Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04082429
Sponsor trial ID:	NN7415-4307
Official title of study:	Efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors (explorer8)
Document date:	25-March-2021

*Document date refers to the date on which the document was most recently updated.

Protocol

explorer8

Protocol title:

Efficacy and Safety of Concizumab prophylaxis in patients with haemophilia A or B without inhibitors

Substance: Concizumab

Universal Trial Number: U1111-1225-9722

EUdraCT Number: 2018-004891-36

Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document	**Date**	**Applicable in country (-ies) and/or site(s)**
Updated protocol, version 5.0	25 March 2021	All countries
Updated protocol, version 4.0	06 July 2020	All countries
Updated protocol, version 3.0	17 December 2019	All countries
Updated protocol, version 2.0	06 June 2019	All countries
Original protocol, version 1.0	03 June 2019	All countries, not submitted

Protocol version 5.0 (25-Mar-2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.[1]

Overall rationale for preparing protocol version 5.0

The protocol has been amended to further reflect upon the concizumab ELISA in vitro diagnostic (IVD) device specifically used for samples collected for dose adjustment, as introduced and approved with amendment 4.0. Moreover, the FDA has approved an investigational device exemption (IDE) to use the concizumab-ELISA for dose adjustment.

Furthermore, a number of corrections and minor adjustments have been implemented throughout the protocol for clarification purposes. Due to the clarifying and corrective nature of the updates, and as the use of the IVD in the trial already has been approved in a previous amendment, this amendment is considered non-substantial.

Section # and name	***Description of change***	***Rationale***
Section 1 - Synopsis	Updated in alignment with changes specified below.	For alignment
Section 2 – Flowchart	Assessment of Target joints at visit 10a has been removed.	In version 4.0 of the protocol the trial design was updated to have two different timepoints for end of main for on demand (arm 1) and concizumab (arm 2-4). The target joint assessment at V9 which was meant as a concizumab baseline assessment for arm 1 was by mistake moved to both V9a (arm 1) and V10a (arms 2-4), but not needed for arms 2-4, since their baseline is at V2a where they start concizumab.

Section 2 – Flowchart	Footnote f) has been removed and subsequent footnotes are adjusted accordingly.	The information on details of haemophilia and haemophilia treatment and bleed history should be collected for all patients
Section 2 – Flowchart	Footnote added for concizumab ELISA: the ELISA IVD is performed on Visits 4a and 9a.2.	Concizumab plasma concentration for dose adjustment will be analysed using the concizumab ELISA IVD.
Section 4.2 – Estimands	Correction of typo in the brief sum-up of the estimand: For the previous PPX treatment (study 4322): From the point in time where PPX treatment is stable and up until start of concizumab treatment. Corrected to: For the previous PPX treatment (study 4322): From the point in time where PPX treatment is stable and up until the end of the study.	To align with the detailed specification of the estimand in Section 4.2 and in the synopsis, Section 1.
Section 4.3.1 – Primary endpoints	The mentioning of arm 4 in the primary endpoints is deleted.	The estimands used to address the two primary objectives includes the primary endpoints, see Section 4.2. In particular, it is only the two randomised arms (arms 1 and 2) that are to be compared. In Section 4.3.1 the primary endpoints are also specified but unfortunately here arm 4 was included as part of the endpoint. That was a mistake because arm 4 was clearly never intended to be included when addressing the primary objective which is also clear from the statistical analyses specified in Section 10.3.1. Instead with respect to arm 4 there are separate estimands (and thereby separate endpoints – called the confirmatory secondary endpoints) to address the two secondary efficacy objectives.
Section 4.3.2.2 – Supportive secondary endpoints	For secondary endpoints for effect, treated joint bleeds and treated target joint bleeds have been clarified to treated spontaneous and traumatic joint bleeds and treated spontaneous and traumatic target joint bleeds.	For clarification.
Section 4.3.2.2 – Supportive secondary endpoints	The mentioning of arm 4 in supportive secondary endpoint for efficacy/effect has been deleted.	To align with the primary endpoints.

Section 4.3.2.2 – Supportive secondary endpoints	Concizumab (arm 1) has been included for supportive secondary endpoints for safety.	To include all patients treated with concizumab up until the confirmatory analysis cut-off.
Section 4.3.2.2 – Supportive secondary endpoints	For the secondary endpoints for safety (concizumab arm 2-4) the time frame after treatment pause has been clarified.	For clarification.
Section 4.3.2.2 – Supportive secondary endpoints	On demand (arm 1 main part) removed from the supportive secondary endpoint; Number of patients with antibodies to concizumab.	Correction, as concizumab antibodies are not assessed for on demand (arm 1 main part).
Section 5.1 – Overall design	Figure 1: Minor text update.	For clarification.
Section 5.1 – Overall design	The patient will receive his last dose on the day prior to visit 26a instead of on the day of Visit 26a.	To align with the flowchart and protocol requirements of patients not injecting medication on the day of the visit before blood samples are taken, in order to ensure blood samples are collected pre-dose.
Section 5.1 – Overall design	The 56-week cut-off has been further defined.	For clarification.
Section 5.2.1 – Concizumab prophylaxis	For patients on prior PPX, wash-out period of aPCC, ByClot® and other products, has been clarified.	For clarification.
Section 5.2.1 – Concizumab prophylaxis	Use of factor-product PPX before intramuscular injections (e.g. vaccinations) allowed.	To allow use of factor PPX before intramuscular injections (e.g. vaccinations), which is common practice in many centres.
Section 5.2.3 – Treatment of break-through bleeding episodes	Table 3: It is clarified that the patient must contact the centre before initiating treatment of a bleeding episode.	For clarification.
Section 5.2.3 – Treatment of break-through bleeding episodes	Footnote b and c from Table 3, updated to body text in front of the table.	For clarification.
Section 5.2.3 – Treatment of break-through bleeding episodes	Section of Severe and life-threatening bleeding episodes added in alignment with Appendix 11 (Breakthrough bleed treatment guidance).	For clarification.
Section 5.3 – Patient and trial completion	Number of patients planned to be screened has been adjusted from 161 to 180.	To adjust for patients who were screen failed at Sponsor's decision due to the treatment pause, and the replacement of withdrawn patients following the treatment pause.

Section 7.1.2 - Investigational medical device (in vitro diagnostic device)	Section added to the protocol.	Concizumab plasma concentration for dose adjustment will be analysed using the concizumab ELISA IVD.
Section 8.1.1 - Temporary discontinuation of concizumab in relation to COVID-19	Text edit to allow COVID-19 to be considered as resolved based either on a negative PCR test or a clinical judgement.	To comply with local practises for handling of COVID-19, and to account for possible false positive COVID-19 tests in the time after resolved disease.
Section 9 – Trial assessments and procedures	Sentence deleted: Any additional transfer of relevant data from NN7415-4322 (explorer 6) to be used for analyses in this trial will be specified in the SAP.	All data needed will be transferred as appropriate. There is no need for further specification.
Section 9.2.2 – Treatment with concizumab	Time frame for visit windows specified.	For clarification.
Section 9.2.5 – Physical activity tracker (ActiGraph)	Description of safety reporting for the activity tracker has been added.	For clarification.
Section 9.2.6 – Patient-reported outcome questionnaires	Mandatory completion of PRO questionnaires on the day of the visit at visit 2a and visit 9a.	Change is included to emphasize the importance of completing visit 2a and visit 9a PRO questionnaires on the day of the visit and hereby ensure data quality and integrity. For the Hemo-TEM questionnaire, the patient is asked to think about their current treatment while answering the questionnaire and therefore, it is important to have the questionnaires administered just before the patients start concizumab treatment (v2a for arms 2,3 and 4; v9a for arm 1) for a baseline measure based on their pre-concizumab treatment.
Section 9.2.7 – Clinical efficacy laboratory assessments	Primary analysis cut-off corrected to confirmatory analyses cut-off for reporting of thrombin generation results.	For clarification.
Section 9.3 - Adverse events	Reference to Appendix 8 has been added.	To cover adverse device effects related to the concizumab ELISA IVD.
Section 9.3.5 - Reporting requirement for safety information related to the physical activity tracker	New section has been added to the protocol	Description of safety reporting for the activity tracker has been added to the protocol for clarification.
Section 9.3.6 - Disease-related events and/or disease-related outcomes and other information not qualifying as an AE or SAE	To clarify that bleeds recorded as AE/SAE also are reported as bleeds in the bleed diary.	To avoid any contradiction (between Section 9.2.3 and 9.3.6) potentially resulting in bleeding episodes only being recorded as AE/SAE and not also as bleeding episodes in accordance with Section 9.2.3.

9.3.7 - Technical complaints	Figure 5 deleted and reference to Appendix 7 added regarding timelines for reporting of technical complaints.	Figure deleted as it did not sufficiently cover timelines for the investigational medical device. Timelines added in Appendix 7.
Section 9.4.6 - Clinical safety laboratory assessments	Exception on urinalysis for reporting to the sites by the central laboratory is added.	For clarification.
Section 9.4.6 - Clinical safety laboratory assessments	Section for concizumab ELISA (PK ELISA and ELISA IVD) added	To describe samples collected for analysis of plasma concizumab exposure using the concizumab ELISA IVD and validation of the assay
Section 9.5 - Pharmacokinetics	Specified that visit 4a (arm 2, 3, 4) and visit 9a.2 (arm 1) should be re-scheduled if the patient has taken the daily dose of concizumab before collection of the concizumab ELISA sample	To clarify the importance that the patient has not taken his daily dose before coming to the clinic. Dosing should be performed after blood collection for dose adjustment.
Section 9.9 - Surgery	Sentence added: In the instance of acute major surgery, it is recommended to pause concizumab at the discretion of the investigator.	For clarification
Section 10.3 – Statistical analyses	Simplification of the sentence for multiple bleeding episodes: 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.	Data are not collected on whether bleeding episodes in multiple locations occur from the same event. However, if there are any such, they will occur at the same time point and this is still collected and taken into account.
Section 10.3.2.1 – Confirmatory secondary endpoints	Correction of typo. "No" changed to "previous" in the following sentence: The estimated ratio of ABR between the treatment regimens (concizumab prophylaxis versus ~~no~~ **previous** prophylaxis) with corresponding 95% confidence interval and also estimates of the actual ABRs with corresponding 95% confidence intervals in each treatment period will be presented.	For alignment with the confirmatory secondary endpoints and the estimands addressing the two secondary efficacy objectives described in Sections 4.3.2.1, 4.2 and in the synopsis, Section 1.
Appendix 1 - Abbreviations and Trademarks	Abbreviations list updated	New abbreviations used throughout the protocol
Appendix 2 – Clinical laboratory tests	Specification of pre-dose sampling of laboratory tests	For clarification

Appendix 2 - Clinical laboratory tests	Concizumab ELISA IVD added to Table 17 for protocol-required efficacy laboratory assessments	To cover the concizumab ELISA IVD device
Appendix 4 - Trial governance considerations	Updated description of responsibility for Novo Nordisk safety committee:	To clarify the responsibility of the internal safety committee
Appendix 7 - Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting	Technical complaints on investigational medical device has been included and reference to new appendix 8 added	To cover the concizumab ELISA in vitro diagnostic device
Appendix 8 - AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in Medical device studies	New Appendix has been added the protocol	To cover adverse device effects related to the concizumab ELISA IVD
Appendix 11 - Breakthrough bleed treatment guidance	Table 22: It is clarified that the patient must contact the centre before initiating treatment of a bleeding episode.	For clarification
Appendix 11 - Breakthrough bleed treatment guidance	Footnote b and c from Table 3, updated to body text in front of the table	For clarification

Disclosure

The contents of all local amendments are included in this version of the protocol. The changes are specified in the column '*Implementation in protocol version 4.0 and any update thereof*' below.

Local amendment number	***Date***	***Applicable in country (-ies) and/or site(s)***	***Brief rationale***	***Implementation in updated protocol version 4.0 and any update thereof***
1.0	18-Jul-2019	Israel	It was decided that the genetic testing and biobank part will be omitted from the protocol.	Amendment implemented in appendix 10 – Country-specific requirements
1.0	11-Sep-2019	Japan	PMDA required an update of the text in Section 5.1.1 (Dose escalation) and Section 9.2.3 (Bleeding episode). The aim of the update is to clarify the criteria for dose escalation considering all available laboratory results (including coagulation parameters) to ensure the safety of the patient. As well as, a clear explanation on how the patient should treat bleeding episodes beforehand.	This amendment has not been fully implemented in this updated protocol Section 5.1.1 has been deleted since the described dose escalation option has been removed hence the changes outline in the amendment is no longer applicable. The changes outlined in Section 5.2.3 have been implemented by updating the text as follows: If an additional dose is needed **because a single dose was insufficient to treat the bleed**, the patient must come to the site. The changes outlined in Section 9.2.3 have been implemented by updating the text as follows: In case a patient cannot get in contact with the site, bleeds must be treated ~~according to local standards~~ **as previously agreed with the investigator**.
1.0	08-Oct-2019	Turkey	The protocol was updated to comply with local reimbursement rules in Turkey.	Amended Sections 5.2.2, 5.2.3,5.2.4 and 7.1 have been implemented in Appendix 10 – Country-specific requirements in this updated protocol.
2.0	09-Jul-2019	Germany/ Site [redacted]	The rationale for this amendment, is to ensure that at selected sites, patients participating in NN7415-4307 (explorer 8) will be offered to consent to take part in a site-specific sub-study to evaluate the use of rotational thrombelastometry (ROTEM) parameters as a possible marker for evaluation of concizumab.	Appendix 10 – Country-specific requirements/ ROTEM Sub-Study has been added to reflect the text as specified in this local amendment.

Local amendment number	***Date***	***Applicable in country (-ies) and/or site(s)***	***Brief rationale***	***Implementation in updated protocol version 4.0 and any update thereof***
3.0	27-Nov-2019	Spain/ Site [redacted]	The rationale for this amendment, is to ensure that at selected sites, patients participating in NN7415-4307 (explorer 8) will be offered to consent to take part in a site-specific sub-study to evaluate the use of rotational thrombelastometry (ROTEM) parameters as a possible marker for evaluation of concizumab.	Appendix 10 – Country-specific requirements/ ROTEM Sub-Study has been added to reflect the text as specified in this local amendment.
4.0	09-Jul.2019	Sweden/ Site [redacted]	The rationale for this amendment, is to ensure that at selected sites, patients participating in NN7415-4307 (explorer 8) will be offered to consent to take part in a site-specific sub-study to evaluate the use of rotational thrombelastometry (ROTEM) parameters as a possible marker for evaluation of concizumab.	Appendix 10 – Country-specific requirements/ ROTEM Sub-Study has been added to reflect the text as specified in this local amendment.
5.0	14-Nov-2019	UK/ Site [redacted]	The rationale for this amendment, is to ensure that at selected sites, patients participating in NN7415-4307 (explorer 8) will be offered to consent to take part in a site-specific sub-study to evaluate the use of rotational thrombelastometry (ROTEM) parameters as a possible marker for evaluation of concizumab.	Appendix 10 – Country-specific requirements/ ROTEM Sub-Study has been added to reflect the text as specified in this local amendment.
6.0	26-Nov-2019	Russia	Local legal requirements on how to conduct Clinical trials in Russia were included in the protocol.	Amendment implemented in Appendix 10 – Country-specific requirements
7.0	N/A	N/A	Not in use	N/A
8.0	24-Mar-2020	South Korea	The protocol was updated to comply with local reimbursement rules for South Korea	Amendment implemented in Appendix 10 – Country-specific requirements

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1 Synopsis

Rationale:

The purpose of this phase 3 trial is to establish the effect and investigate safety of daily subcutaneous treatment with concizumab prophylaxis when given to adult and adolescent haemophilia patients without inhibitors.

Objectives and endpoints:

Primary objectives

- To compare the effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors
- To compare effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors

Primary endpoints

Endpoint title	Time frame	Unit
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count

Secondary objectives

- To compare the effect of concizumab prophylaxis to the patients' previous prophylaxis treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors

- To compare the effect of concizumab prophylaxis to the patients' previous prophylaxis treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors
- To investigate the safety of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B without inhibitors
- To investigate the PK and PD parameters of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B without inhibitors

Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Effect		
For haemophilia A patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	**Arm 4 patients who have been on stable PPX at least 24 weeks in study 4322** • For previous PPX (study 4322): From the point in time where PPX treatment is stable[a] and up until the end of study. • For concizumab PPX (trial 4307): From the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks).	Count
For haemophilia B patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	**Arm 4 patients who have been on stable PPX at least 24 weeks in study 4322** • For previous PPX (study 4322): From the point in time where PPX treatment is stable[a] and up until the end of study. • For concizumab PPX (trial 4307): From the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks).	Count

[a]Stable is defined as the time after an initial period on PPX treatment of at least 24 weeks

Estimands:

The five components of the estimand for the primary objective for HA patients are as follows:
Endpoint:

- On demand (arm 1): The number of treated spontaneous and traumatic bleeding episodes from randomisation after the pause (week 0) up until start of concizumab treatment (week 24)
- Concizumab (arm 2): The number of treated spontaneous and traumatic bleeding episodes from start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)
- **Treatment regimens**: Either a) on demand treatment with intravenous replacement with factor-containing products, or b) PPX treatment regimen with subcutaneous concizumab consisting of

an initial loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.20 mg/kg (during the dose adjustment period), followed by a maintenance dose of either 0.15, 0.20 or 0.25 mg/kg where breakthrough bleeds are treated with intravenous replacement with factor-containing products.

- **Population-level summary**: The treatment ratio of the ABRs between the two randomised treatment regimens.
- **Intercurrent events**: 1) permanent treatment discontinuation, 2) temporary treatment discontinuation, 3) use of factor-containing products not related to treatment of a bleed and 4) minor surgery.
- **Target patient population**: HA patients previously treated on demand before entering the trial.

