Cover Page for SAP

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NN7415-4307

Statistical Analysis Plan
Week 56 cut-off

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

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Biostatistics, RD&AT 1

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Version history

This Statistical Analysis Plan (SAP) describes the data evaluation planned for the 56-week cut-off as mentioned in the NN7415-4307 trial protocol version 5.0 (dated 25-Mar-2021).

1 Introduction

This SAP describes descriptive analyses for the endpoints/assessments related to bleeding episodes, safety and PK/PD at the 56-week cut-off of trial NN7415-4307. The 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment). For a description of the analyses planned for the confirmatory analyses cut-off of the trial please refer to the SAP for the confirmatory analyses cut-off version 5.

All confirmatory conclusions for this trial are based on the analyses done at the confirmatory analyses cut-off. Therefore no further confirmatory conclusions can be made based on the descriptive analyses described in this SAP.

Additional details on the derivation and calculation based on the measurements collected in this trial will be described in the analysis data reviewer's guide (ADRG). In addition, specifications of tables, figures and listings (TFL) are described in the mock TFLs.

1.1 Objectives and endpoints

No specific objectives are defined in relation to the 56-week cut-off. For the objectives related to the confirmatory analyses cut-off, please refer to the trial protocol version 5.

All the details of the endpoints, assessments and timeframes for the 56-week cut-off are explained in appendix 2.

1.2 Trial design

The following is a brief sum up of the most important parts of the trial design. For further details refer to the trial protocol version 5.

- This is a prospective, multicentre, open label clinical trial with four arms with the aims to evaluate the effect and safety of daily concizumab prophylaxis administered s.c. in patients with HA and HB. The four arms of the trial consist of:
    - Arms 1 and 2 consist of patients previously treated on demand who are randomised to
        - Arm 1: On-demand administration
        - Arm 2: Concizumab PPX treatment
    - Arms 3 and 4 are allocated to receive concizumab PPX treatment and consist of
        - Arm 3: Patients that are transferred from trial NN7415-4255 (explorer 5) prior to the treatment pause
        - Arm 4:
            - Patients who have been on stable PPX at least 24 weeks in study NN7415-4322 (explorer 6)
            - Patients that were randomised to concizumab or on demand prior to the treatment pause
            - Patients that were in NN7415-4255 at the time of the treatment pause and have completed NN7415-4255 when the trial was restarted
            - Additional on demand patients included after arms 1 and 2 are closed
- In the second quarter of 2020, the protocol was amended (protocol version 4.0) to incorporate measures to mitigate the risk of thromboembolic events. These measures include the handling of factor treatment for breakthrough bleeds and changes to the dosing regimen. As a result of these changes and the pause in the treatment while the protocol was to be amended, all statistical analyses were reconsidered and adjusted accordingly.
- The confirmatory analyses are made when all patients in arm 1 have completed visit 9/9a (or withdrawn) and all patients in arm 2 and 4 have completed visit 10a (or withdrawn).
- After the main part of the trial, all patients have been offered to continue in the extension part of the trial and receive treatment with concizumab for up to an additional 128 weeks (arms 2−4) or 136 weeks (arm 1)
- After 56 weeks of treatment in arms 2, 3 and 4, an additional evaluation will be made assessing bleeding episode related endpoints and safety for concizumab. This SAP describes in more detail the descriptive analyses that are relevant for this cut-off.

2 Statistical hypotheses

For the analyses related to the 56-week cut-off no statistical hypotheses are tested.

3 Sample size determination

The sample size considerations are described in detail in section 10.1 of the protocol version 5.

4 Analysis sets

For the purposes of analysis, the following analysis sets are defined for the 56-week cut-off.

Subject Analysis Set	Description
Full Analysis Set (FAS)	All patients randomised to the new concizumab PPX dosing regimen or on-demand treatment after the treatment pause or allocated to arm 3 or 4 with the new concizumab PPX dosing regimen. Patients from arms 1 and 2 will contribute to the evaluation 'as randomised'.
Safety Analysis Set (SAS)	All patients exposed to concizumab PPX or randomised to on-demand treatment. All patients will contribute to the evaluation 'as treated'.

