CPoC criterion of patients in concizumab arm 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 of patients in concizumab arm is the log of the individual exposure time in the main part. For patients in the on-demand arm regardless of criterion, the offset is the log of the exposure time in the main part. The analysis provides an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is "missing at random", i.e. missing at random (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 estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

2.3.2 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 to the observed bleeding episodes in the main part of the trial of the concizumab patients before analysing the data. The offset is maintained as being the exposure during the main part 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 concizumab prophylaxis no longer is superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis will be considered robust if the tipping point is above what is considered clinically 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 and using log of exposure time excluding those days as the offset.

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.

2.3.3 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/pharmacodynamics (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 at visit 9, maximum plasma concentration (C_{max}) of concizumab throughout the trial, tissue factor pathway inhibitor (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. This model will only include observations from subjects exposed to concizumab.

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 number of spontaneous bleeding episodes during at least 24 weeks from treatment onset will be addressed in terms of the same estimand as for the primary endpoint The estimand will be estimated using the same negative binomial regression model as for the primary endpoint and performing the same two analyses as for the primary endpoint; one only including observations from the period on the last dose level for patients treated with concizumab 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
- Number of TEAEs within 24 hours of rFVIIa administration
- 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.

TEAE is defined as an event that has onset after randomisation 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 eptacog alpha, 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 Hemophilia Treatment Experience Measure (Hemo-TEM) after 24 weeks from treatment onset
- Change in Hemo-TEM after 76 weeks from treatment onset
- Change in 36-Item Short Form Health Survey (SF-36v2) after 24 weeks from treatment onset
- Change in SF-36v2 after 76 weeks from treatment onset
- Change in Sheehan Disability Scale (SDS) after 24 weeks from treatment onset
- Change in SDS after 76 weeks from treatment onset
- Change in Treatment Satisfaction Questionnaire for Medication (TSQM) after 24 weeks from treatment onset
- Change in TSQM after 76 weeks from treatment onset
- Change in Injection Site Reaction Questionnaire domain of Self-Injection Assessment Questionnaire (SIAQ-ISRQ) after 24 weeks from treatment onset
- Change in SIAQ-ISRQ after 76 weeks from treatment onset
- Status of Patient's Global Impression of Change (PGI-C) after 24 weeks from treatment onset

Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®), SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change after 24 weeks from treatment onset for SF-36v2, SDS and TSQM will be analysed with an ANCOVA model including regimen (concizumab or eptacog alfa) as a factor and baseline score as covariate. The VERITAS-PRN questionnaire is only taken at visit 1 so no ANCOVA is performed for it.

All the patient reported outcome (PRO) endpoints will be summarised using descriptive statistics. The PRO-questionnaires (Hemo-TEM, PGI-C, SIAQ-ISRQ) will not be analysed with an ANCOVA.

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. For patients in

the concizumab s.c. prophylaxis arm, main part is 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. For patients in the on-demand arm, the main part consists of observations from randomisation until transfer to concizumab s.c. prophylaxis treatment or withdrawal from trial, whichever comes first. All observations for these patients after transfer to concizumab treatment is regarded as extension part 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 trial reports might in such case be issued. A clinical trial report describing results from the main and the 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.