The same five components apply for the estimand for HB patients where HA in the target patient population is substituted with HB.

Utilizing these five components, the estimand for the primary objectives can be described as the treatment ratio of the ABRs for treated spontaneous or traumatic bleeding episodes up until the confirmatory analyses cut-off between the two randomised treatment regimens in the target patient population while patients are adhering to the allocated treatment regimen.

The strategies for how to account for the intercurrent events in the primary estimand are as follows:

1) Permanent treatment discontinuation. For this intercurrent event, the data from the period after permanent discontinuation of trial treatment are not included and there will be no imputation of missing data. It is to be noted that for patients in the on demand arm, permanent treatment discontinuation will mean initiation of PPX.
2) Temporary treatment discontinuation. For this intercurrent event the 'treatment policy' strategy is used meaning that the data from this period are included.
3) Use of factor products not related to treatment of a bleed. For this intercurrent event, the data during this period are not included and there will be no imputation of missing data.
4) Minor surgery. For this intercurrent event the 'treatment policy' strategy is used.

The five components of the estimand for the secondary efficacy endpoints addressing the secondary efficacy objectives are as follows for HA patients:

- **Endpoint**:
  Arm 4 patients who have been on stable PPX for at least 24 weeks in study 4322:
- For previous PPX (study 4322): The number of treated spontaneous or traumatic bleeding episodes from the point in time where PPX is stable and up until the end of study.
- For concizumab PPX (trial 4307): The number of treated spontaneous or traumatic bleeding episodes from the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off.
- **Treatment regimens**: a) intravenous PPX treatment with factor-containing products and b) PPX treatment regimen with subcutaneous concizumab consisting of an initial loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.20 mg/kg (during the dose adjustment period) and followed by a maintenance dose of either 0.15, 0.20 or 0.25 mg/kg. During both treatment regimens, breakthrough bleeds can be treated intravenously with factor-containing products.
- **Population-level summary**: The treatment ratio of the ABRs between the two treatment regimens.

- **Intercurrent events**: 1) permanent treatment discontinuation in trial 4307, 2) temporary treatment discontinuation, 3) use of factor products not related to treatment of a bleed in trial 4307, 4) minor surgery, and 5) major surgery (during the non-interventional study 4322).
- **Target patient population**: HA patients on stable PPX treatment for at least 24 weeks in the non-interventional study 4322 and have started the concizumab maintenance dose PPX regimen (i.e., completed the dose adjustment period).

The same five components apply for the estimand for HB patients where HA in the target patient population is substituted with HB.

Utilizing these five components, the estimand for the secondary efficacy objectives can be described as the treatment ratio of the ABRs for treated spontaneous or traumatic bleeding episodes:

- For the previous PPX treatment (study 4322): From the point in time where PPX treatment is stable and up until the end of the study.
- For concizumab PPX (trial 4307): from the point in time where the maintenance dose is confirmed, escalated or de-escalated and up until the confirmatory analyses cut-off.

between the two PPX treatment regimens in the target patient population while patients are adhering to the allocated treatment regimens.

The strategies for how to account for the intercurrent events in the estimand are as follows:

1. Permanent treatment discontinuation. This intercurrent event is only applicable when a patient is part of trial 4307 (after the dose adjustment period) because if permanent PPX treatment discontinuation occurs for a patient in the non-interventional study 4322 then this patient is not part of the target patient population. If the intercurrent event occurs in trial 4307 then the data from the period after permanent discontinuation of trial treatment are not included and there will be no imputation of missing data.
2. Temporary treatment discontinuation. For this intercurrent event the 'treatment policy' strategy is used meaning that the data from this period are included.
3. Use of factor products not related to treatment of a bleed in trial 4307. For this intercurrent event, the data during this period are not included and there will be no imputation of missing data.
4. Minor surgery. For this intercurrent event the 'treatment policy' strategy is used.
5. Major surgery: This intercurrent event is only applicable when a patient is part of the non-interventional study 4322 because planned major surgery is not allowed in trial 4307 after restart. Thus, for a fair comparison this intercurrent event will be handled by use of the 'hypothetical strategy' meaning that the data, from the start of the major surgery and until the stop date when post-surgical period has ended and the patient resumes the regular treatment regimen, will be excluded.

Overall design:

This is a prospective, multicentre, open label clinical trial with two randomised arms and two non-randomised arms. The trial aims to evaluate the effect and safety of daily concizumab prophylaxis administered s.c. in patients with haemophilia without inhibitors. After screening patients will be assigned to randomisation or to allocation into non-randomised treatment arms based on their treatment regimen before the trial. Patients who were randomised to arms 1 and 2 before the pause will enter arm 4 when restarting the trial. Patients who were allocated to arms 3 and 4 before the

pause will re-enter the arm they were initially allocated to. The randomisation into arms 1 and 2 will be restarted with new patients after the treatment pause.

The trial consists of a main part (24 or 32 weeks), an extension part (up to 136 weeks) and a safety follow-up part (7 weeks). The main part of the trial is completed for a patient when the patient has completed 24 weeks of participation (arm 1) or 32 weeks of participation (arms 2,3 and 4). After the main part of the trial, all patients will be offered to continue in the extension part of the trial and receive treatment with concizumab for up to an additional 136 weeks.

Key inclusion criteria:

- Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
- Male aged ≥12 years at the time of signing informed consent.
- Congenital severe haemophilia A (FVIII <1%) or B (FIX ≤2%).

Key exclusion criteria:

- Known or suspected hypersensitivity to any constituent of the trial product or related products.
  - Known inherited or acquired coagulation disorder other than congenital haemophilia.
  - Presence of confirmed inhibitors ≥ 0.6 BU at screening.
  - History of thromboembolic disease[a]. Current clinical signs of, or treatment for thromboembolic disease. Patients who in the judgement of the investigator are considered at high risk of thromboembolic events[b].

[a]Includes arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion.'

[b]Thromboembolic risk factors could include, but are not limited to, hypercholesterolemia, diabetes mellitus, hypertension, obesity, smoking, family history of thromboembolic events, arteriosclerosis, other conditions associated with increased risk of thromboembolic events.

Number of patients:

Number of patients planned to be screened: 180
Number of patients planned to be started on trial product: 158

Of note, patients who were screen-failed at Sponsor's decision due to the treatment pause are allowed to be re-screened; in that case they will count twice in the number of screened patients.

Treatment groups and duration:

Duration of treatment will be up to 160 weeks.

The following trial products will be supplied by Novo Nordisk A/S:

- concizumab 40 mg/ml in prefilled PDS290 pen-injector
- concizumab 100 mg/ml in prefilled PDS290 pen-injector

The trial products will be administered subcutaneously.

2 Flowchart

Flowcharts for patients enrolled or reinitiated after the treatment pause

The below flowchart is applicable for patients who reinitiate treatment with concizumab after the treatment pause or for new patients enrolled in the trial after the treatment pause. Patients enrolled in the trial before the treatment pause and who will not reinitiate treatment with concizumab must follow the flowchart in Appendix 12.

Treatment arm 1	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**														**Extension Part**																			**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
SUBJECT RELATED INFORMATION AND ASSESSMENTS																																		
Informed Consent	X[d]	X[e]																																
In/exclusion Criteria	X	X																																
Demography	X																																	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant illness	X																																	

Treatment arm 1	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**														**Extension Part**																			**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Medical history	X																																	
Details of Haemophilia	X																																	
Haemophilia treatment and bleed history	X																																	
Target Joints	X	X[e]								X[f]																								
Treatment discontinuation criteria		X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation		X[i]																																
EFFICACY																																		
Bleeding Episode		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements[j]	X	X		X		X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Thrombin generation		X[k]	X	X		X	X	X	X	X[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Treatment arm 1	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Sport activity		X							X[f]			X[g]																					X	
Concizumab ELISA[l]		X[k]	X	X[m]		X	X	X	X	X[k]	X	X[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Free TFPI		X[k]	X	X		X	X	X	X	X[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY																																		
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Reaction		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X																																	
Coagulation Parameters	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Factors[n]	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X																																	
Physical examination	X	X								X[f]				X[g]						X						X							X	X

Treatment arm 1	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**														**Extension Part**																			**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Vital signs	X	X	X	X	X[o]	X	X	X	X	X	X	X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-concizumab antibodies[l]	X	X[g]		X[g]		X[g]	X[g]	X[g]	X[g]	X				X[g]		X				X			X			X			X				X	X
FVIII/FIX inhibitor analysis	X																																	
Total TFPI		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OTHER ASSESSMENTS																																		
PRO questionnaires																																		
SF36 V2.0 Health Survey		X		X		X		X		X				X[g]																				
Patient preference questionnaire										X																								
PROMIS Short Form Upper Extremity		X		X		X		X		X				X[g]																				
PROMIS Numeric		X		X		X		X		X				X[g]																				

Treatment arm 1	**Main Part**										**Extension Part**																							**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**														**Extension Part**																			**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Rating Scale - Pain Intensity																																		
Haemophilia Treatment Experience Measure		X								X				X[g]																				
Haem-A-QoL[p]	X	X[q]		X		X		X		X				X[g]																				
PGI-S on physical functioning		X		X		X		X		X				X[g]																				
PGI-C on physical functioning				X		X		X		X				X[g]																				
TRIAL MATERIAL																																		
Administration of Trial Poduct (on site)		X[g]								X[f]																								
Dose Adjustment[r]					X								X																					
Drug Dispensing		X				X		X		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		

Treatment arm 1	**Main Part**										**Extension Part**																						**Follow-up**
Visits (V)	V 1a	V 2a	V 3a[a]	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Treatment arms 2, 3 and 4	**Main Part**														**Extension Part**																			**Follow-up**
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a
Timing of Visit (Weeks)	-3	0[b]	1	4	6[c]	8	12	16	20	24	25	28	30[c]	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±7[c]	±3	±3	±3	±3	±3	±1	±3	±7[c]	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Drug Accountability		X				X		X		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																																		
Human biological specimen for storage[s]	X[t]						X			X[f]				X[g]						X							X						X	
actGraph dispensing[u]	X							X[f]		X[g]																								
actiGraph collection[u]		X								X[f]				X[g]																				
Hand out Direction for Use		X[g]								X[f]																								
Hand out patient ID card and patient material	X	X[q]																																
Hand out eDiary		X																																
End of Treatment																																	X	
End of Trial																																		X

Footnote	
a)	Phone visit is allowed for patients randomised to arm 1 (on-demand patient)
b)	Week 0 is the time of trial restart
c)	Visit will take place after the concizumab exposure levels are available according to Section 9.2.2
d)	Only patients enrolled in the trial after the treatment pause, will sign the Informed Consent at visit 1a
e)	Only patients enrolled in the trial before the treatment pause, will re-consent at visit 2a
f)	Only applicable for patients in arm 1, who are receiving concizumab at visit 9a
g)	Only applicable for patients in arm 2, 3 and 4, who are receiving concizumab at visit 2a
h)	Only applicable for patients enrolled in the trial before treatment pause. Site must ensure patients do not violate discontinuation criteria according to Section 8 before reinitiating dosing with concizumab.
i)	Patients randomised to arm 1 and 2 before the treatment pause will not be re-randomised at visit 2a
j)	Weight only, except at visit 1 where height is measured
k)	For patients having concizumab dosing at visit 2a there will be a 24-hour PK session at visit 2a and 9a. Please see details for PK sampling in Section 2.1. For on-demand patients (arm 1) only the pre-dose sample will be taken
l)	Sample is taken pre-dose. Patients must not inject trial medication on this visit day before the sample is taken.
m)	Concizumab plasma concentration for dose adjustment (visit 4a for arm 2-4 and visit 9a.2 for arm 1) will be analysed using the concizumab ELISA in vitro diagnostic (IVD) device
n)	Only one sample to be taken, either factor VIII for HA patients or factor IX for HB patients
o)	Only applicable for patients having site visit due to dose-escalation
p)	Only for patients above ≥17 years old (at visit 1a)
q)	Only applicable for patients enrolled in the trial before the treatment pause
r)	Site visit must be performed in case of dose escalation. Phone visit is allowed for patients having dose de-escalation or dose unchanged. See Section 9.2.2 for further details
s)	A separate Informed Consent Form must be signed before any samples are taken. See Section 9.7 for further details
t)	Whole blood for DNA is only taken at screening
u)	See Section 9.2.5 for further details

2.1 Pharmacokinetic (PK)/Pharmacodynamic (PD) sampling flowchart

	Visit 2a and Visit 9a (PK/PD profile only applicable for patients on concizumab treatment from visit 2a)[a]				
PK sampling timepoint (hours)	Pre-dose	3 hours	6 hours	9 hours	24 hours
Sampling window	-1 − 0 hours	±30 min	±30 min	±1 hour	±3 hours
PK ASSESSMENTS					
Concizumab ELISA	X	X	X	X	X
Free TFPI	X	X	X	X	X
Thrombin generation	X		X		X

[a]For patients who had a full 24-hour PK/PD profile measured at visit 2 prior to the treatment pause, only pre-dose (i.e. prior to loading dose) and 24-hour post-dose samples should be taken at visit 2a

3 Introduction

3.1 Trial rationale

Concizumab is a therapeutic monoclonal antibody that is being developed for prophylaxis treatment of bleeding episodes in haemophilia A (HA) and haemophilia B (HB). It is a new treatment concept involving inhibition of TFPI and has the potential to treat HA and HB patients with or without inhibitors. Concizumab is intended for subcutaneous administration.

Concizumab aspires to address the high unmet medical need in haemophilia patients by offering a s.c. administered bleeding prophylaxis in a pen-injector. Concizumab is not expected to be effective in the treatment of bleeding episodes, and breakthrough bleeds would therefore require a coagulation factor or bypassing treatment.

Due to the mode of action of concizumab and existing clinical data showing a similar response across haemophilia subtypes, the clinical development of concizumab is conducted in parallel for HA and HB, i.e., HA and HB patients are included in the same trials.

3.2 Background

Haemophilia is an inherited bleeding disorder characterised by an increased bleeding tendency, typically in weight bearing joints. HA is caused by a partial or complete deficiency of blood coagulation factor VIII (FVIII). In HB, it is factor IX (FIX) that is deficient. Inheritance is chromosome X-linked; therefore, the disease mainly affects males. The incidence is estimated to be about 1 in 5,000 live male births for HA[2] and 1 in 25,000 live male births for HB. According to the World Federation of Haemophilia global survey of 2017, about 196,706 persons are diagnosed with haemophilia worldwide.[3] Of these, about 80% have HA.

Haemophilia is classified as “severe”, “moderate” or “mild” according to the plasma activity of the affected coagulation factor.[4] With a deficiency of FVIII or FIX, the degree of activation of coagulation FX becomes insufficient. Consequently, the thrombin burst is delayed and insufficient for normal haemostasis.[5] If formed, the haemostatic plug is fragile and easily dissolved by normal fibrinolytic activity. This leads to impaired haemostasis and spontaneous prolonged bleeding episodes. In severe haemophilia, bleeding in joints often occurs spontaneously and is the most frequent symptom of the disease. Recurrent bleeding episodes in the same location, most commonly a weight bearing joint, lead to chronic arthropathy, muscular atrophy and deformities. Treatment of bleeding episodes as they manifest (on-demand treatment) may delay arthropathy but does not prevent it.

The most common complication of replacement therapy in HA and to a lesser extent HB is development of inhibitory antibodies against FVIII and or FIX respectively. These binding antibodies might neutralise the effect of exogenous FVIII or FIX and are then called inhibitors. In patients who have developed clinically relevant inhibitors towards FVIII or FIX, replacement therapy is rendered ineffective.

Of the 196,706 people diagnosed with haemophilia, 6,290 have a clinically identified inhibitor corresponding to a prevalence of approximately 3.2%. According to the World Federation of

Haemophilia global survey of 2017, the inhibitor prevalence is highest in HA accounting for 94% of the inhibitor cases.[3] Inhibitors in HB are very rare with a reported global prevalence of 342 cases.[3]

Bleeding episodes in inhibitor patients may be treated intravenously with bypassing agents, activated FVII or an activated prothrombin complex concentrate (aPCC) given as intravenous injections.

The majority of current replacement therapy with coagulation factor VIII and IX or bypassing treatment options are hampered by the fact that most of these products must be given as intravenous injections. A new therapeutic agent that can be administered subcutaneously in small volume will represent a major improvement in the treatment convenience and thereby compliance of these patients in a prophylaxis setting.

Concizumab is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype with a molecular weight of 149 kilo Daltons. To prevent formation of half-antibodies, the serine at position 241 in the heavy chain has been replaced with a proline (S241P (Kabat annotation)). Concizumab is directed against the tissue factor pathway inhibitor (TFPI), which is involved in down-regulation of the initiation of the coagulation cascade. Concizumab prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). This compensates for the limited FXa generation in the absence of a functional FIXa/FVIIIa complex in haemophilia. When the TFPI inhibitory activity is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve haemostasis. More information about the physiological role of TFPI and the mode of action of concizumab is provided in the Investigator's Brochure (IB).

The key differentiator to current treatment options is thus a new mode of action (MoA), and the key benefit of concizumab in patients with HA, HB, HAwI and HBwI is a reduced treatment burden due to subcutaneous administration potentially leading to better adherence, more patients on prophylactic treatment and ultimately potentially better disease outcome.

The concizumab clinical development programme in patients ≥12 years of age comprises four phase 1 trials, two phase 2 trials, two phase 3 trials and a non-interventional study. Details on the individual trials are provided in the IB. Phase 3 clinical trials were initiated in October 2019; trial NN7415-4307 (explorer 8) in patients with HA and HB and trial NN7415-4311 (explorer 7) in patients with HAwI and HBwI. In February and March 2020, 5 serious thromboembolic events were reported in 3 patients included in the phase 3 trials (2 patients in trial 4307 and 1 patient in trial 4311). As a result of the occurrence of these events, clinical development was paused and investigations to understand what may have contributed to the non-fatal thromboembolic events were conducted. The findings from the investigations have led Novo Nordisk to implement a number of changes to the trial protocols (as reflected by this protocol amendment (protocol version 4.0)) to reduce the risk that additional patients treated with concizumab will experience thromboembolic events. The changes have been accepted by the external independent Data Monitoring Committee.