Defined Analysis Data Sets	Description
On-treatment	The time period where patients are considered to be affected by on-demand treatment or concizumab treatment. For safety endpoints/assessments relating to events (number of thromboembolic events, number of hypersensitivity type reactions, number of injection site reactions, number of patients with antibodies to concizumab, number of adverse events) the 'on-treatment' analysis data set is defined as follows. For patients in **arm 1 (before or after restart) during on-demand treatment**, the period begins on the date of randomisation (as registered in IWRS) and ends at the first occurrence of: 1. Time of permanently ending on-demand administration and the day before initiation of any PPX regimen 2. The last direct patient-site contact, at or prior to the 56 weeks cut-off 3. Withdrawal date for patients who withdraw informed consent 4. The last patient-investigator/site contact as defined by investigator for patients who are completely lost to follow up 5. Date of death for patients For patients in **arm 1 during concizumab PPX treatment**, the period begins at the time of initiation of concizumab PPX treatment and ends at the first occurrence of: 6. Date of last dose of concizumab + 7 weeks 7. Items 2., 3., 4. or 5. Above

	For all patients **randomised/allocated to arm 2-4 either before or after the treatment pause**: • For patients only exposed to the initial concizumab PPX dosing regimen the period begins at the start of the initial concizumab PPX regimen and ends at the first occurrence of items 2-6 above • For patients only exposed to the new concizumab PPX dosing regimen the period begins at the time of start of the new concizumab PPX dosing regimen and ends at the first occurrence of items 2-6 above • For patients exposed to both the initial and the new concizumab PPX dosing regimen the period consists of two parts with a pause in between. The first period begins at the time of start of the initial concizumab PPX dosing regimen and ends 7 weeks after concizumab treatment was paused while the second period begins at the time of start of the new concizumab PPX dosing regimen and ends at the first occurrence of items 2-6 above Note that patients randomised to arm 1 or 2 before the treatment pause will be allocated to arm 4 after the restart and will fall in either of the three groups above when treated with concizumab. For all other endpoints/assessments the 'on-treatment' analysis data set is defined similarly as above with the exceptions that: • The addition of 7 weeks to the date of last dose of concizumab is instead set to 1 day
On-treatment without data before restart	The time period after the restart where patients are considered to be affected by on-demand treatment or treatment with the new concizumab dosing regimen. The analysis data set is defined similarly as the 'on-treatment' analysis data set with the exception: • Observation time before restart is excluded
On-treatment without ancillary therapy[a] excl. data before restart	The time period after the restart where patients are treated by concizumab treatment or are treated by on-demand treatment and additionally have not used factor-containing products not related to treatment of a bleeding episode. The analysis data set is defined similarly as the 'on-treatment' analysis data set with the exception: • Observation time before restart is excluded • Periods where factor containing products not related to a bleeding episode have been used are excluded

[a] Ancillary therapy is defined as use of factor-containing products not related to treatment of a bleeding episode except when used in relation to diagnostic procedures, intramuscular injections and minor surgery.

5 Statistical analyses

5.1 General considerations

This SAP will address the details of the descriptive statistics implemented on all arms (1, 2, 3 and 4) at the 56-week cut-off of trial NN7415-4307. The 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment).

In general, all TFLs will differentiate between HA and HB patients. For some endpoints/assessments HA and HB may be pooled.

Unless specified otherwise, the endpoints/assessments will be presented using the analysis sets as displayed in Table 1.

Table 1 Analysis sets used for analyses and/or presentations of endpoints/assessments

Endpoint/assessment categories[a]	Subject Analysis Set	Analysis Data Sets
Bleeding episodes	FAS	On-treatment without ancillary therapy excl. data before restart
PK, PD and safety not relating to events	SAS	On-treatment without data before restart
Safety relating to events[b]	SAS	On-treatment and On-treatment without data before restart

[a]Which endpoints/assessments that belong under each category can be found in section 9 of the protocol version 5.
[b]This specifically refers to: number of thromboembolic events, number of hypersensitivity type reactions, number of injection site reactions, number of patients with antibodies to concizumab, and number of adverse events.

Continuous endpoints/assessments will be presented using descriptive statistics which will include min, max, mean, SD, median, and quartiles. For PK endpoints/assessments, the descriptive statistics will also include geometric mean and CV. Event data (including AEs) will be summarised including number of patients with an event/episode, percentage of patients with an event/episode, number of events/episodes and rate of events/episodes. Categorical assessments will be summarised by number and percent of patients in each category.