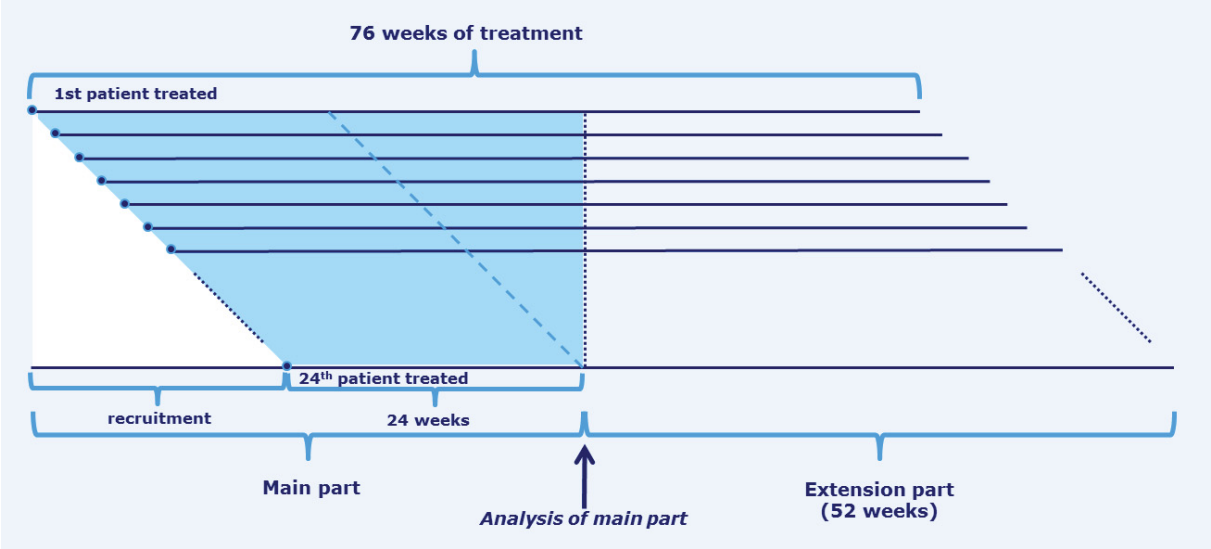

Figure 2–1 Definition of main and extension part

3 Changes to the statistical analyses planned in the protocol

3.1 Definition of rebleed

Section 17 page 113 in the protocol describes the definition of a re-bleed. The text below is a clarification of this definition included in section 2 of this document. Words written with italic font is added words and strikethrough words are deleted words.

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* ~~treatment~~ is defined as a new bleeding episode.

3.2 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.

3.3 Clarification of initiation of alternative treatment options

Section 17.3.1 of the protocol describes the estimand which is the "if all patients had adhered" estimand. In the definition below it is mentioned that it is mentioned that it includes "all randomised patients if all patients adhered to trial drug and did not initiate alternative treatment options." In section 2.3.1 the definition of initiation alternative treatment options is clarified.

3.4 Offset definition for negative binomial regression for primary endpoint

Section 17.3.1 of the protocol defines the offset of the negative binomial regression as log of exposure time in the main period. For patients in the concizumab arm, this definition only accounts for the second CPoC criterion. The offset should reflect the observation period which differs for subjects in the concizumab treatment arm for the first CPoC which has been further clarified in section 2.3.1 of this document.

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 after randomisation.

The offset for first CPoC criterion of patients in concizumab arm 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 of patients in concizumab arm is the log of the individual exposure time in the main part. For both criteria and patients in the on-demand arm, the offset is the log of the exposure time in the main part.

3.5 Sensitivity analysis for primary endpoint

Section 17.3 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 in section 17.3.2 how additional sensitivity analyses will be performed.

Since the first 2 weeks of the concizumab treatment is considered as a run-in period therefore an additional sensitivity analysis for CPoC criterion 2 is described in section 2.3.2 where observations for the first 2 weeks of treatment are excluded.

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 2.3.2 of this document.

3.6 Additional analyses for primary endpoint

Section 17.3.3 of the protocol describes the additional analyses of the primary endpoint. Section 2.3.3 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. The section also clarifies how the series of additional analyses will be performed with each of the PK/PD variables taken prior to last dose at 24 weeks.

3.7 Clarification of analyses for supportive secondary endpoints

In section 17.4.1 of the protocol the analyses for the supportive secondary endpoints are defined. In section 2.4.1 of this document it is further clarified that the analyses are performed using observations from concizumab patients at the last dose level as well as throughout the escalation regimen.

3.8 Definition of TEAE

In section 17.4.2 a TEAE is defined as "an event that has onset from the first exposure to treatment until the last visit in the trial." Since the trial design is concizumab s.c. prophylaxis with on-demand treatment of bleeds with eptacog alfa versus placebo with on-demand treatment of with eptacog alfa then first exposure for the eptacog alfa on-demand arm is actually at randomisation. To treat each arm similarly TEAE is defined as an event that has onset after randomisation as defined in section 2.4.2 of this document.

3.9 Causal relation between eptacog alfa and AE

On the adverse event (AE) case report form for the trial it is possible to fill in causality to rVIIa. The form states that rVIIa causality is only applicable for rVIIa administered at visit 3 and 9.1. 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.

3.10 Exploratory analyses of patient reported outcome endpoints

In section 17.4.5.2 of the protocol the endpoints for patient reported outcomes are described. In section 2.4.5.2 of this document it is clarified that ANCOVA will not be performed for the VERITAS-PRN scores since they are only supplied by visit 1 and for Hemo-TEM, PGI-C, SIAQ-ISRQ since they do not supply scores.

3.11 Main part definition for subjects on eptacog alfa on-demand

In section 17 of the protocol it is specified that "Data from when the on-demand treated patients are transferred to concizumab s.c. prophylaxis will not be included in this evaluation. Observations from the extension part in the on-demand arm will be summarised separately as well as combined with observations from the main part when reporting the extension part data." However in section 17.5 of the protocol it is stated that "Main part is 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."

Section 2.5 of this document has been updated to clarify that the main part for the on-demand treated patients is defined to end when they are transferred to concizumab s.c. prophylaxis treatment.