3.3 Benefit-risk assessment

Concizumab is under development for the prevention of bleeding episodes, including long-term prophylaxis, in patients with haemophilia A and B, regardless of inhibitor status. Until recently, all

available haemophilia treatment options required frequent intravenous administration of pro-coagulant compounds. However, a monoclonal antibody therapy emicizumab (Hemlibra®) has now been approved for subcutaneous prophylaxis in HA patients with and without inhibitors. Inhibition of TFPI is a potential new option for the treatment of patients with haemophilia. Concizumab is administered subcutaneously, thus potentially improving convenience compared to clotting factor prophylaxis. Concizumab does not itself involve the risk of inhibitor formation against FVIII or FIX. Therefore, concizumab could represent a major improvement over current treatment options.

As observed for other pro-coagulant compounds, there is a potential risk of thrombosis due to exaggerated pharmacology. Thromboembolic events were observed in toxicity studies in non-human non-haemophiliac primates at high concizumab exposures. In pathological conditions, in which TF is expressed more extensively than considered physiological, e.g. advanced atherosclerosis, cancer, crush injury, or septicaemia, the risk of developing thrombosis and disseminated intravascular coagulation (DIC) may be increased by anti-TFPI treatment.[6, 7] Vascular changes observed in the nonclinical toxicity studies were shown to be mediated by disposition of immune complexes (ICs). This is the result of an overwhelmed clearance of ICs, containing concizumab and antibodies against concizumab. Similar changes, if they occur in humans, could lead to organ damage and potentially become life-threatening. It is, however, generally recognised that animal studies are limited in their ability to predict human immune responses to a therapeutic protein.

No significant thromboembolic events or signs of DIC were reported in the phase 1 or phase 2 concizumab clinical trials with an exposure time of up to 102 weeks for the individual patient in the phase 2 trials. After initiation of the phase 3 clinical trials, 5 serious thromboembolic events (all non-fatal) were reported in 3 patients; the events were of different pathological aetiology, i.e. arterial and venous. All events occurred within 3 months of concizumab treatment initiation. All 3 patients experiencing thromboembolic events had different types of thromboembolic risk factors and all 3 patients had used breakthrough bleed treatment just before the onset of symptoms for the thromboembolic event. In 2 of the cases, either a relatively high dose or prolonged treatment with factor product was reported. The concizumab exposure levels for these 2 patients were also among the highest levels observed across the phase 2 trials (4310 and 4255) and the phase 3 trials (4307 and 4311), and it was also noted that overall, the concizumab exposure levels in phase 3 at the 0.25 mg/kg dose-level were higher than expected. For the remaining patient, a possible/potential renal infarct prior to trial entry is being assessed (not confirmed). The findings from the investigations of the cases have led Novo Nordisk to make several changes to the trial protocols to reduce the risk that additional patients treated with concizumab will experience thromboembolic events.

These changes include:

- A new guidance for treatment of mild and moderate breakthrough bleeds, with specific guidance for use of the lowest dose of factor product or bypassing agent while on concizumab PPX (see Section 5.2.3).
- That patients **must** contact the site when they have a suspected bleed (see Section 5.2.3).
- Continuation of previous PPX for up to two weeks after initiation of concizumab dosing is no longer allowed (see Section 5.2.1)

- A new concizumab dosing regimen including an initial daily dose of 0.20 mg/kg concizumab (instead of 0.25 mg/kg). Criteria for an increase or decrease in the daily maintenance dose to 0.25 mg/kg or 0.15 mg/kg, respectively (based on concizumab exposure levels at the week 4 visit) are provided. The loading dose remains 1.0 mg/kg (see Section 5.2.1).
- Elective major surgery is no longer allowed (see Section 9.9).
- Trial stopping rule requiring urgent evaluation by the Novo Nordisk Safety Committee and consultation with the DMC in case of one *(instead of two)* significant thromboembolic event, DIC, TMA or death of trial patient which may be related to the trial product (see Section 9.3.9).

Anaphylactic reactions towards therapeutic mAbs have been reported but are rare.[8] Acute generalised hypersensitivity reactions are generally known to occur within the first few hours after the infusion or injection and may include headache, nausea, vomiting, dizziness, sweating, flushing, change in blood pressure and difficulties in breathing. In rare cases, the reaction may be life-threatening. No serious hypersensitivity reactions have been reported in the phase 1 and main part of phase 2 clinical trials with concizumab. A severe hypersensitivity reaction in a patient with HBwI has been reported in a phase 3 clinical trial with concizumab (prior to the treatment pause).

TFPI is an inhibitor of tissue factor (TF) which is the most potent initiator of coagulation. In addition to its role in coagulation, TF is involved in a variety of coagulation-independent processes, including inflammation.[6, 9] Therefore, in pathophysiological conditions with increased TF expression, e.g. infection, sepsis, inflammation, and crush injuries, there may be a potential risk of adverse reactions due to potentiation of inflammatory response. No AEs indicating an increased inflammatory response due to concizumab treatment has been reported.

When the coagulation system is excessively activated, not only thrombosis, but also bleeding could potentially occur due to consumption of coagulation factors. This has not been observed in clinical trials with concizumab.

With the implementation of mitigations to minimise the risk of thromboembolic events in the restart of the phase 3 trials, concizumab is considered to still have the potential for a favourable benefit-risk profile within all haemophilia subtypes.

More detailed information about the identified and potential benefits as well as the potential risks of concizumab can be found in the IB.

4 Objectives and endpoints

4.1 Primary, secondary and exploratory objectives

4.1.1 Primary objectives

- To compare the effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors
- To compare effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors

4.1.2 Secondary objectives

- To compare the effect of concizumab prophylaxis to the patients' previous prophylaxis treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors
- To compare the effect of concizumab prophylaxis to the patients' previous prophylaxis treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors
- To investigate the safety of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B without inhibitors
- To investigate the PK and PD parameters of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B without inhibitors

4.1.3 Exploratory objectives

- To compare the patient-reported outcomes (PRO) in adult and adolescent patients with haemophilia A or B without inhibitors treated with concizumab prophylaxis to the PROs in patients treated with no prophylaxis
- To explore treatment preference for concizumab prophylaxis versus no prophylaxis or previous prophylaxis treatment in adult and adolescent patients with haemophilia A or B without inhibitors

4.2 Estimands

The five components of the estimand for the primary objective for HA patients are as follows:

- **Endpoint**:
- On demand (arm 1): The number of treated spontaneous and traumatic bleeding episodes from randomisation after the pause (week 0) up until start of concizumab treatment (week 24)
- Concizumab (arm 2): The number of treated spontaneous and traumatic bleeding episodes from start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)
- **Treatment regimens**: Either a) on demand treatment with intravenous replacement with factor-containing products, or b) PPX treatment regimen with subcutaneous concizumab consisting of an initial loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.20 mg/kg (during the dose adjustment period), followed by a maintenance dose of either 0.15, 0.20 or 0.25 mg/kg

where breakthrough bleeds are treated with intravenous replacement with factor-containing products.

- **Population-level summary**: The treatment ratio of the ABRs between the two randomised treatment regimens.
- **Intercurrent events**: 1) permanent treatment discontinuation, 2) temporary treatment discontinuation, 3) use of factor-containing products not related to treatment of a bleed (see Section 5.2.1) and 4) minor surgery.
- **Target patient population**: HA patients previously treated on demand before entering the trial.

The same five components apply for the estimand for HB patients where HA in the target patient population is substituted with HB.

Utilizing these five components, the estimand for the primary objectives can be described as the treatment ratio of the ABRs for treated spontaneous or traumatic bleeding episodes up until the confirmatory analyses cut-off between the two randomised treatment regimens in the target patient population while patients are adhering to the allocated treatment regimen.

The strategies for how to account for the intercurrent events in the primary estimand are as follows:

1) Permanent treatment discontinuation. For this intercurrent event, the data from the period after permanent discontinuation of trial treatment are not included and there will be no imputation of missing data. It is to be noted that for patients in the on demand arm, permanent treatment discontinuation will mean initiation of PPX.
2) Temporary treatment discontinuation. For this intercurrent event the 'treatment policy' strategy is used meaning that the data from this period are included.
3) Use of factor products not related to treatment of a bleed. For this intercurrent event, the data during this period are not included and there will be no imputation of missing data.
4) Minor surgery. For this intercurrent event the 'treatment policy' strategy is used. The definition of minor surgery is outlined in Table 14.

The five components of the estimand for the secondary efficacy endpoints addressing the secondary efficacy objectives are as follows for HA patients:

- **Endpoint**:
  Arm 4 patients who have been on stable PPX for at least 24 weeks in study 4322:
- For previous PPX (study 4322): The number of treated spontaneous or traumatic bleeding episodes from the point in time where PPX is stable and up until the end of study.
- For concizumab PPX (trial 4307): The number of treated spontaneous or traumatic bleeding episodes from the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off.
- **Treatment regimens**: a) intravenous PPX treatment with factor-containing products and b) PPX treatment regimen with subcutaneous concizumab consisting of an initial loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.20 mg/kg (during the dose adjustment period) and followed by a maintenance dose of either 0.15, 0.20 or 0.25 mg/kg. During both treatment regimens, breakthrough bleeds can be treated intravenously with factor-containing products.
- **Population-level summary**: The treatment ratio of the ABRs between the two treatment regimens.

- **Intercurrent events**: 1) permanent treatment discontinuation in trial 4307, 2) temporary treatment discontinuation, 3) use of factor products not related to treatment of a bleed in trial 4307, 4) minor surgery, and 5) major surgery (during the non-interventional study 4322).
- **Target patient population**: HA patients on stable PPX treatment for at least 24 weeks in the non-interventional study 4322 and have started the concizumab maintenance dose PPX regimen (i.e., completed the dose adjustment period).

The same five components apply for the estimand for HB patients where HA in the target patient population is substituted with HB.

Utilizing these five components, the estimand for the secondary efficacy objectives can be described as the treatment ratio of the ABRs for treated spontaneous or traumatic bleeding episodes:

- For the previous PPX treatment (study 4322): From the point in time where PPX treatment is stable and up until the end of the study.
- For concizumab PPX (trial 4307): from the point in time where the maintenance dose is confirmed, escalated or de-escalated and up until the confirmatory analyses cut-off.

between the two PPX treatment regimens in the target patient population while patients are adhering to the allocated treatment regimens.

The strategies for how to account for the intercurrent events in the estimand are as follows:

1. Permanent treatment discontinuation. This intercurrent event is only applicable when a patient is part of trial 4307 (after the dose adjustment period) because if permanent PPX treatment discontinuation occurs for a patient in the non-interventional study 4322 then this patient is not part of the target patient population. If the intercurrent event occurs in trial 4307 then the data from the period after permanent discontinuation of trial treatment are not included and there will be no imputation of missing data.
2. Temporary treatment discontinuation. For this intercurrent event the ‘treatment policy’ strategy is used meaning that the data from this period are included.
3. Use of factor products not related to treatment of a bleed in trial 4307. For this intercurrent event, the data during this period are not included and there will be no imputation of missing data.
4. Minor surgery. For this intercurrent event the ‘treatment policy’ strategy is used. The definition of minor surgery is outlined in Table 14.
5. Major surgery: This intercurrent event is only applicable when a patient is part of the non-interventional study 4322 because planned major surgery is not allowed in trial 4307 after restart. Thus, for a fair comparison this intercurrent event will be handled by use of the ‘hypothetical strategy’ meaning that the data, from the start of the major surgery and until the stop date when post-surgical period has ended and the patient resumes the regular treatment regimen, will be excluded. The definition of major surgery is outlined Table 14.

4.3 Primary, secondary and exploratory endpoints

4.3.1 Primary endpoints

Endpoint title	Time frame	Unit
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count

4.3.2 Secondary endpoints

4.3.2.1 Confirmatory secondary endpoints

Endpoint title	Time frame	Unit
Effect		
For haemophilia A patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	**Arm 4 patients who have been on stable PPX at least 24 weeks in study 4322** • For previous PPX (study 4322): From the point in time where PPX is stable[a] and up until the end of study. • For concizumab PPX (trial 4307): From the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks).	Count
For haemophilia B patients without inhibitors: The number of treated spontaneous and traumatic bleeding episodes	**Arm 4 patients who have been on stable PPX at least 24 weeks in study 4322** • For previous PPX (study 4322): From the point in time where PPX is stable[a] and up until the end of study. • For concizumab PPX (trial 4307): From the point in time where the concizumab	Count

	maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks).	

[a]Stable is defined as the time after an initial period on PPX treatment of at least 24 weeks

4.3.2.2 Supportive secondary endpoints

Endpoint title	Time frame	Unit
Effect		
For haemophilia A patients without inhibitors: 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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
For haemophilia B patients without inhibitors: 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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
For haemophilia B 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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count

Endpoint title	Time frame	Unit
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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
For haemophilia B 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 2)** • From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)	Count
Safety		
Number of thromboembolic events	**On demand (arm 1 main part)** • From randomisation to on demand treatment up until start of concizumab treatment[d] **Concizumab (arms 2-4)** • Before the pause[b]: From start of concizumab treatment (week 0[c]) up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment (week 0[a]) up until the confirmatory analyses cut-off (at least 32 weeks) **Concizumab (arm 1 extension part)** • From start of concizumab treatment (visit 9a) up until the confirmatory analysis cut-off	Count
Number of thromboembolic events	**Concizumab** • Before the pause[b]: From start of treatment (week 0[c]) up until 7 weeks after the treatment was paused	Count

Endpoint title	Time frame	Unit
	as well as • After the pause[b]: From start of concizumab treatment up until the end of trial (week 167)	
Number of hypersensitivity type reactions	**On demand (arm 1 main part)** • From randomisation to on demand treatment up until start of concizumab treatment[d] **Concizumab (arms 2-4)** • Before the pause[b]: From start of concizumab treatment (week 0[c]) up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment (week 0[a]) up until the confirmatory analyses cut-off (at least 32 weeks) **Concizumab (arm 1 extension part)** • From start of concizumab treatment (visit 9a) up until the confirmatory analysis cut-off	Count
Number of hypersensitivity type reactions	**Concizumab** • Before the pause[b]: From start of treatment (week 0[c]) up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment up until the end of trial (week 167)	Count
Number of injection site reactions	**On demand (arm 1 main part)** • From randomisation to on demand treatment up until start of concizumab treatment[d] **Concizumab (arms 2-4)** • Before the pause[b]: From start of concizumab treatment (week 0[c]) up until 7 weeks after the treatment was paused	Count

Endpoint title	Time frame	Unit
	as well as • After the pause[b]: From start of concizumab treatment (week 0[a]) up until the confirmatory analyses cut-off (at least 32 weeks) **Concizumab (arm 1 extension part)** • From start of concizumab treatment (visit 9a) up until the confirmatory analysis cut-off	
Number of injection site reactions	**Concizumab** • Before the pause[b]: From start of treatment (week 0[c]) up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment up until the end of trial (week 167)	Count
Number of patients with antibodies to concizumab	**Concizumab (arms 2-4)** • Before the pause[b]: From start of concizumab treatment (week 0[c]**)** up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment (week 0[a]) up until the confirmatory analyses cut-off (at least 32 weeks) **Concizumab (arm 1 extension part)** • From start of concizumab treatment (visit 9a) up until the confirmatory analysis cut-off	Count

Endpoint title	Time frame	Unit
Number of patients with antibodies to concizumab	**Concizumab** • Before the pause[b]: From start of treatment (week 0[c]) up until 7 weeks after the treatment was paused as well as • After the pause[b]: From start of concizumab treatment up until the end of trial (week 167)	Count
Pharmacokinetic and pharmacodynamic endpoints		
Pre-dose (trough) concizumab plasma concentration (C_{trough})	Prior to the concizumab administration at week 24 (after restart)	ng/mL
Pre-dose thrombin peak	Prior to the concizumab administration at week 24 (after restart)	nmol/L
Pre-dose free TFPI concentration	Prior to the concizumab administration at week 24 (after restart)	ng/mL
Maximum concizumab plasma concentration (C_{max})	From 0 to 24 hours where 0 is time of the concizumab dose at week 24 (after restart)	ng/mL
Area under the concizumab plasma concentration-time curve (AUC)	From 0 to 24 hours where 0 is time of the concizumab dose at week 24 (after restart)	ng*hr/mL

[a]Defined as time of randomisation to on-demand administration after the pause or time of start of the new concizumab dosing regimen.

[b]Defined as the pause in the concizumab clinical development programme during March to August 2020, while thromboembolic events were investigated.

[c]Defined as time of the initial randomisation to on-demand administration or time of start of the previous concizumab dosing regimen (0.25 mg/kg/day).

[d]Safety will be described separately for patients randomised to on demand treatment before the pause.

4.3.3 Exploratory endpoints

Endpoint title	Time frame	Unit
Patient reported outcomes		
Change in SF-36v2 bodily pain	From baseline (week 0[a]) until week 24	Score
Change in SF-36v2 physical functioning	From baseline (week 0[a]) until week 24	Score
Patient preference assessed by questionnaire	Week 24	%
Change in patient's treatment burden using the Hemo-TEM total score	From baseline (week 0[a]) until week 24	Score
Change in PROMIS Short Form v2.0 -Upper Extremity 7a	From baseline (week 0[a]) until week 24	Score
Change in PROMIS Numeric Rating Scale v.1.0 – Pain Intensity 1a	From baseline (week 0[a]) until week 24	Score
Change in Haem-A-QoL total score	From baseline (week 0[a]) until week 24	Score
Change in Haem-A-QoL physical health domain score	From baseline (week 0[a]) until week 24	Score
Physical activity measured by accelerometer		
Change in time spend in moderate to vigorous physical activity (MVPA) per day	From baseline to end of the main part (week 24 for the on-demand arm and week 32 for the concizumab arms)	Minutes per day

[a]Defined as time of randomisation to on-demand administration after the pause or time of start of the new concizumab dosing regimen.