Presentations of results will be by arm and visit (when applicable) and when relevant arm 1 will be split into two parts with on-demand treatment and concizumab treatment.

Event data relating to safety where the ‘on-treatment’ analysis data set is used will include both data on the initial and the new concizumab dosing regimen.

Baseline after the pause is defined as the latest measurement recorded before the start of the new concizumab dosing regimen (arms 2-4 and arm 1 concizumab part) or recorded before randomisation to the on-demand administration (arm 1) after the pause. If this measurement is missing, then the latest measurement recorded before the start of the initial concizumab dosing regimen (arms 2-4) or recorded before the on-demand randomisation before the pause (previous arm 1 (now arm 4) on-demand part) will be used (if available).

Baseline for the period before the treatment pause is defined as the latest measurement recorded before the start of the initial concizumab dosing regimen (arms 2-4) or recorded before the on-demand randomisation (arm 1 on-demand).

The target joints at baseline will be used for the definition of target joint bleeds.

In terms of bleeding episode related endpoints, the bleed rate is defined as the number of bleeding episodes over the respective observation periods. Multiple bleeding locations at the same time point will be counted as one bleeding episode. As a general rule, a treated bleeding episode is defined as any bleeding episode where the use of a factor-containing product is reported between the start and stop time of a bleed. Further, the endpoints will not include re-bleeds. A re-bleed is defined as a bleed (worsening of bleeding site conditions e.g. swelling, pain) starting within 72 hours after stopping treatment of a previous treated bleed (or re-bleed) at the same anatomical location. Note that there can be more than one re-bleed related to the same bleed. If a bleed occurs in the same location more than 72 hours after stopping treatment of a previous bleed (or re-bleed) in the same location, the bleed is defined as a new bleeding episode.

Pharmacokinetic concentration values below lower limit of quantification (LLOQ) is handled as described below:

Timing of values below LLOQ	Imputation	Use of imputed values
Values below LLOQ obtained before time of the first administration with concizumab and the pre-dose measurement collected at restart for those patients who restarts	Set to 0 (zero)	Plots
All other values below LLOQ	Set to LLOQ/2	Plots

5.2 Subject disposition

See mock TFLs.

5.3 Primary endpoint analysis

Refer to SAP for confirmatory analyses cut-off version 5.

5.4 Secondary endpoint analysis

Refer to SAP for confirmatory analyses cut-off version 5.

5.5 Exploratory efficacy endpoints analysis

5.5.1 Bleed-related assessments

The assessments related to bleeding episodes are defined in section 6.2, and will be addressed by use of the FAS and the “On-treatment without ancillary therapy excl. data before restart” analysis dataset as described in section 5.1.

In the SAP for the confirmatory analyses cut-off version 5, the bleeding episode related endpoints (including the primary endpoints and supportive secondary efficacy endpoints) are only defined for

the on-demand treatment in arm 1 and until the confirmatory analyses cut-off in arm 2. In this SAP, they will also be assessed for arm 1 after concizumab treatment is initiated and for arm 2-4 until the 56-week cut-off. The confirmatory secondary endpoints for intra-patient comparison had been concluded at the confirmatory analyses cut-off therefore will not be repeated again at the 56-week cut-off.

The number of treated spontaneous and traumatic bleeding episodes as event/count data will be presented using descriptive statistics as described in section 5.1, and by cause of bleeding episodes (Spontaneous, Traumatic, Surgical), anatomical location of bleeding episodes (Target joints, Joints, Muscular, Skin, Gastrointestinal, Mouth-gums-nose, Urinary system, Central nervous system, Other), classification of bleeding episodes (Mild/moderate, Severe) and location of severe bleeding episodes,

Furthermore, an ABR will be calculated at an individual basis as

$$ABR = \left(\frac{\text{Number of treated spontanous or traumatic bleeding episodes}}{\text{Number of days in the analysis data set}}\right) x\ 365.25$$

These continuous assessments will be presented using descriptive statistics as described in section 5.1,

The descriptive statistics for the bleeding episode related assessments up until week 56 will be presented by treatment arms and 'Total concizumab'. Furthermore, it will be presented by haemophilia types (HA, HB).

5.5.2 Pharmacokinetic and pharmacodynamic assessments

The assessments related to PK and PD are defined in section 6.2, and will be addressed by use of the SAS and the "On-treatment without data before restart" analysis dataset as described in section 5.1.