5 Trial design

5.1 Overall design

This is a prospective, multicentre, open label clinical trial with two randomised arms and two non-randomised arms. The trial aims to evaluate the effect and safety of daily concizumab prophylaxis administered s.c. in patients with HA and HB. Patients will be randomised to concizumab PPX or no PPX or assigned into the non-randomised treatment arms, based on their treatment regimen before entering the trial. Upon restart, patients who were randomised to arms 1 or 2 before the pause will enter arm 4. Patients who were allocated to arms 3 and 4 before the pause will re-enter the arm they were initially allocated to. The randomisation into arms 1 or 2 will be restarted with new patients. The main part of the trial is completed for a patient when the patient has completed 24 weeks of participation (screening period not included) for patients in arm 1 or 32 weeks of participation (screening period not included) for patients in arms 2,3 and 4. After the main part of the trial, all patients will be 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) (Figure 1).

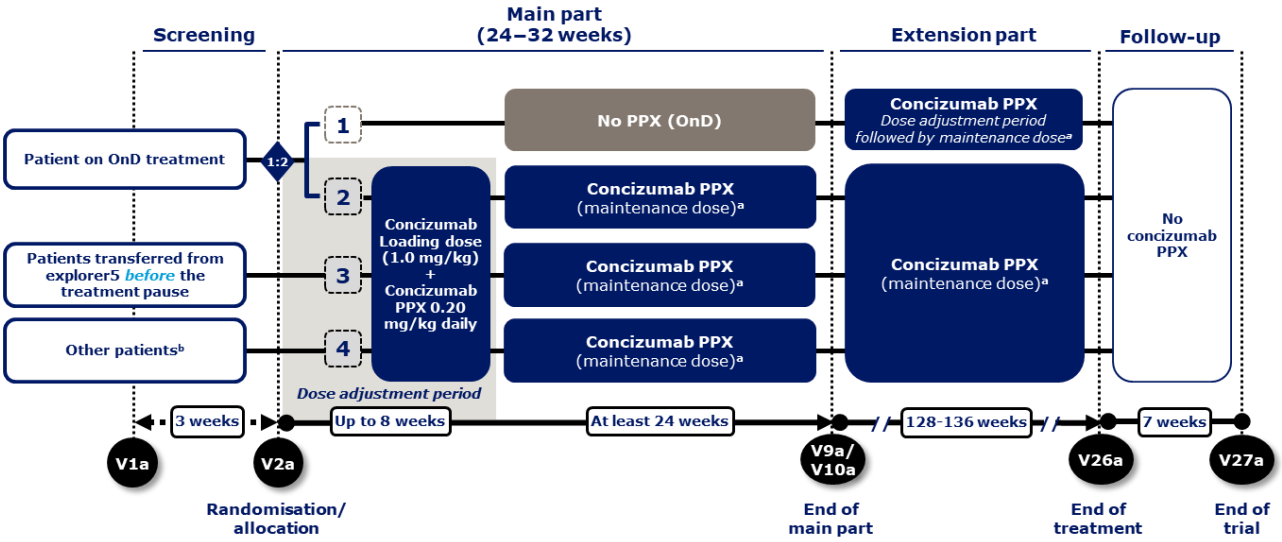
A *confirmatory analyses cut-off* will be defined as when all patients in arm 1 have completed visit 9a (or withdrawn) and all patients in arms 2 and 4 have completed visit 10a (or withdrawn). This will ensure that all patients in arms 2 and 4 have completed the dose adjustment period and at least an additional 24 weeks of concizumab PPX on their final maintenance dose (or withdrawn). Furthermore, a 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment). At this 56-week cut-off, an additional evaluation will be made assessing bleed related endpoints and safety.

After up to 128/136 weeks in extension part the patient will enter the safety follow-up part of the trial. The patient will receive his last dose at home on the day prior to visit 26a. The follow-up part of the trial lasts for 7 weeks and the patient will continue to report bleeding episodes until visit 27a.

In this version of the protocol, patients not already enrolled at the time of the re-start, will be defined as new patients recruited from the non-interventional study NN7415-4322 (explorer 6) and from outside the concizumab programme. New patients can belong to the following categories:

- patients who previously participated in NN7415-4255 (explorer 5)
- patients who were in screening phase at the time of the pause
- patients entering from NN7415-4322 (explorer 6)
- new patients coming from outside the concizumab programme.

All of the above-mentioned new patients will start the trial at visit 1a (screening visit).



Note: [a]The individual maintenance dose will be either 0.15, 0.20 or 0.25 mg/kg concizumab (see Section 9.2.2); [b]Additional patients on OnD treatment or patients on PPX with factor replacement, patients from explorer5 enrolled *after* the treatment pause and patients randomised to arms 1 or 2 *before* the treatment pause.

Abbreviations: OnD = on demand; PPX = prophylaxis; V = visit

Figure 1 Trial design

The randomisation between the treatment arms 1 and 2 will be stratified according to haemophilia type and bleeding frequency during the 24 weeks prior to screening; see Section 7.2.

Treatment arms 1 and 2:

Approximately 60 patients (24 HA and 36 HB patients), previously treated on-demand, will be randomised 1:2 to no prophylaxis versus concizumab prophylaxis.

Patients randomised to arm 1 before the pause were instructed to continue their on demand treatment and report data until trial restart. Patients who were randomised to arms 1 and 2 prior to the treatment pause should re-enter the trial in arm 4. Instead 60 new patients will be identified to be randomised into arms 1 or 2.

Treatment arm 3:

The HA patients enrolled into the concizumab phase 2 trial NN7415-4255 (explorer 5) were offered enrolment into arm 3. These patients continued concizumab PPX and had a combined visit 1 and 2. Upon trial restart, these patients will receive the new concizumab dosing regimen. After the initial dose adjustment period, patients will receive at least 24 weeks of treatment on their final maintenance dose (main part). Subsequently, these patients will be offered up to 128 weeks of concizumab PPX (extension part).

Patients who were in NN7415-4255 (explorer 5) at the time of the treatment pause, and who have now completed explorer 5, will be offered screening in this trial and should enter arm 4 (visit 1a) as outlined below.

Treatment arm 4:

Arm 4 will include at least 60 patients (30 HA and 30 HB patients) previously on prophylaxis with factor products with a minimum of 24 weeks observation in NN7415-4322 (explorer 6).

In addition, arm 4 will also include:

- Patients who were randomised to arms 1 and 2 before the treatment pause
- HA patients who were in NN7415-4255 (explorer 5) at the time of the treatment pause, and who have now completed explorer 5
- On demand patients included after arms 1 and 2 are closed

Patients who were enrolled before the pause

Patients who were randomised or allocated to treatment in this trial before the pause, should re-enter the trial as outlined in Table 1.

Table 1 Visit overview for patients restarting this trial

Allocation before the pause	Allocation at restart
Arm 1	Arm 4 - visit 2a
Arm 2	Arm 4 - visit 2a
Arm 3	Arm 3 - visit 2a
Arm 4	Arm 4 - visit 2a

Table 2 below summarises the expected numbers of randomised/enrolled patients in each arm. In total 158 patients are expected to be enrolled. The aim is to have approximately 21 HA and 14 HB unique adolescent patients defined as patients between ≥12 to <18 years at trial start.

Table 2 Randomisation/enrolment overview

	Minimum number of patients randomised/enrolled			
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4** **Minimum number of PPX patients from NN7415-4322 (explorer 6) with at least 24 weeks observation period on stable PPX**
HA	8	16	10	30
HB	12	24	N/A	30

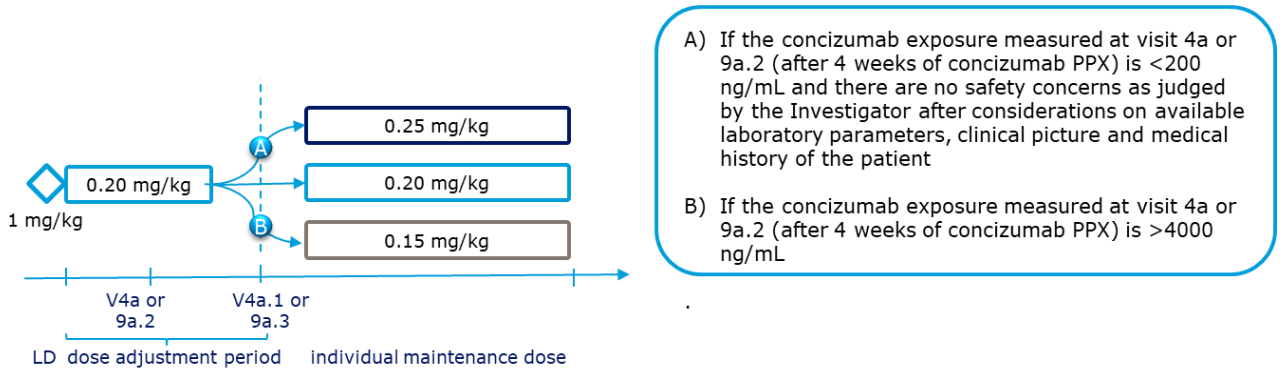
Note: In addition to the 60 patients needed for the confirmatory secondary analysis (within-patient comparison), arm 4 will also include patients who were randomised to arms 1 or 2 before the treatment pause, HA patients from NN7415-4255 (explorer 5) included after the treatment pause as well as on demand patients included after arms 1 and 2 are closed.

5.2 Treatment of patients

5.2.1 Concizumab prophylaxis

When patients are randomised/allocated to concizumab prophylaxis, they will receive a loading dose of 1.0 mg/kg concizumab at visit 2a (arm 2, 3 and 4) or visit 9a (arm 1) followed by an initial daily dose of 0.20 mg/kg concizumab from treatment day 2. Within an initial 5−8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab. A potential dose adjustment will take place at visit 4a.1 or

9a.3 and will be based on the concizumab exposure level measured at the previous visit 4a or 9a.2. Patients who have concizumab exposure levels of 200−4000 ng/mL will stay at 0.20 mg/kg concizumab. The new concizumab dosing regimen is shown schematically in Figure 2 and explained in further detail in Section 9.2.2.



Abbreviation: LD = loading dose

Notes: Concizumab exposure level is measured at V4a/9a.2; Potential dose adjustment will take place at V4a.1/9a.3.

Figure 2 Concizumab dosing regimen upon re-initiation of trial

Doses, including the loading dose, given at PK/PD visits (i.e. visit 2a and 9a) will be administered at the site; all other injections may be administered at home by the patient or caregiver.

Prior to visit 2a, patients must be in a non-bleeding state 48 hour prior to the visit however patients can have treatment for up to 24 hours prior to visit 2a, except for treatment with aPCC and ByClot® where the wash-out is 48 hours prior to visit 2a. For patients coming from a PPX treatment regimen, an interval of 2 half-lives from the given factor product to first concizumab dose is required.

A pre-filled, multi-dose pen-injector for the drug administration will be provided by Novo Nordisk, details can be found in Section 7.1.1.

Use of factor-containing products not associated to a bleed is not allowed, except for diagnostic procedures, intramuscular injections (e.g. vaccinations) and minor surgery, e.g. dental treatment, endoscopies etc.

5.2.2 On-demand treatment

Patients in arm 1 will continue on-demand treatment with their usual replacement therapy until visit 9a (end of main part). Novo Nordisk will not provide or reimburse on-demand treatment for patients in arm 1. In the extension part, patients in arm 1 will receive daily concizumab subcutaneous injections (see Section 5.2.1).

As noted in Section 5.1, Patients randomised to arm 1 before the pause will go to arm 4 upon restart of the trial. Thus, additional patients will be randomised to arm 1 (and 2) when restarting the trials.

5.2.3 Treatment of break-through bleeding episodes

The patient must contact the site when they have a suspected bleed, see Section 9.2.3 for further details.

Novo Nordisk will not provide or reimburse treatment for bleeding episodes. Any bleeds occurring in the trial can be treated with the patient's usual factor-containing product, taking the treatment guidance in Appendix 11 into consideration. Table 3 provides a tabular overview of the guidance on management of mild and moderate bleeds. Prophylactic treatment with concizumab should continue independent of bleeding episodes and their treatment, i.e. the original dosing schedule should be maintained unless investigator judges otherwise.

For treatment of bleeds, the dose must not exceed a single dose of 50 U/kg aPCC (FEIBA®), and not exceed 100 U/kg within 24 hours. The first treatment should be at the hospital, with observation of the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with FEIBA® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 50 U/kg. If an additional dose is needed because a single dose was insufficient to treat the bleed, the patient must come to the site.

For treatment of bleeds, the dose must not exceed 60 µg/kg ByClot®, and not exceed 90 µg/kg ByClot® within 24 hours. Additional dose can be given at an interval of 8 hours or longer. The first treatment should be at the hospital, with observation of the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with ByClot® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 60 µg/kg. If an additional dose is needed because a single dose was insufficient to treat the bleed, the patient must come to the site.

Table 3 Guidance on management of mild and moderate bleeds during concizumab PPX

	FVIII SHL	FVIII EHL	FIX SHL	FIX EHL	rFVIIa	aPCC	ByClot®
Contact centre (PI)	The patient must contact the centre before initiating treatment of a bleeding episode. If more doses are needed, the patient should contact the centre before each dose.						
First dose[a]	20 IU/kg	20 IU/kg	30 IU/kg	30 IU/kg	90 µg/kg	Single dose must not exceed 50 U/kg, and not exceed 100 U/kg within 24 hours	Single dose must not exceed 60 µg/kg ByClot®, and not exceed 90 µg/kg ByClot® within 24 hours
Second dose	20 IU/kg	20 IU/kg	30 IU/kg	At investigator's discretion	90 µg/kg	At investigator's discretion	Additional dose can be given at an interval of 8 hours or longer
Dose interval	Time between first and second dose must not be shorter than stated in local labelling[b]						
Anti-fibrinolytics	Local/topical use is allowed. Use of single systemic doses is allowed after careful benefit-risk evaluation					Not recommended	Not recommended

Notes: [a]Lowest dose in accordance with local labelling. [b]The interval between the two doses could be increased based on clinical case-by-case judgment keeping in mind that early breakthrough bleed control remains crucial.
Abbreviations: SHL=standard half-life, EHL=extended half-life

Severe and life-threatening bleeding episodes

From a patient safety perspective, specific recommendations for the management of severe and life-threatening bleeding episodes (see definition in Table 10) are not considered feasible as such management often poses several complex clinical challenges that need to be addressed case by case by the treating physicians hereby tailoring and securing the optimal treatment, which in some cases may be high factor replacement doses for extended periods of time. In the rare event of a severe (life-threatening) bleed the patient should be in immediate and close contact to the investigator and be treated with relevant doses of factor containing products at the discretion of the investigator.

Please see Section 9.2.3 and Appendix 11 for further instructions on bleeding episodes.

5.2.4 Treatment during screening and follow-up period

Patients should follow their normal prophylaxis schedule or on-demand regimen during the screening period and follow-up period. Treatments will not be reimbursed by Novo Nordisk. Bleeds during screening and follow-up should be treated as specified in Section 5.2.3.

5.3 Patient and trial completion

Approximately 180 patients will be screened to achieve that at least 60 patients are randomly assigned to either no prophylaxis or trial product in the treatment arms 1 and 2. To achieve that up to 98 patients are assigned to prophylaxis with concizumab in treatment arms 3 and 4; please see Table 2. For definition of screen failures; see Section 6.3

Trial period completion for a patient:

Trial period completion for a patient is defined as when the patient has completed visit 27a, or at the global end of trial date 20 June 2024 whichever comes first.

Treatment period completion for a patient:

Treatment period completion for a patient is defined as when the patient has completed visit 26a.

5.4 End of trial definition

The end of trial is defined as the date of the last visit of the last patient in the trial or 20 June 2024 whichever comes first.

5.5 Scientific rationale for trial design

The trial design follows to the extent possible requirements and makes use of applicable elements outlined in the EMA guidelines on the clinical investigation of recombinant and human plasma-derived factor VIII/IX products in terms of; endpoints, patient population, sample size, eligibility criteria, exposure time, PK and immunogenicity assessment etc.

The primary objective for patients with HA is to show the effect of concizumab prophylaxis (arm 2) is superior to no prophylaxis (arm 1, on-demand treatment) in adult and adolescent patients. The primary objective for patients with HB is to show the effect of concizumab prophylaxis (arm 2) is superior to no prophylaxis (arm 1, on-demand treatment). The first confirmatory secondary objective for HA patients aims at showing that the effect of concizumab prophylaxis is non-inferior to standard of care prophylaxis treatment. The first confirmatory secondary objective for HB

patients aims at showing that the effect of concizumab prophylaxis is non-inferior to standard of care prophylaxis treatment.

Patients to be included in the on-demand arm of the trial will be coming from on-demand treatment regimens at their clinics reflecting local standards of care. After completion of the main part of the trial, all patients will be offered concizumab prophylaxis in the extension part for up to an additional 136 weeks.

5.5.1 Rationale for non-inferiority margin

Within this trial a secondary confirmatory hypothesis is tested comparing patients previous PPX treatment with concizumab administration using a non-inferiority approach. The non-inferiority margin associated with this hypothesis is determined using the 95%-95% fixed margin approach as described in the FDA guidance.[10] In the lack of placebo-controlled trials within haematology, a historical effect measure based on bleeding episodes has been estimated in a pooled analysis between on demand and PPX treatment. This analysis was conducted on 20 trials selected based on a literature search where both PPX treatment and on demand treatment is used. The treatment ratio (on demand over PPX treatment) and associated 95% confidence interval for ABR was estimated to 7.47 [5.90;9.46]. By setting the non-inferiority margin at 2, approximately 60% of the effect will be preserved

With this non-inferiority margin, in this rare disease indication, it will be possible to have sufficient number of patients to investigate the effect of concizumab PPX in patients previously treated with PPX. The choice of the non-inferiority margin is influenced by the expected PPX population in this global trial, where highly variable bleeding phenotype can be expected, as described above and observed in the phase 2.

5.6 Justification for dose

Upon restart, the dosing regimen for this phase 3 trial is a loading dose of 1.0 mg/kg concizumab s.c. on the first day of treatment, followed by an initial daily dose of 0.20 mg/kg concizumab. Within the initial 5−8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab (or they can stay on 0.20 mg/kg); this will be based on the concizumab exposure level at visit 4a/9a.2 (see Section 9.2.2).

The reduction in the initial daily dose as compared to the previous maintenance dose of 0.25 mg/kg, is based on the finding that 2 of the 3 patients experiencing thromboembolic events were among the patients with the highest concizumab exposure level observed. Furthermore, the concizumab exposure levels observed in phase 3 on the original dosing regimen (0.25 mg/kg/day) were higher than expected based on the phase 2 results as well as population PK modelling. The safety of the initial daily dose of 0.20 mg/kg is supported by results from the phase 2 trials, since the exposure range observed in phase 2 covers the exposure range predicted when restarting all patients on daily dosing with 0.20 mg/kg concizumab. The exposure ratio between the initial daily dose of 0.20 mg/kg and the exposure level at the no adverse effect level (NOAEL) in the nonclinical studies is given in the Investigator's Brochure.

Some patients will need to increase or decrease the daily dose to 0.25 or 0.15 mg/kg; this will be based on the exposure level after 4 weeks of concizumab PPX (see Section 9.2.2). The target of concizumab exposure levels above 200 ng/mL emanates from an exploratory exposure-response analysis performed based on the phase 2 trials (NN7415-4255 (explorer 5) and NN7415-4310 (explorer 4) main part data, indicating a lower ABR with exposure levels above 200 ng/mL. The upper limit of 4000 ng/mL is a precaution to avoid patients reaching very high exposure levels. Despite the lack of data showing that high exposure per se is causative of thromboembolic events, the evaluations of the thromboembolic events suggests that the concizumab exposure in combination with other risk factors could contribute to thrombosis.

5.7 Rationale for Trial Population

The trial population is defined in Section 6. The eligibility criteria have been defined to allow inclusion of patients from the non-interventional study NN7415-4322 (explorer 6) and trial NN7415-4255 (explorer 5), and of patients who were screen-failed at Sponsor's decision due to the treatment pause as well as new patients. Additionally, the eligibility criteria were defined to ensure that the resulting population will be homogeneous in terms of unmet medical needs.

The patient population has been defined based on severity of haemophilia, because severity is known to correlate with the endogenous factor activity and the bleeding phenotype in patients without inhibitors. This is to select patients who have a high medical need or a bleeding frequency of 5 per 24 weeks.

The exclusion criteria are defined to ensure safety of the patients. Due to the pro-coagulant nature of the drug, patients at increased risk of thromboembolic events according to the Investigator's discretion are excluded from the trials. Pre-existing inhibitors or development of inhibitors during the trial would complicate and treatment of breakthrough bleeds in the affected patient. Therefore, patients with existing inhibitor or at risk for reoccurrence of inhibitor are excluded.

6 Trial population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male aged ≥12 years at the time of signing informed consent.
3. Body weight >25 kg at screening.
4. Congenital severe haemophilia A (FVIII < 1%) or moderate/severe B (FIX ≤ 2%).
5. Documented treatment with coagulation factor containing product in the last 24 weeks (not applicable for NN7415-4255 (explorer 5) patients enrolled prior to the treatment pause).

6.2 Exclusion criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Known or suspected hypersensitivity to any constituent of the trial product or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent. However, this is not applicable for patients who were screen failed at Sponsor's decision due to the treatment pause.
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 5 half-lives or 30 days from screening, whichever is longer (not applicable for NN7415-4255 patients enrolled prior to the treatment pause).
4. Platelets ≤100x10^9/L at screening.
5. Fibrinogen below laboratory lower normal limit at screening.
6. Hepatic dysfunction defined as AST and/or ALT >3 times the upper limit combined with total bilirubin > 1,5 times the upper limit at screening.
7. Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) ≤30 ml/min/1.73 m^2 for serum creatinine measured at screening.
8. Known inherited or acquired coagulation disorder other than congenital haemophilia.
9. History of thromboembolic disease[a]. Current clinical signs of, or treatment for thromboembolic disease. Patients who in the judgement of the investigator are considered at high risk of thromboembolic events[b].
10. A known systemic inflammatory condition requiring systemic treatment at screening.
11. Treatment with emicizumab within 180 days before screening.
12. Presence of confirmed inhibitor ≥0.6 BU at screening.
13. Known history of inhibitors ≥0.6 BU in the last 5 years according to the medical records.
14. Any disorder, except for conditions associated with haemophilia, which in the investigator's opinion might jeopardise patient's safety or compliance with the protocol.

[a]Includes arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery

occlusion. [b]Thromboembolic risk factors could include, but are not limited to, hypercholesterolemia, diabetes mellitus, hypertension, obesity, smoking, family history of thromboembolic events, arteriosclerosis, other conditions associated with increased risk of thromboembolic events.

6.3 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information to be collected during the screening period includes demography, screen failure details, eligibility criteria, and any SAEs. A screen failure session must be made in the IWRS.

Individuals who do not meet the criteria for participation in this trial may not be re-screened unless the patient was screen failed at Sponsor's decision due to the treatment pause. Re-sampling is not allowed if the patient has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

6.4 Randomisation criteria

To be randomised into arm 1 or arm 2 in this trial, one of following randomisation criteria must be answered "yes".

Randomisation criteria:

1. On-demand patient transferred from NN7415-4322 (explorer 6)

or

2. On-demand patient who has ≥5 documented treated bleeds in the last 24 weeks or ≥10 treated bleeds during 52 weeks before screening.

7 Treatments

7.1 Treatments administered

Trial product must only be used, if it appears almost clear and colourless to slightly yellow.

Table 4 Trial products provided by Novo Nordisk A/S

Trial product name:	Concizumab C 40 mg/ml (IMP, test product)	Concizumab C 100 mg/ml (IMP, test product)
Dosage form:	Solution for injection	Solution for injection
Route of administration:	Subcutaneous	Subcutaneous
Initial (loading) dose - dose at day one:	1.0 mg/kg	1.0 mg/kg
Dosing instructions daily dose from day 2 and onwards:	Initially 0.20 mg/kg followed by 0.15, 0.20 or 0.25 mg/kg	Initially 0.20 mg/kg followed by 0.15, 0.20 or 0.25 mg/kg
Packaging	Prefilled Pen-injector (PDS290 pen-injector)	Prefilled Pen-injector (PDS290 pen-injector)

The investigator must document that directions for use is given to the patient orally and in writing at the first dispensing visit. The investigator, or a person designated by the investigator/institution, will train the patient in the correct use of the investigational product. See Section 7.1.1 for further details.

Other haemostatic medication including treatment used for breakthrough bleeds and prophylactic treatment for the screening and follow-up period will not be supplied or reimbursed by Novo Nordisk.

Needles for the pen injector will be delivered as auxiliary. Only needles provided by Novo Nordisk must be used for administration of trial product.

7.1.1 Medical devices

Only the Prefilled pen-injector, Concizumab PDS290 pen-injector, is to be used for administration of the trial product, concizumab, in this trial.

Table 5 Pen-injector and strengths

Investigational Medicinal Product	Route of administration	Strength	Cartridge volume	Dosage increment
Concizumab (in prefilled Pen-injector PDS290 pen)	For subcutaneous use	40mg/ml	1.5 ml	0.3 mg
Concizumab (in prefilled Pen-injector PDS290 pen)	For subcutaneous use	100mg/ml	1.5 ml	0.75 mg

Training in the Concizumab PDS290 pen-injector

The patients must be trained according to the Directions for Use (DFU) in how to handle the concizumab PDS290 pen-injector. Patient training must be documented in the patients' medical records. Training must be repeated, based on patients' needs as judged by the investigator, during

the trial at regular intervals to ensure correct use of the PDS290 pen-injector. The following should be emphasised:

- Trial product must be administered subcutaneously either in the abdomen or in the thigh.
- Always use a new needle for each injection as this will prevent contamination and ensure correct dosing.
- The needle should be kept in the skin while counting slowly to 10 after the dose counter has returned to zero. If the needle is removed too early, then the full dose may not have been delivered.
- Remember the scale drum does not reflect the dose in mg. Refer to the conversion table in the Trials Materials Manual for the correct dose. Incorrect dose setting may lead to under-/overdosing.
- Remind the patient to consult the DFU or contact the site if in doubt on how to use the pen-injector.

7.1.2 Investigational medical device (in vitro diagnostic device)

The concizumab-ELISA is an enzyme-linked immunosorbent assay (ELISA) intended to quantitate the concentration of concizumab in human citrated plasma from patients included in the concizumab clinical trials. The concizumab-ELISA has been used throughout the clinical development programme for measuring concizumab exposure (PK). The concentration of concizumab in human citrated plasma measured by this assay will also be used as the point of reference for dose adjustments in the phase 3 clinical trials for concizumab. Samples collected specifically for dose adjustment will be analysed using the concizumab-ELISA in vitro diagnostic (IVD) device. All other samples will be analysed using the concizumab-ELISA. FDA has approved an investigational device exemption for concizumab-ELISA measurements to be used for dose adjustment. Risk management documentation for the concizumab-ELISA IVD is available in the IB.

7.2 Method of treatment assignment

All screened patients will receive a unique subject number at the screening visit, which will be assigned to the patient throughout the trial. Patients who were screen-failed at Sponsor's decision due to the treatment pause and who are re-screened at trial restart will receive a new unique subject number. Patients meeting the randomisation criteria will be centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart in Section 2.

Stratification of the randomised on-demand patients into treatment arms 1 and 2 will be performed in the IWRS.

The stratification variables are:
- haemophilia type (HA, HB)
- bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ≥9 bleeding episodes)

7.3 Blinding

This is an open-label trial where the trial product is packed open-label; however, the specific treatment for a patient will be assigned using IWRS. The site will access the IWRS before the start of trial product administration for each patient.

7.4 Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive trial product and only authorised site staff may supply or administer trial product.

Instructions on home treatment of patients and handling of auxiliaries are described in the latest version of the DFU. Authorised site staff having the responsibility for patient training and administering trial product at site will be requested to follow the similar instructions in the latest version of the Trial Materials Manual.

Long term storage and in use storage

Table 6 Trial product storage conditions

Trial product name	Storage conditions (not-in-use)	In-use conditions	In-use time[a]
Concizumab 40 mg/ml	Do not freeze Store in refrigerator (2 °C – 8 °C) Protect from light	Do not refrigerate Store at 8°C - 30°C Protect from light Use within 28 days	28 days
Concizumab 100 mg/ml			

[a]In-use time for concizumab starts when first dose is administered from the pen-injector.

Any changes to trial product storage conditions will be communicated to all sites in the latest version of the Trial Materials Manual.

Drug accountability of all trial products received is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial products as specified in the flowchart Section 2.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS. Trial product will be distributed to the trial sites according to the status of screening and randomisation.

- The investigator must confirm that appropriate temperature conditions have been maintained during transit for all trial products received and any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual.

- Trial product that has been stored improperly must not be dispensed to any patient before it has been evaluated and approved for further use by Novo Nordisk.
- The investigator is responsible for drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- All concizumab containing pen-injectors must be accounted for as used, partly used or unused.
- Destruction of concizumab can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- Destruction of trial products must be documented in the IWRS.
- All returned, expired or damaged trial products (for technical complaint samples see Appendix 7) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the trial site.

For country-specific requirements; please refer to Appendix 10.

7.5 Treatment compliance

Throughout the trial, the investigator will remind the patients to follow the trial procedures and requirements to ensure patient compliance. If a patient is found to be non-compliant the investigator will remind the patient of the importance of following the instructions given including taking the trial products as prescribed. Training of the patient should be documented accordingly.

When patients are dosed at the site, they will receive trial product directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the patient medical records.

When patients self-administer trial product(s) at home, compliance with trial product administration will be assessed and the assessment documented in patient medical records at each dispensing visit where information is available. If any suspicion of non-compliance arises, apart from occasionally missed doses, the site must enter into a dialogue with the patient, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented.

Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned trial product
- Review of prophylaxis treatment diaries
- Patient’s body weight measured at last site visit
- Investigators input to concizumab daily dose at last visit
- Questioning of subjects

The importance of patient retention will be addressed by Novo Nordisk in the training and communication with the trial sites.

The patients will be carefully informed about the trial procedures before signing informed consent, so that they know the implications of participating in the trial.

Close surveillance of patient retention will be performed throughout the trial by Novo Nordisk with focus on reasons for premature discontinuation of trial product or withdrawal of consent to secure early mitigations in collaboration with the trial sites.

The investigator will make every effort to ensure that all assessments are performed, and data are collected. If missing data do occur, the reason will be collected via the protocol deviation process, see Appendix 4. Novo Nordisk will monitor protocol deviations on an on-going basis throughout the trial followed by appropriate actions (e.g. re-training of site staff).

7.6 Concomitant medication

Any medication other than the trial product concizumab that the patient is receiving at the time of the first visit or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates or continuation.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to Section 9.3.

Concomitant haemostatic medication must be collected regardless of the duration and relation to a bleed. The haemostatic medication will primarily be collected in the eDiary and StudyWorks, please see Section 9.2.3 for details.

7.6.1 Prohibited medication

- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anti-coagulants (DOACs)
- Emicizumab
- Anti-fibrinolytics, except for local/topical use. Use of single systemic doses is allowed after careful benefit-risk evaluation.

7.7 Treatment after the end of the trial

When discontinuing trial products, either at the scheduled end of treatment visit or if trial product is discontinued, the patient should be transferred to a suitable marketed product at the discretion of the investigator.

8 Discontinuation/Withdrawal criteria

8.1 Discontinuation of trial treatment

The patient may be discontinued from trial product at any time during the trial at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts must be made so that patients, who discontinue trial product, attend and complete all scheduled visit procedures according to the flowchart in Section 2. Patients should stay in the trial irrespective of lack of adherence to the treatment, lack of adherence to visit schedule or missing assessments. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

The patient must be discontinued from trial product, if the following applies:

1. Included in the trial in violation of the inclusion and/or exclusion criteria
2. Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product
3. Incapacity or unwillingness to follow the trial procedures
4. Significant thromboembolic event[a]
5. Event of Disseminated Intravascular Coagulation (DIC)
6. Event of Thrombotic Microangiopathy (TMA)
7. Event of severe or serious hypersensitivity reaction related to concizumab

[a]The definition of a significant thromboembolic events is provided in Appendix 5. For venous thromboembolic events where treatment of concizumab has been discontinued, re-initiation of concizumab can be considered by the investigator in the extension part of the trial, after the patient has fully recovered. The investigator must contact and agree with Novo Nordisk before reinitiating concizumab treatment.

See the flowchart in Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for further evaluations that need to be completed.

The primary reason for discontinuation of trial product must be specified in the end-of-treatment-form in the eCRF, and final drug accountability must be performed. A treatment discontinuation session must be made in the IWRS.

8.1.1 Temporary discontinuation of concizumab in relation to COVID-19

Regular testing for COVID-19 will not be part of the protocol, but will be done at the investigator's discretion only. Testing should be performed according to the locally recommended testing methodology.

In case a patient is tested positive for ongoing COVID-19 infection prior to the first concizumab dose, then visit 2a/9a (allocation/randomisation visit) should be postponed until a negative COVID-19 result exists or the patient has fully recovered from the COVID-19 infection as judged by the investigator. During the trial, in the case a patient is tested positive for ongoing COVID-19, concizumab should be paused immediately and not restarted until the patient tests negative again or has fully recovered from COVID-19 as judged by the investigator. In the interim period, patients should be treated as per judgement of the investigator.

If access to COVID-19 testing is limited, then the pause and postponement should be based on a strong suspicion, as judged by the investigator.

A positive COVID-19 test, or suspicion of COVID-19, is considered an AE and should be reported as such following the procedures in Section 9.3 and Appendix 5.

In case of a suspected thromboembolic event, it is encouraged to perform a COVID-19 test. If a thromboembolic event is diagnosed, COVID-19 testing must be performed. Additionally, analysis for COVID-19 antibodies may be performed; see Section 9.4.6.

8.1.2 Sponsor-initiated discontinuation of trial product in relation to the treatment pause

All patients enrolled in the trial at the time of the treatment pause were temporarily discontinued from treatment with concizumab.

The following must be documented in the eCRF in relation to the treatment pause:

- For **all patients**:
- The stop date of concizumab treatment after announcement of the treatment pause
- For **patients who reinitiate treatment** with concizumab after the treatment pause:
- The date of signing the addendum to the informed consent form (see Appendix 4)
- The start date of the initiation of the new concizumab dosing regimen.

Patients enrolled in the trial before the treatment pause and who will not reinitiate treatment with concizumab will consequently have permanently discontinued from treatment and must follow the flowchart in Appendix 12.

If a patient decides to withdraw consent prior to trial restart, the investigator should ask the patient if he, as soon as possible, is willing to have assessments performed according to visit 9. If the patient withdraws consent after visit 9, then he should have assessments performed according to visit 26 (last treatment visit in the extension part of the trial). See the flowchart in Appendix 12 for data to be collected. For further instructions concerning withdrawals; see Section 8.2.

8.2 Withdrawal from the trial

A patient may withdraw consent at any time at his own request, or at the request of the patient's parent or the patient's legally acceptable representative (LAR).