The full 24-hour PK/PD profiles were measured at Visit 2a and Visit 9a, which were already presented at the confirmatory analyses cut-off and will not be repeated again at the 56-week cut-off. In this SAP, only pre-dose PK/PD assessments up till 56-week cut-off will be presented.

All PK and PD endpoints and assessments are continuous and will be presented using the descriptive statistics as described under section 5.1.

5.6 Exploratory safety analyses

For arm 2 patients who were randomised before the treatment pause and who restarted in arm 4, all the safety data collected while on concizumab will be presented as arm 4 data.

5.6.1 Extent of exposure

A summary showing patients that escalate, deescalate, or remain on the 0.20 mg/kg/day dose will be presented separately for HA and HB.

The length of the periods constituting the analysis data sets will be presented descriptively.

5.6.2 Adverse events

All exploratory safety endpoints are defined in section 6.2.

All adverse events will be coded using the current version of MedDRA. Hypersensitivity reactions, medication errors and injection site reactions are categorised in the CRF as AEs requiring additional data collection. Additional information on these events will be collected using separate forms. Further, a MedDRA search will also be used to define these events. Thromboembolic events are defined and categorised as AESIs.

Adverse events will be evaluated using descriptive statistics based on the analysis data sets as described in section 5.1. The outputs will differentiate between haemophilia type.

Furthermore, for the on-treatment analysis data set the outputs on adverse events will also include information on

- System organ class
- Severity (mild/moderate/severe), seriousness (serious/non-serious) and relation to treatment (possibly/probably/unlikely)
- Adverse events leading to drug discontinuation
- Most frequent adverse events (occurring in more or equal to 5% of patients)
- Deaths
- Medication errors

5.6.3 Additional safety assessments

Assessments in relation to planned safety laboratory measurement, body measurements, vital signs and physical examinations are defined in section 6.2. The assessments will be presented using descriptive statistics as described in section 5.1. Number of patients with a positive antibody test will be presented as described in section 5.1 and furthermore a list of all positive antibodies recorded during the trial will be presented.

5.7 Subgroup analyses

As mentioned under section 5.1, all TFLs in general will differentiate between HA and HB.

5.8 Interim analyses

No formal interim analyses are planned.

Several evaluations are to be made during the conduct of the trial:

- at the confirmatory analyses cut-off
- after 56 weeks cut-off

- at the end of the extension part

After the initial evaluation at the confirmatory analyses cut-off no further confirmatory conclusions can be made.

5.8.1 Data monitoring committee

A Data Monitoring Committee (DMC) is established to review and evaluate accumulating data from the trial in order to protect the safety of the patients.

The DMC members are not having direct contact with any Novo Nordisk staff involved with the trial except for Novo Nordisk global safety. Details in relation to DMC can be seen in Appendix 4 of the protocol.

6 Supporting documentation

6.1 Appendix 1: List of abbreviations

ABR	Annual Bleeding Rate
ADRG	Analysis Data Reviewer's Guide
AE	Adverse event
AESI	Adverse event of special interest
DMC	Data monitoring committee
FAS	Full analysis set
HA	Haemophilia A
HB	Haemophilia B
IWRS	interactive web response system
LLoQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PPX	Prophylaxis
SAP	Statistical Analysis Plan
SAS	Safety analysis set
TFL	tables, figures and listings
TFPI	Tissue factor pathway inhibitor

6.2 Appendix 2: Definition of exploratory efficacy/safety endpoints and assessments

Type	Title	Time frame	Unit	Details	Section
Assessment	For haemophilia A patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1
Assessment	For haemophilia B patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1

		Concizumab (arms 2-4) From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off			
Assessment	For haemophilia A patients without inhibitors: The number of treated spontaneous bleeding episodes	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1
Assessment	For haemophilia B patients without inhibitors: The number of treated spontaneous bleeding episodes	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1

		regimen up until week 56 cut-off Concizumab (arms 2-4) From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off			
Assessment	For haemophilia A patients without inhibitors: Number of treated spontaneous and traumatic joint bleeds	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1
Assessment	For haemophilia B patients without inhibitors: Number of treated	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1)	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1

	spontaneous and traumatic joint bleeds	• From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off			
Assessment	For haemophilia A patients without inhibitors: Number of treated spontaneous and traumatic target joint bleeds	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1
Assessment	For haemophilia B patients without inhibitors:	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24)	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment.	5.5.1