If a patient withdraws consent prior to visit 9a/10a (last treatment visit in the main part of the trial), the investigator should ask the patient if he is willing, as soon as possible, to have assessment performed according to visit 9a/10a. If the patient withdraws consent after visit 9a/10a, he should have assessment performed according to visit 26a (last treatment visit in the extension part of the trial). See the flowchart in Section 2 for data to be collected.

Final drug accountability must be performed even if the patient is not able to come to the trial site. A treatment discontinuation session must be made in the IWRS.

If a patient withdraws from the trial, he may request destruction of any samples taken and not tested, and the investigator must document this in the medical records.

If the patient withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent.

Although a patient is not obliged to give his reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the eCRF.

8.2.1 Replacement of patients

Patients who discontinue trial product or withdraw from the trial after restart will not be replaced.

Patients who were initially randomised to arms 1 or 2 before the pause will be transferred to arm 4 when restarting the trial (see Section 5.1). Therefore, additional patients will be randomised to meet the required number for the primary analysis. Additionally, the required number of patients in NN7415-4322 (explorer 6) subsequently entering arm 4 will be ensured for the confirmatory secondary analysis.

8.3 Lost to follow-up

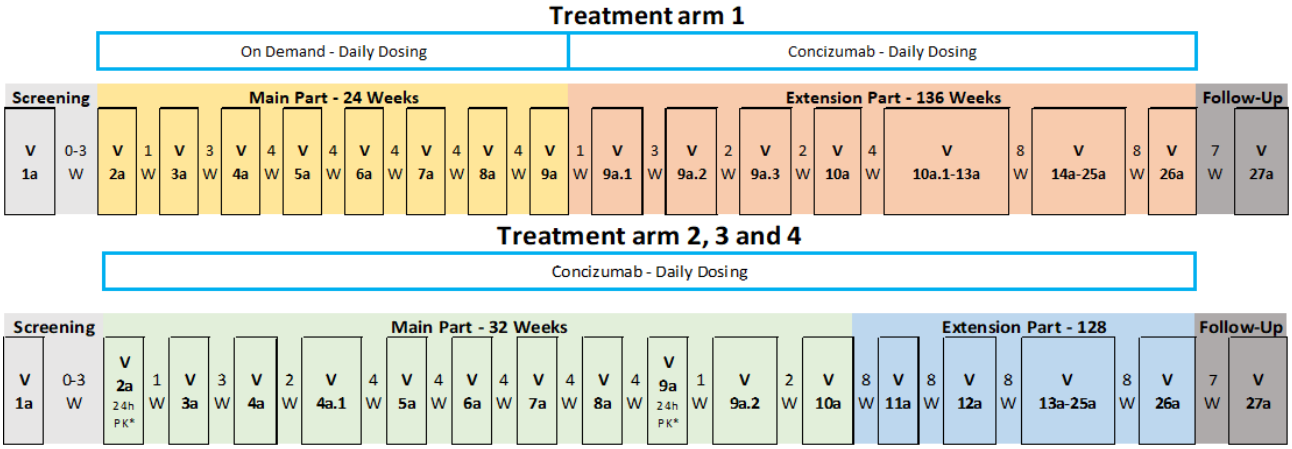
A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the trial site for a required visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator must make every effort to regain contact with the patient (where possible, at least three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's source document.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

9 Trial assessments and procedures

Figure 3 provides a visit schedule overview. Trial procedures and their timing are summarised in details in the flowchart in Section 2.



Note: [a]For patients who had a 24-hour PK/PD profile measured at visit 2 prior to the treatment pause, only pre-dose (i.e. prior to loading dose) and 24-hour post-dose samples should be taken at visit 2a

Figure 3 Overview of trial visits

Informed consent must be obtained before any trial related activity, see Appendix 4. This applies for patients restarting the trial as well as for patients in arm 1 who start concizumab treatment.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.

At screening, patients will be provided with an ID card stating that they are participating in a trial and giving contact details of relevant trial site staff.

Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.

Review of completeness of the diaries, laboratory reports etc. must be documented either on the documents or in the patient's source documents. If clarification of entries or discrepancies in the diary or PRO instruments is needed, the patient must be questioned, and a conclusion made in the patient's source documents. Care must be taken not to bias the patient. Any necessary changes to the eDiary data should be requested to the vendor and documented accordingly. See Section 9.2.6 for further instructions on review of PRO questionnaires.

The maximum amount of blood collected from each patient upon trial restart (after the treatment pause, including the screening, main, extension and follow-up parts) will be approximately 950 mL depending on which treatment arm the patient is allocated to. In addition, for patients enrolled in the trial prior to the treatment pause, the total amount of blood collected will depend on the number of site visits the patient attended with an average of 28 mL of blood collected per site visit.

Blood sampling in adolescent patients aged 12−17 years must be performed according to local guidelines. The blood volume taken in patients below 18 years should not exceed 3 % of the total volume during a 4-week period and should not exceed 1% at any single time point.[11] See Appendix 3 for further details concerning blood sampling in adolescent patients.

Shared assessments and data transfer from NN7415-4255 (explorer 5) and NN7415-4322 (explorer 6)
For patients enrolled into this trial from NN7415-4255 (explorer 5) and NN7415-4322 (explorer 6) assessments related to the patient´s end of trial and screening visit, respectively, will be baseline assessments for this trial when feasible. The data will automatically be transferred to the database for this trial.

For patients transferring from NN7415-4255 (explorer 5) before the pause, the following assessments are in scope:
- Laboratory data (End of Trial). See the laboratory manual for details on laboratory sampling for patients who are transferred.
- Details of Haemophilia (screening)
- Haemophilia Treatment and Bleed History (screening)
- ECG (screening)
- PROs (collected visit 15.1)

For previous NN7415-4255 (explorer 5) patients enrolled after the pause, there will be no shared assessments. These patients will have assessments made according to the flowchart in Section 2 (visit 1a).

For patients transferring from NN7415-4322 (explorer 6), the following assessments are in scope:
- Details of Haemophilia (screening)
- Physical Activity Tracker (screening)

For patients who have previously participated in NN7415-4255 (explorer 5) and NN7415-4322 (explorer 6) following information will be collected in the eCRF:
- Trial ID for previous trial
- Subject number in previous trial

9.1 Patient related information/assessments

9.1.1 Demography

Demography will be recorded in the eCRF at screening and consists of:
- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

9.1.2 Details of Haemophilia

All available information on haemophilia, prior to screening should be recorded in the eCRF.

- Diagnosis of haemophilia (date)
    - Classification of haemophilia type (haemophilia A or B)
- Family history of
    - Haemophilia
    - Prothrombotic disorders
    - Thromboembolism
    - Inhibitors
- Inhibitor tests taken (date, result (BU))
- Cut-off for positive inhibitor result
- Deficiency factor level

9.1.3 Haemophilia Treatment and Bleed History

The following information on haemophilia treatment and bleed history 12 months prior to screening should be recorded in the eCRF:

- Type of treatment/regiment
    - Prophylaxis or on-demand
    - Start date
    - Stop date
- Number of bleeding episodes
    - If possible, specify number of spontaneous bleeding episodes.
- Coagulation factor product(s)
    - Brand name, or if the brand is not known, the type of product, (plasma derived or recombinant)
- Dosage used for prophylaxis (for prophylaxis patients only)
- Dosing frequency during prophylaxis (for prophylaxis patients only)
- Approximate dose to treat a bleeding episode
- Approximate number of doses to treat a bleeding episode

9.1.4 Target Joints

All current target joints, including number of bleedings during the last 12 months, must be registered. A target joint is defined as three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤ 2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint. Surgical joint bleeds should not be included in the target joint count.
Following information will be collected in the eCRF:

- Location
- Position (left/right)
- Number of bleeding episodes the last 12 months

9.2 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart in Section 2.

9.2.1 eDiary

Novo Nordisk will provide the patient with an eDiary for electronic recording of following assessments:

- Treatment with concizumab, see Section 9.2.2
- Bleeding episodes including treatment of bleeds, see Section 9.2.3
- PRO questionnaires see Section 9.2.6
- Health economic questions see Section 9.8

The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

Patients or patient's caregiver will be trained in the use of the eDiary by the investigator or delegated personnel before entering of any data. The eDiary will be dispensed to the patient at visit 2a (unless an eDiary has already been dispensed). After visit 2a and onwards, data will be entered by the patient or patient´s caregiver in the eDiary at home. The patient should bring his eDiary at all visits to ensure the eDiary is working properly. The eDiary will be returned by the patient at the end of trial visit (visit 27a).

For data collected in the eDiary, the investigator must review treatment data, bleeding episodes and specific PRO´s, as specified in Section 9.2.6. The review should be documented accordingly. It is the responsibility of the investigator to instruct the patient about the timelines for timely completion of the eDiary.

If the investigator finds it necessary to amend or correct eDiary data, the patient must be consulted, and outcome documented prior to requesting the actual data change. A Data Correction Request must be submitted to the eDiary vendor. An audit trail will be maintained.

All data entered will be transferred from the eDiary to an electronic database, where it is kept as a certified copy of the source data by the eDiary vendor. Data entered in the eDiary will upon confirmation of a successful back-up be deleted from the eDiary.

The eDiary will have built in edit checks and reminders, to ensure that all relevant questions are answered. eDiary data transferred to the electronic database will be viewable to relevant trial site staff and Novo Nordisk personnel on a secure, password protected web portal.

From the re-start of the trial, and if allowed according to local regulations, patients will be offered to use an app (Bring Your Own device) that can be downloaded to the patient's own smartphone instead of the handheld eDiary device currently used in the trial. It is voluntary for the patients if they want to use the app, and an addendum to the Informed Consent Form must be signed before use. If it is not possible for the patient to use the app e.g., due to technical or other issues, then the patient will use/continue to use the provisioned device. The patient can start using the app solution at any time during the trial.

9.2.2 Treatment with concizumab

For in-between visit administrations of trial drug, patients will self-administer concizumab and will record their treatment in the eDiary which will be reviewed at each visit by trial site staff in StudyWorks and periodically by the sponsor staff.

In addition, the following items will be recorded in the eCRF at scheduled visits:

- Injection site location for the last dose taken prior to visit
- Time of last dose the day before the visit

Adjusting the concizumab dose based on concizumab exposure level

As depicted in Figure 2, the daily concizumab maintenance dose can be decreased to 0.15 mg/kg or increased to 0.25 mg/kg (or the patients can stay on 0.20 mg/kg); this will be based on the concizumab exposure level from the sample taken at visit 4a (arms 2, 3 and 4) or visit 9a.2 (arm 1). The concizumab exposure level will be communicated to the investigator via a report from the central laboratory. Based on that exposure level, the investigator can/must call the patient for an additional dose adjustment visit, i.e., visit 4a.1 (arms 2, 3 and 4) or visit 9a.3 (arm 1) to adjust the dose as outlined in Table 7.

Table 7 Dose adjustment based on concizumab exposure level

Concizumab exposure level	Type of visit	Visit window[a]	Action
>4000 ng/mL	Site or phone visit allowed	2 working days from receipt of the laboratory report on the concizumab exposure level to patient contact	The investigator must decrease the daily maintenance dose to 0.15 mg/kg
200-4000 ng/mL	Phone visit	1 week from receipt of the laboratory report on the concizumab exposure level.	The patient must be informed that no dose adjustment was needed. Also, the investigator must document that the report from the central laboratory was received and that no action was needed.
<200 ng/mL	Site visit required	1 week from receipt of the laboratory report on the concizumab exposure level. Note: this visit cannot be earlier than 6 weeks after the previous dispensing visit 2a (arms 2−4) or 9a (arm 1).	The investigator can increase the daily maintenance dose to 0.25 mg/kg concizumab, if there are no safety concerns based on available laboratory parameters, clinical picture and medical history of the patient.

[a]Visit window for 4a.1/9a.3 must not exceed the timing of visit (weeks) and visit window (days) defined in the flowchart in Section 2

Data on dose adjustment will be collected in the eCRF. No additional dose adjustments may be performed.

9.2.3 Bleeding episodes

At all visits the patients/or patient's caregiver must be asked if all bleeding episodes, both treatment requiring and non-treatment requiring, have been recorded in the eDiary, including treatment of bleeds (if applicable), since the last visit. After visit 2a bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site). Information about bleeding episodes prior to visit 2a (screening period) will be recorded in eCRF.

The investigator must instruct the patient to contact the site before administering breakthrough bleed therapy to ensure breakthrough medication is administered when applicable, taking the treatment guidance in Appendix 11 into consideration. The trial site should be informed of the details of all bleeding episodes, including those that are treated outside of the trial site. All contacts to the patient must be recorded in the patient's medical record. In case a patient cannot get in contact with the site, bleeds must be treated as previously agreed with the investigator.

The following must be recorded for any bleeding episode, including bleeding episodes that do not require treatment with factor products:

- Start date and time
- Stop date and time (see Table 8 for definitions)
- Anatomical location(s)
- Cause (see Table 9 for definitions)
    - spontaneous
    - traumatic
    - post-surgical
- Severity (see Table 10 for definitions)
    - mild/moderate, severe (classification and recording of severe bleeding episodes is the responsibility of the investigator)
    - Severity of bleeding episodes must be evaluated by the investigator according to Table 9 and reported in StudyWorks by site
- Contact between patient and site prior to every bleed treatment not administered at the haemophilia clinic (recorded in StudyWorks by investigator)
- Treatment, if any
    - product administration(s)
        - Type of treatment (brand name and concentration) will be entered in StudyWorks by site
        - Amount of treatment in mL, date and time of injection will be entered by the patient
    - other medicinal treatments related to the bleeding episode (tranexamic acid, pain relieving medication etc.) will be entered in the eCRF by site
- Symptoms during bleeding episodes
    - Pain
    - Pain intensity
    - Blood in urine

- Tingling sensation
- Swelling
- Mouth/Gum bleed
- Warmth
- Loss of movement
- Bruises
- Nose bleed

Only report the bleeding episode as an AE/SAE, (see Section 9.3), if one of the following criteria are fulfilled:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
- The event was life-threatening or resulted in death.

Table 8 Definition of stop of bleed

Stop time is:	When the patient/parent or LAR experiences/observes signs of cessation of the active bleed such as; pain relief, no increase in swelling/limitation of motion and improvement in other objective signs of the bleeding episode.
Stop time is not:	When pain and objective signs of the bleeding episode are completely resolved.

Table 9 Definitions of bleeding episodes (cause of bleed)

Category	Definition
Spontaneous	Not linked to a specific, known action or event
Traumatic	Caused by a specific, known action or event (e.g. injury or exercise)
Post-surgical	Bleeding episodes after surgery from the surgical wound. Bleeding episodes during surgery do not fall under this category

Table 10 Definition of bleeding episode severity

Category	Definition
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeds (joint, muscular bleeds without compartment syndrome), mucosal- or subcutaneous bleeds Mild/moderate bleeds may occur in other anatomical locations
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeds; muscle bleeds with compartment syndrome; bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeds may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes

9.2.4 Sport activity

Patients will be interviewed by the site staff about any sport activity practiced during the previous month. The sports activity rating, according to the list found in Appendix 6, will be recorded in the eCRF on visits according to the flowchart in Section 2.

9.2.5 Physical activity tracker (ActiGraph)

In this trial, data on physical activity will be collected. Historically, people with haemophilia were discouraged from participation in sports, given the perceived risk of sports associated trauma and subsequent haemorrhage and morbidity. Recent studies have since documented physical, medical and psychosocial benefits of exercise and appropriate sports activities (non-collision, non-contact sports) in people with haemophilia. Patients with haemophilia who engage in physical activity experience improvements in proprioception, muscle strength and joint health (stabilisation, range of motion, pain and bleed protection).[12-20]

Physical activity data will be collected using a small wrist worn physical activity tracker from ActiGraph designed for documenting physical activity and approved for clinical research (FDA class II grade). Data will be collected and transferred to Novo Nordisk from the physical activity tracker without site or patient interaction by a small data hub placed at the patient's home. Data can also be transferred at the trial site. The patient and the trial site will be blinded to the physical activity data which are collected. During the course of the trial, the trial site will have access to data on patients wearing compliance and it is recommended that the trial site encourages the patient e.g. via phone and/or email to wear the physical activity tracker, if not done so.

When to use ActiGraph

The ActiGraph activity tracker will only be used in the main part of the trial.

Phase 2 patients
Patients already enrolled in arm 3 from phase 2, NN7415-4255 (explorer 5), before the treatment pause, should not wear the physical activity tracker.

Patients from NN7415-4255 (explorer 5) that were not enrolled in the trial at the time of the treatment pause should wear the tracker as described below.

Remaining patients
The instruction below includes new patients, patients currently in the trial, patients enrolled from NN7415-4322 (explorer 6) and patients from NN7415-4255 (explorer 5) who were not enrolled prior to the treatment pause.

Baseline measurement:

- Patients who already have a baseline measurement either from NN7415-4322 (explorer 6) or this trial (patients who started treatment before the treatment pause) will not have a new baseline measurement taken. Patients who were in screening at the time of the treatment pause and who are re-starting the trial will have a new baseline measurement taken.
- For new patients or patients who do not have a sufficient baseline measurement from NN7415-4322 (explorer 6), the physical activity tracker will be handed out to the patient at screening (visit 1a). The patients will be instructed to wear the tracker for approximately two consecutive

weeks or as much as possible to establish a baseline value. The patient will be instructed to return the activity tracker at visit 2a.

Efficacy Measurement:

- To investigate the effect of concizumab daily PPX on patients physical activity, the patients will be instructed to wear the physical activity tracker for eight consecutive weeks or as much as possible at the end of the patient's main part of the trial (weeks 16−24 for arm 1 and weeks 24−32 for arm 2 and 4 patients).
- Patients who are restarting the trial at visit 2a and already have an ActiGraph measurement (from before the treatment pause) will be asked to repeat the ActiGraph activity measurement at visit 9a.

Table 11 shows an overview of when to use the ActiGraph physical activity tracker in this trial.

Table 11 Physical Activity Tracker handout overview

Treatment arm	Patients trial history	Baseline Measurement	Wear-period in trial
Arm 1	Patients with no or insufficient baseline measurement who will start the trial at visit 1a	Visits 1a – 2a	Visits 7a – 9a
	Patients with baseline measurement who will start the trial at visit 1a	N/A	Visits 7a – 9a
Arms 2 and 4	Patients with no or insufficient baseline measurement who will start the trial at visit 1a	Visits 1a – 2a	Visits 9a – 10a
	Patients with baseline measurement who will start trial at visit 1a	N/A	Visits 9a – 10a
	Patients who will re-start trial at visit 2a	N/A	Visits 9a – 10a
Arm 3	Patients who re-start the trial in arm 3	N/A	N/A

Instructions to patients

The site staff should instruct the patient according to the following recommendations:

- The physical activity tracker should be worn on the non-dominant arm
- The physical activity tracker should be firmly attached to the wrist and the tracker should not be able to slide up and down when the arm moves
- The patient should wear the physical activity tracker as much as possible, preferably 24 hours per day
- The patient should wear the physical activity tracker as much as possible for approximately eight consecutive weeks between relevant visits
- The physical activity tracker should be returned to the site according to the flowchart in Section 2

The measurements from the physical activity tracker are summarised into daily measures representing different aspects of physical activity.

All safety information and/or other issues judged by the investigator to be related to wearing the activity monitor should be reported by the site directly to the manufacturer (support@actigraphcorp.com).

9.2.6 Patient-reported outcome questionnaires

This trial includes eight Patient-Reported Outcome (PRO) questionnaires, see Table 12.

PRO questionnaires will be completed, if available in local language, by the patient (not the caregiver) in accordance the trial flow chart in Section 2. PRO-questionnaires will be completed as ePROs by the patient using the same eDiary, except for Haem-A-QoL (all countries) and PROMIS (some countries) which will be completed on paper.

At visit 2a and visit 9a, patients must complete the PRO questionnaires on the day of the site visit, preferably before any other assessments. For the remaining visits, patients should preferably complete the PRO questionnaires on the day of the visit before any other assessments.

Patients re-entering the trial after the treatment pause should fill out all forms according to the flowchart in Section 2. For these patients, previous treatment will be defined as the treatment they received during the concizumab treatment pause. The site staff must inform the patients about this 'previous treatment' definition prior to completing the questionnaires.

Review of PROs

The review of the PRO´s should be documented in the patient's source documents.

PRO questionnaires reported on paper, the Haem-A-QOL (and PROMIS in some countries) must be reviewed by the investigator to ensure that all AE´s are reported. In addition, the electronically reported Hemo-TEM questionnaires must be reviewed by the investigator to ensure that AE´s concerning injection site reactions are recorded in the eCRF at the investigator's discretion. The electronically questionnaire will be available in the eDiary web portal, StudyWorks. The other electronically reported PRO questionnaires do not have to be reviewed by the investigator.

Table 12 Overview of PRO questionnaires

PRO questionnaire as per flow chart	Name of questionnaire	Concept
SF-36 V2.0 Health Survey	36 Item Short Form Health Survey (SF-36 v2)	Generic health state measure, capturing physical and mental health.
Patient preference questionnaire	Haemophilia Patient Preference Questionnaire (H-PPQ)	Patient's haemophilia treatment preference
PROMIS Short Form Upper Extremity	PROMIS Short Form v. 2.0 Upper Extremity 7a	Physical functioning in upper limbs
PROMIS Numeric Rating Scale - Pain Intensity	PROMIS Numeric Rating Scale v. 1.0 Pain Intensity1a	Average pain intensity experienced
Haemophilia Treatment Experience Measure	Haemophilia Treatment Experience Measure (Hemo-TEM)	Haemophilia specific treatment burden
Haem-A-QOL	Haemophilia Quality of Life Questionnaire for Adults	Haemophilia specific HRQoL, capturing physical, emotional and social components of HRQoL. **For patients ≥ 17 years only (at visit 1a)**
PGI-S on physical functioning	Patient Global Impression of Severity (PGI-S) on physical functioning	Physical functioning level (overall)
PGI-C on physical functioning	Patient Global Impression of Change (PGI-C) on physical functioning	Change in physical functioning level (overall)

9.2.7 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 and Appendix 3, must be conducted in accordance with the flowcharts in Section 2 and Section 2.1 and the laboratory manual. The laboratory will provide instructions on sampling, handling of samples, labelling and shipment of samples.

For the efficacy laboratory paraments (concizumab ELISA, Thrombin generation, Free TFPI) a PK/PD profile will be made at visit 2a and visit 9a, for all patients receiving concizumab at visit 2a (patients in arms 2, 3 and 4). See PK/PD sampling flowchart in Section 2.1 for further details.

Concizumab-ELISA

Concizumab-ELISA PK profile and trough will be performed as specified in the flowchart see Sections 2 and 2.1. Samples for assessment of concizumab trough values will be collected pre-dose when patients are assigned to concizumab prophylaxis, i.e. patients in arm 1 will only have baseline samples taken in the main part of the trial. Patients must be instructed to take their daily dose of concizumab after the initial blood sampling have taken place when visiting the site. See Section 9.5 for further details.

Validation of the assay followed current bioanalytical guidelines for method validation. The sample taken at visit 4a/9a.2, to determine whether the dose should be adjusted, will be communicated directly to the investigator via a report from the central laboratory (see Section 9.2.2). All other

results will be reported to the sites and in a bioanalytical report after the confirmatory analyses cut-off and at the end of the extension part.

Thrombin generation

The Thrombin Generation Assay (TGA) will be performed as specified in the flowcharts in Sections 2 and 2.1.

In this assay set-up, thrombin generation is initiated by low-dose tissue factor that is combined with phospholipid. The result is obtained by comparison to a constant known thrombin activity in a parallel non- tissue factor-initiated sample. The assay has been validated fit-for-purpose.

Thrombin generation results will be reported at the confirmatory analyses cut-off and at the end of the extension part.

Free TFPI

Free TFPI will be measured as specified in the flowcharts in Sections 2 and 2.1.

Free TFPI measures TFPI not bound to concizumab. This enzyme-linked immunosorbent assay (ELISA) test will be sampled for at all assessment visits, including 24-hour PK visit. For details please see pharmacokinetics Section 9.5.

The assay is commercially available from [redacted] ([redacted]).

Free TFPI results will be reported at the confirmatory analyses cut-off of the trial and at the end of the extension part.

9.3 Adverse events

The definitions of AEs and SAEs can be found in Appendix 5 for the IMP and on demand treatment, and in Appendix 8 for the investigational medical device.

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

9.3.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the first trial-related activity after obtaining informed consent and until end of trial visit, at the time points specified in the flowchart.

All SAEs will be recorded and reported to Novo Nordisk or designee within 24 hours, as indicated in Appendix 5 for the IMP and on demand treatment, and in Appendix 8 for the investigational medical device. The investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

Investigators are not obligated to actively seek for AE or SAE in former trial patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discontinued from/completed the trial, and the investigator considers the event to be possibly/probably related to the investigational trial product or trial participation, the investigator must promptly notify Novo Nordisk.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 5 for the IMP and on demand treatment, and in Appendix 8 for the investigational medical device.

Timelines for reporting of AEs, including AESIs are listed in Figure 4.

Some AEs require additional data collection via a specific event form. This includes medication errors observed during the trial. The relevant specific events are listed in Table 13 and the reporting timelines in Figure 4.

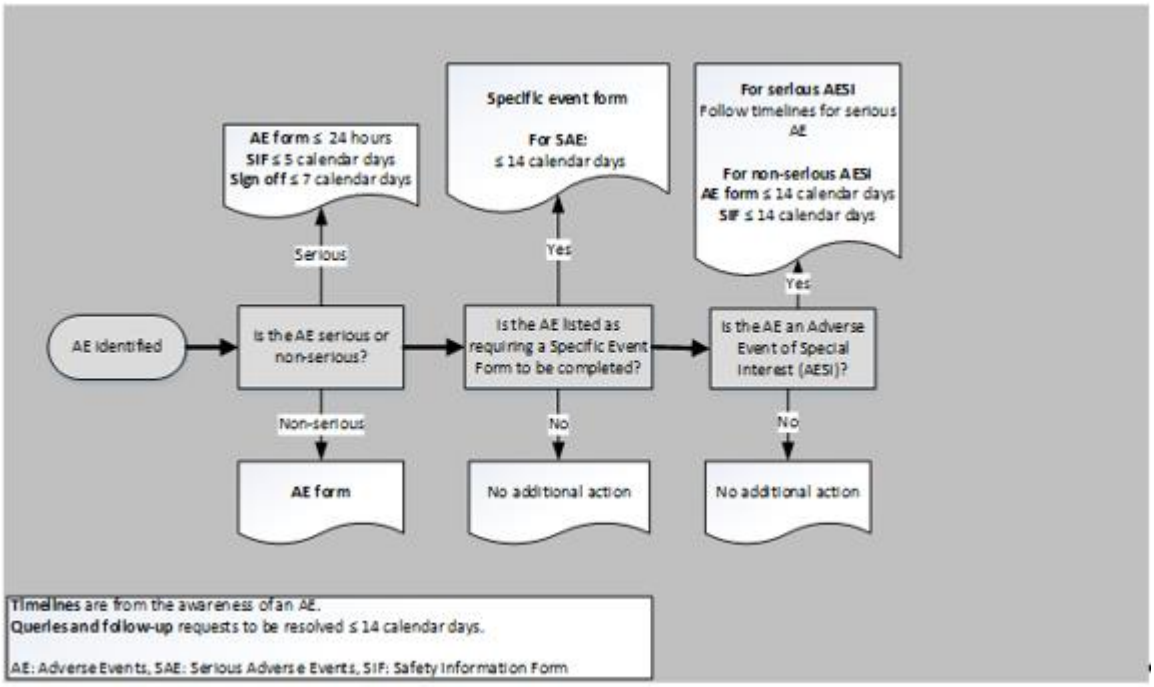


Figure 4 Decision tree for determining the event type and the respective forms to complete with associated timelines

Table 13 AEs requiring additional data collection (via specific event form) and AESIs[a]

Event type	AE requiring additional event form	AESI
Thromboembolic events		X
Hypersensitivity reaction	X	
Injection site reaction	X	
Medication error	X	

[a]Refer to Section 9.3.6 for reporting details

9.3.1.1 Adverse event of special interest

The AESIs for this trial are thromboembolic events as listed in Table 13 and must be reported according to Figure 4.

In this trial, the following AEs fulfil the AESI criteria:

- Thromboembolic events including but not limited to,
  - disseminated intravascular coagulation (DIC)
  - thrombotic microangiopathy (TMA)

- myocardial infarction
- pulmonary embolism
- stroke
- deep vein thrombosis
- other clinically significant thromboembolic events and peripheral artery occlusion

The AESIs must be reported on an AE form and a safety information form.

The definitions and further information on additional testing on the AESIs and AE requiring additional data collection can be found in Appendix 5.

9.3.2 Method of detecting AEs and SAEs

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about events.

9.3.3 Follow-up on AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AESIs will be followed until resolution, stabilization, or if the event is otherwise explained (e.g. chronic condition) or the patient is lost to follow-up as defined in Section 8.3. Further information on follow-up procedures is given in Appendix 5 for the IMP and on demand treatment, and in Appendix 8 for the investigational medical device.

9.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial product under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial product under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Novo Nordisk policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs), from Novo Nordisk will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Reporting requirement for safety information related to the physical activity tracker

All safety information and/or other issues judged by the investigator to be related to wearing the activity monitor should be reported by the site directly to the manufacturer

(support@actigraphcorp.com). If the patient is on a Novo Nordisk product within the haemophilia indication, the safety information must also be reported to Novo Nordisk.

9.3.6 Disease-related events and/or disease-related outcomes and other information not qualifying as an AE or SAE

The following Disease-Related Events (DREs) are common in patients with haemophilia and can be serious/life-threatening:

- Bleeding episodes

Bleeding episodes in relation to AE/SAEs

Because bleeding episodes are associated with the disease under study, they will not be reported according to the standard process for reporting of AEs/SAEs, even though the bleeding episode (event) may meet the definition of an AE/SAE unless they meet the criteria as specified below.

Note: The event must be recorded and reported as an AE/SAE if one of the following applies:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product.
- The event was life-threatening or resulted in death.

9.3.7 Technical complaints

The investigator must assess whether a technical complaint is related to an AE.

The definitions, reporting process and timelines for reporting for technical complaints can be found in Appendix 7.

9.3.8 Treatment of overdose

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAE and laboratory abnormalities and symptomatic medical treatment according to the clinical condition should be applied as relevant. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the patient.

The overdose must be reported as medication error. Refer to Section 9.3.1 for further details.

For more information on overdose, also consult the current version of the concizumab IB.

9.3.9 Trial stopping rules

If one of the below mentioned criteria is fulfilled, the Novo Nordisk Safety Committee will urgently evaluate all available data and decide on further actions:

- Significant thromboembolic event
- Event of DIC
- Event of TMA
- Death of trial patient which may be related to the trial product

If enrolment is put on temporary hold, relevant data will be submitted to regulatory authorities, according to local regulations, to support restart of enrolment.

9.4 Safety assessments

Planned timepoints for all safety assessments are provided in the flowchart Section 2.

9.4.1 Concomitant illness and Medical History

A **concomitant illness** is any illness that is present at the start of the trial (i.e. at the first visit) or found as a result of a screening procedure or other trial procedures performed before exposure to trial product.

Medical history is a medical event that the patient has experienced in the past.

In case of an abnormal and clinically significant finding, the investigator must record the finding on the Medical History/Concomitant Illness form if it is present at screening. Any new finding fulfilling the AE definition (see Appendix 5) during the trial and any clinically significant worsening from baseline (visit 1/1a) must be reported as an AE (see Section 9.3).

Recording of haemophilia arthropathy in medical history must be performed.

9.4.2 Physical examinations

The physical examination includes the following:

- General appearance
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Genito-Urinary system
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

Investigators should pay special attention to clinical signs related to previous serious illnesses.

The investigator must evaluate the results of the examination and record the outcome in the eCRF as:

- normal or abnormal.
- if abnormal the investigator must:
    - specify the abnormality
    - record if the result is clinically significant (Yes/No)
    - if observed before or at Screening: record as Medical History (Section 9.4)
    - if observed after screening: report a AE/SAE (Section 9.3).

9.4.3 Body measurements

Body measurements will be assessed according to the flowchart in Section 2.

- Height (cm), at screening
- Body Weight (kg), with 1 decimal at all visits

The body weight assessed at each visit will be used for determination of the concizumab dose to be administered until next visit.

Measurements will be reported in the eCRF.

9.4.4 Vital signs

- Oral, Rectal, Axillary, Ear or Skin temperature (°C), pulse rate (beats/min), respiratory rate, as well as diastolic and systolic blood pressure (mmHg) will be assessed as specified in the flowchart in Section 2.
- Blood pressure and pulse measurements or vital signs assessment should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g. television, cell phones).
- Blood pressure at screening will consist of 3 diastolic and systolic blood pressure measurements with intervals of at least 1 minute. All three readings must be entered in the eCRF and the average of the 3 blood pressure readings will be recorded on or calculated in the eCRF. At the subsequent visits, the blood pressure should only be measured once.
- Blood pressure and pulse measurements will be assessed in sitting position, if applicable with a completely automated device. Manual techniques will be used only if an automated device is not available.

The investigator must evaluate the results and classify the outcome as either:
- Normal or abnormal
- If abnormal the investigator must:
    - Specify the abnormality
    - Record if the result is clinically significant (Yes/No)
    - If observed before or at screening: record as concomitant illness/Medical History (Section 9.4.1)
    - If observed after screening: report an AE/SAE (Section 9.3)

Measurements will be reported in the eCRF.

9.4.5 Electrocardiogram (ECG)

For patients in arms 1, 2 and 4, an ECG must be taken according to flowchart 2. For patients in arm 3, the data collected in phase 2 will be reused.

The investigator must evaluate the ECG (standard 12 lead) at screening and classify the outcome as either:
- Normal or abnormal
- If abnormal the investigator must:
    - Specify the abnormality

- Record if the result is clinically significant? (Yes/No)
- If observed before or at Screening: record as concomitant illness/Medical History (Section 9.4.1)
- If observed after screening: report and AE/SAE (Section 9.3)

The ECG results must be dated and signed by the investigator to verify that the data have been reviewed. Outcome will be reported in the eCRF.

9.4.6 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 and Appendix 3, must be conducted in accordance with the laboratory manual and the flowchart in Section 2.The laboratory will provide instructions on sampling, handling of samples, labelling and shipment of samples.

For the clinical safety laboratory assessments: Coagulation parameters, Haematology, Biochemistry and Urinalysis the investigator must evaluate the results and classify the outcome as either:

- Normal or abnormal
- If abnormal the investigator must:
  - Specify the abnormality
  - Record if the result is clinically significant (Yes/No)
  - If observed before or at screening: record as concomitant illness/Medical History (Section 9.4.1)
  - If observed after screening: report an AE/SAE (Appendix 5)

For clinical safety laboratory assessments FVIII/FIX activity and FVIII/FIX inhibitors investigator will only evaluate the results according to inclusion/exclusion criteria.

Above mentioned measurements, except urinalysis, will be reported to the sites by the central laboratory on an ongoing basis.

If deemed relevant as per the investigator's discretion, Novo Nordisk may perform blood analyses for COVID-19 antibodies. These analyses will be performed at a special laboratory and will only be performed if back-up material from other samples are available. No additional blood sampling will be performed. The results from such tests will be reported directly to site(s) via Novo Nordisk.