	Number of treated spontaneous and traumatic target joint bleeds	Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off		Concizumab (arm 1) data available up until week 56 cut-off will be presented.	
Assessment	The number of all spontaneous and traumatic bleeding episodes (treated and untreated)	On demand (arm 1) • From randomisation after the pause (week 0) up until start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.5.1
Assessment	The rate of consumption of coagulation	On demand (arm 1) • From randomisation after the pause (week 0) up until	IU/kg/year	Calculated as the total consumption of coagulation	

	factors/bypass products	start of concizumab treatment (week 24) Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off		factors and/or bypassing products divided by the length (in years) of the time period in the analysis data set. The rate will be calculated by the type of treatment (FVIII, FIX, rFVIIa, aPCC and FVIIA+FX)	
Assessment	Pre-dose concizumab plasma concentration	Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	ng/mL	Summary of pre-dose assessments from start of the new concizumab dosing regimen (week 0) up until week 56.	5.5.2
Assessment	Thrombin peak	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	nmol/L	Summary of these assessments up until week 56. From start of the new concizumab dosing regimen up until week 56.	5.5.2
Assessment	Free TFPI concentration	At visits where free TFPI assessments are planned to be measured in the trial up to 56 weeks	ng/mL		5.5.2
Assessment	Endogenous thrombin potential (ETP)	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	nmol/L*min		5.5.2

Assessment	Endogenous thrombin Potential ratio	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	Ratio		5.5.2
Assessment	Velocity index	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	nmol/L*min		5.5.2
Assessment	Thrombin lag time	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	min		5.5.2
Assessment	Time to thrombin peak	At visits where thrombin generation assessments are planned to be measured in the trial up to 56 weeks	min		5.5.2
Assessment	Number of adverse events	On demand (arm 1) • From randomisation to on demand treatment up until start of concizumab treatment Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • Before the pause: From start of concizumab treatment (week 0) up until	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.6.2
Assessment	Number of thromboembolic events		Count		5.6.2
Assessment	Number of hypersensitivity type reactions		Count		5.6.2
Assessment	Number of injection site reactions		Count		5.6.2

		7 weeks after the treatment pause as well as • After the pause: From start of the new concizumab treatment (week 0) up until week 56 cut-off			
Assessment	Number of patients with antibodies to concizumab	Concizumab (arms 2-4) • From start of the new concizumab dosing regimen (week 0) up until week 56 cut-off	Count	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment.	5.6.3
Assessment	Change in <safety laboratory parameter>	On demand (arm 1) • From randomisation to on demand treatment after the pause up until start of concizumab treatment Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen up until week 56 cut-off	Multiple units	<safety laboratory parameter> refers to each safety laboratory parameter for haematology, biochemistry and coagulation parameters as listed in table 19 of the protocol version 5. Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.6.3

		From start of treatment after the pause (week 0) to every visit where the <safety laboratory parameter> is planned to be measured up until V13a (week 56)			
Assessment	Change in body weight	On demand (arm 1) • From randomisation to on demand treatment after the pause up until start of concizumab treatment Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen up until week 56 cut-off From start of treatment after the pause (week 0) to every visit where body weight is planned to be measured up until V13a (week 56)	kg	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.6.3
Assessment	Change in systolic blood pressure	On demand (arm 1)	mmHg	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment.	5.6.3

Assessment	Change in diastolic blood pressure	• From randomisation to on demand treatment after the pause up until start of concizumab treatment Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing regimen up until week 56 cut-off From start of treatment after the pause (week 0) to every visit where the vital signs are planned to be measured up until V13a (week 56)	mmHg	Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.6.3
Assessment	Change in pulse rate		beats/min		5.6.3
Assessment	Change in physical examination	Concizumab (arm 1) • From start of the new concizumab dosing regimen up until week 56 cut-off Concizumab (arms 2-4) • From start of the new concizumab dosing	%	Week 56 cut-off is when all patients from arm 2-4 have completed visit 13a or permanently discontinued treatment. Concizumab (arm 1) data available up until week 56 cut-off will be presented.	5.6.3

		regimen up until week 56 cut-off From start of the new concizumab treatment to every visit where physical examination is planned to be measured up until V13a (week 56)			