Concizumab ELISA (PK ELISA and ELISA IVD)

Concizumab will be quantified using a validated enzyme-linked immunosorbent assay (ELISA). Recombinant human TFPI will be used to capture concizumab. A colorimetric detection signal is obtained by the enzymatic reaction of horseradish peroxidase labelled anti-human IgG4 specific antibodies with the chromogenic substrate TMB (3,3′,5,5′-tetramethylbenzidine). The amount of concizumab present in the calibration, quality control and test samples correlate with the obtained signal strength.

Validation of the assay has been performed following current bioanalytical guidelines for method validation. Additional assay validation of the concizumab ELISA IVD, specifically with regards to assay precision, has been performed to support the Investigational Device Exemption.

Plasma concizumab concentrations will be measured pre-dosing (trough) as specified in the flowchart in Section 22. Samples for assessment of concizumab trough values will be collected pre-dose to concizumab prophylaxis. Patients must be instructed to take their daily dose of concizumab after the blood sampling have taken place when visiting the site.

The sample taken at visit 4a (arm 2, 3, 4) and visit 9a.2 (arm 1) is to determine whether the dose should be adjusted. The sample is analysed using the concizumab ELISA IVD. These results (in ng/mL) will be communicated directly to the investigator by the central laboratory (see Section 9.2.2). All other samples will be analysed using the concizumab PK ELISA. The ELISA data will be reported in a bioanalytical report after the end of the trial at the latest.

Safety laboratory data evaluation

In the event of confirmed central laboratory test results including one or more of below:

- platelets <LLN (central lab)
- fibrinogen < LLN (central lab)
- any other laboratory parameters of concern to the investigator

It is recommended that the investigator considers clinical evaluation of the patient and determine if further medical action is needed.

Total TFPI

Total TFPI ELISA sampling will be performed according to the flowchart in Section 2.

The total TFPI level (free TFPI and concizumab bound TFPI) will be included as an exploratory biomarker assessment. The assay is a classic sandwich ELISA, where TFPI is captured via a polyclonal anti-TFPI antibody. This antibody binds to a region distant to the binding site of concizumab hence both, free TFPI and concizumab bound TFPI will be captured. Detection is done using a monoclonal antibody targeting TFPI. This antibody will not bind to the concizumab epitope of TFPI. Results will be reported in ng/mL TFPI.

9.4.7 Immunogenicity assessments

Samples for the determination of anti-drug antibodies will be collected according to the flowchart in Section 2. All patients will have samples drawn at V1/V1a, but only patients randomised/allocated to concizumab treatment (arms 2, 3 and 4) will have samples drawn at the remaining indicated timepoints in the main part of the trial. In the extension part of the trial, samples must be drawn for all patients (arms 1−4). Sampling should always take place prior to administration of concizumab. In case of suspected hypersensitivity reaction requiring systemic treatment, additional blood samples are to be collected; refer to Section 9.4.8.

Assessment of binding antibodies against concizumab (anti-drug antibodies (ADA) will be performed at specialised laboratories whereas assessment of neutralising antibodies will be performed at Novo Nordisk.

Analysis for ADA will be done with a bridging ECL assay (binding ADA assay) using labelled concizumab for antibody capture and detection. If a sample is confirmed positive in the confirmatory assay, the sample is considered positive for binding antibodies. Confirmed positive

samples will be characterised in a specificity assay for binding to IgG backbone or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a neutralising ADA assay. All antibody assays are validated according to international guidelines and recommendations.

The following data will be available:

- Anti-concizumab antibodies
- Anti-concizumab antibody titres
- Anti-concizumab binding antibodies cross-reacting with IgG4 backbone or S241P mutation
- Anti-concizumab neutralising antibodies

The samples will be analysed and reported to sites at the confirmatory analyses cut-off and at end of extension part (end of trial). A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

Patients positive for binding antibodies at end of follow-up may be followed outside this protocol.

9.4.8 Hypersensitivity reaction

If suspicion of a hypersensitivity reaction occurs, patients should be instructed to contact the site staff as soon as possible for further guidance, see Appendix 5.

In the event of a severe local and/or systemic hypersensitivity reaction possibly or probably related to trial product, blood sampling for assessment of anti-concizumab IgE antibodies as well as anti-concizumab antibodies should be conducted in relation to the reaction and no later than 1-2 weeks after the event. Additional testing may be performed locally if deemed relevant (e.g. anti-Host Cell Proteins (HCP) antibodies).

In the event of a severe systemic hypersensitivity reaction to trial product, it is recommended also to test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary 1-2 weeks after the immediate severe hypersensitivity reaction due to individual variation in tryptase baseline concentration.

A follow up visit should be conducted 3-4 weeks post the allergic reaction with repeated blood sampling for assessment of anti-concizumab IgE antibodies as well as anti-concizumab antibodies and if possible also at a visit 3 month after the hypersensitivity reaction for assessing the persistence of the IgE response. Tryptase measurements are not required at the follow up visits.

Additionally, basophil activation testing may be performed if deemed relevant. This can be performed using existing samples and/or by analysing the patient's basophil cells from an additional blood sample taken 3-4 weeks and no later than 2 months after the event. Similarly, prick tests and/or intra-dermal tests may be performed if relevant using trial product or components of trial product. Complement may be measured in case of suspicion of immune complex mediated hypersensitivity reactions.

The following additional tests can be performed locally or at special laboratories if deemed relevant:

- Anti-concizumab IgE antibodies

- Anti-concizumab antibodies (additional to scheduled time points)
- Anti-Host Cell Proteins (HCP) antibodies
- Anti-HCP IgE antibodies
- Basophil activation results
- Prick test/intra-dermal test
- Complement test results
- Tryptase (total and/or mature tryptase)

In case laboratory samples for severe hypersensitivity reactions are analysed at special laboratories, the results from the analysis will be reported directly to site(s) via Novo Nordisk.

Hypersensitivity reactions including test results should be reported as an AE requiring additional data collection, see Section 9.3.1

9.4.9 Injection site reactions

Injection site reactions must be recorded on the AE form and the injection site reaction form. Signs and symptoms of injection site reactions include but are not limited to pain, numbness, itching, burning, redness, induration, swelling, dimpling, macula, haematoma and bleeding.

9.5 Pharmacokinetics

Concizumab will be quantified using a validated ELISA assay. Recombinant human TFPI will be used to capture concizumab. A colorimetric detection signal is obtained by the enzymatic reaction of horseradish peroxidase labelled anti-human IgG4 specific antibodies with the chromogenic substrate TMB (3,3´,5,5´-tetramethylbenzidine). The amount of anti-TFPI present in the calibration, quality control and test samples correlate with the obtained signal strength.

Validation of the assay follows current guidelines for bioanalytical method validation. Bioanalytical data will be reported in a bioanalytical report.

The concizumab ELISA will be used to evaluate exposure and pharmacokinetics of concizumab.

For patients dosed with concizumab from visit 2a (patients in arms 2, 3 and 4), two 24-hour PK/PD-sessions will be conducted at visits 2a and 9a. The concizumab dose will be administered in the abdomen and blood samples will be drawn pre-dosing, 3, 6, 9 and 24 hours after dosing. Care must be taken to ensure the 24-hour sample is drawn before the next daily dose of concizumab is administered. At the day of visit 9a patients should not dose themselves at home; the dose will be administered at site followed by blood sampling. The dose should be taken at site in the abdomen and care must be taken to ensure the 24-hour sample is drawn before the next daily dose of concizumab is given.

For patients who had a 24-hour PK profile measured at visit 2 prior to the treatment pause, a new 24-hour PK profile at visit 2a should not be conducted after restart of the trial. For these patients, only pre-dose and 24-hour post-dose samples should be taken at visit 2a. Care must be taken to ensure the 24-hour sample is drawn before the next daily dose of concizumab is administered.

Following items must be recorded in the eCRF:

- Time of lab samples taken
- Time of concizumab dose
- Injection site location

See Section 2.1 for the specific timepoints for the PK analysis.

In addition to the two PK/PD sessions, pre-dose concizumab levels (C_{trough}) will be measured throughout the concizumab treatment period. These blood samples must be drawn prior to trial product administration as specified in the flowchart in Section 2. If the patient has taken the daily dose of concizumab before collection of the concizumab ELISA sample, then visit 4a (arm 2, 3, 4) or visit 9a.2 (arm 1) should be rescheduled.

9.6 Pharmacodynamics

Pharmacodynamics assessments Thrombin Generation, and Free TFPI are described in Section 9.2.7. For patients dosed with concizumab from visit 2a (patients in arms 2, 3 and 4), two 24-hour PK/PD-sessions will be conducted at visits 2a and 9a; see Section 9.5 for further details.

9.7 Human Biological Specimen for storage

9.7.1 Genetics

Whole blood samples for DNA genotyping will be collected according to the flowchart in Section 2 for future analysis and long-term storage from patients who have consented to participate in this part of the trial. Participation in the genetic research is optional. Patients who do not wish to participate in the genetic research may still participate in the trial.

In the event of sample handling failure, a replacement genetic blood sample may be requested from the patient.

Genetic samples will not be evaluated by the investigator.

Patients who had a sample taken at visit 1 before the treatment pause should not have that sample re-taken upon trial restart.

Please refer to Appendix 9 for further information regarding the genetic research. Details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual.

9.7.2 Biomarkers

Serum and plasma samples will be collected according to the flowchart in Section 2 for future exploratory laboratory analysis and long-term storage from patients where additional consent has been obtained. Patients who do not wish to participate in this research may still participate in the trial.

Biomarker samples will not be evaluated by the investigator.

Patients who had a sample taken at visit 1 before the treatment pause should not have that sample re-taken upon trial restart.

Please refer to Appendix 9 for further information regarding the biomarker research and details on processes for collection, shipment and destruction of these samples can be found in the laboratory manual.

9.8 Health economics

A set of eDiary screens assembled in a monthly diary will be made available to the patient every 30 days. The screens are designed to collect:

- Number of school or workdays missed
- Number of days where a patient used an aid to move around
- How many days in-home professional nursing was needed.

The monthly diary will be completed by the patient in the eDiary.

9.9 Surgery

Minor surgical procedures are allowed during the trial (for surgery definitions see Table 14). Planned major surgery is not allowed.

Haemophilia A and haemophilia B patients undergoing minor surgical procedures should be managed in accordance with local standard of care. Coagulation factor replacement therapy using either regular or extended half-life products are allowed and should be used in accordance with local label.

Local/topical use of antifibrinolytics e.g. tranexamic acid is allowed. Use of single systemic doses is allowed after careful benefit-risk evaluation.

During the perioperative period patients should continue daily concizumab prophylaxis.

Table 14 Surgery definitions

Category	Definition	Examples
Major surgery:	Any invasive operative procedure that requires ≥3 doses of replacement therapy and/or where any one or more of the following occur	A body cavity is entered
		A mesenchyme barrier (e.g. pleura, peritoneum or dura mater) is crossed
		A fascia plane is opened
		An organ is removed
		Normal anatomy is operatively altered
Minor surgery:	Any invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated	Implanting of central venous access devices (ports, central venous catheter, pumps and other central venous access devices) in subcutaneous tissue
		Skin biopsies
		Simple dental procedures
		Ear tube/drain insertion
		Circumcision
		Port insertion in paediatric patients

For surgery the following should be recorded in the eCRF:

- Type of Surgery
- Data and stop time and dose of preventive treatment (haemostatic medication).
- Other treatments during surgery (concomitant medication)
- Indication of surgery
- Anatomical Location of surgery
- Date of surgery
- Start and stop time of surgery

In the instance of acute major surgery, it is recommended to pause concizumab at the discretion of the investigator.

10 Statistical considerations

10.1 Sample size determination

The estimand for the primary objectives will for patients in arms 1 and 2 be addressed based on the Full Analysis Set (FAS; see Section 10.2) using negative binomial regression.

The sample size calculation has been determined based on the estimand for the primary and confirmatory secondary objectives. In the below calculations it is assumed that the treatment duration is 24 weeks for patients in arms 1 and 32 weeks for patients in arm 2. For the comparison of previous PPX to concizumab PPX in arm 4 it is assumed that the treatment duration is 38 weeks (estimated from NN7415-4322 (explorer 6)) on the previous PPX regimen and 24 weeks on the concizumab maintenance dose.

When evaluating the power of the negative binomial analysis with exposure time as offset and treatment as factor, annual bleeding rates of 24 and 18 are assumed for the no-prophylaxis HA patients, and the no-prophylaxis HB patients, respectively. An ABR of 3-5 is expected for concizumab prophylaxis. Assuming further a yearly over-dispersion of 13, the power for concluding superiority of concizumab prophylaxis versus no-prophylaxis for HA patients becomes at least 82% with 21 patients (14 in the concizumab arm and 7 in the comparator arm). The power for concluding superiority of concizumab prophylaxis versus no prophylaxis for HB patients becomes at least 79% with 33 patients (22 in the concizumab arm and 11 in the comparator arm). When evaluating the power of the negative binomial analysis (with exposure time as offset and treatment as factor and incorporating within-subject repeated measurements using an unstructured covariance matrix) with respect to showing non-inferiority of concizumab prophylaxis vs previous prophylaxis in a within-patient comparison the assumptions are: Concizumab ABR of 3−5, an ABR for previous prophylaxis of 4, a noninferiority margin of 2.0 on the relative scale, a sample size of 30 and a yearly over-dispersion of 13, and a patient's frailty for experiencing bleeds in the first period (on previous PPX) and the second period (on concizumab PPX) is fully correlated. With these assumptions the power will be at least 79% to show non-inferiority for each haemophilia subtype.

ABR assumptions

Based on the available studies and sources, a representative mean ABR on on-demand treatment for the severe haemophilia A patients of 24 bleeds/year and for the haemophilia B patients of 18 bleeds/year is considered appropriate (see Table 15).

Table 15 Annualised bleeding rate recorded in prior Novo Nordisk studies conducted in different haemophilia subpopulations treated on-demand

Regimen	Population	Study	N	ABR
On demand	HA	NN7088-3859[a]	12	32.35
	HA	NN7008-3568[b]	19	24
	HB	NN7999-3747[c]	13	17.6

Note: The ABR is recorded in prior Novo Nordisk studies conducted in different haemophilia subpopulations.
[a]NN7088-3859 CTR extension 1, EOT 14.2.78; [b]NN7008-3568 CTR, EOT 14.2.65; [c]NN7999-3747 CTR, EOT 14.2.45

It is the expectation to show an ABR for concizumab prophylaxis of approximately 3-5 bleeds/year.

Over-dispersion assumptions

A yearly over-dispersion of 13 is deemed realistic based on experience from previous trials.

Power

Primary endpoint

Assuming ABRs of 24 and 18 for the no-prophylaxis HA patients, and the no-prophylaxis HB patients, respectively, an ABR between 3 and 7 for the concizumab arm (arm 2) for both HA and HB patients, a yearly over dispersion varying between 11 and 15 and performing 10,000 simulations of each group will produce different scenarios of power in superiority tabulated in Table 16 below.

Table 16 Power for superiority for patients with HA and HB respectively

Power (HA[a]/HB[b])	Yearly over-dispersion		
ABR concizumab	11	13	15
3	94%/95%	91%/92%	88%/89%
4	92%/91%	87%/86%	83%/83%
5	87%/85%	82%/79%	78%/74%
6	83%/77%	75%/70%	70%/64%
7	76%/68%	70%/62%	66%/56%

[a]For HA, power is calculated with 21 patients randomised 2:1 assuming an ABR for the on-demand treatment of 24
[b]For HB, power is calculated with 33 patients randomised 2:1 assuming an ABR for the on-demand treatment of 18

When evaluating the power of the negative binomial analysis with exposure time as offset and treatment regimen as factor, annual bleeding rates of 24 and 3−5 are assumed for the haemophilia A patient (or 18 and 3-5 for the haemophilia B patient) on no prophylaxis and on concizumab prophylaxis, respectively. Assuming further a yearly over-dispersion of 13, the power for concluding superiority of concizumab prophylaxis becomes at least 82% with 14 patients in the concizumab and 7 patients in the comparator arm for haemophilia A (or at least 79% with 22 patients in the concizumab arm and 11 patients in the comparator arm for haemophilia B; see Table 16).

Confirmatory secondary endpoint

When evaluating the negative binomial analysis (with exposure time as offset, treatment as factor and incorporating within-subject repeated measurements using of an unstructured covariance structure) with respect to showing non-inferiority of concizumab prophylaxis vs previous prophylaxis in a within-patient comparison, the power of showing non-inferiority is at least 79% with a concizumab ABR of 3-5, an ABR for previous prophylaxis of 4, a non-inferiority margin of 2.0 on the relative scale, a sample size of 30, a yearly over-dispersion of 13 and assuming a patient's frailty for experiencing bleeds in the first period (on previous PPX) and the second period (on concizumab PPX) is fully correlated (i.e. a correlation of 1). Other scenarios with different assumptions are displayed in Table 17 below including scenarios where the assumption of a correlation of 1 is lowered to 0.8.

Table 17 Power to demonstrate non-inferiority separately for patients with HA or HB

			Non-inferiority margin on relative scale		
Correlation[a]	**ABR on concizumab**	**ABR on previous prophylaxis**	1.5	1.8	2.0
1.0	3	2	6%	21%	33%
		4	95%	99%	>99%
		6	>99%	>99%	>99%
	5	2	~0%	~0%	~0%
		4	25%	61%	79%
		6	97%	>99%	>99%
	7	2	~0%	~0%	~0%
		4	0%	6%	17%
		6	50%	87%	95%
0.8	3	2	5%	12%	18%
		4	66%	83%	89%
		6	96%	99%	>99%
	5	2	~0%	~0%	~0%
		4	14%	33%	46%
		6	71%	89%	95%
	7	2	~0%	~0%	~0%
		4	~0%	5%	11%
		6	26%	55%	71%

[a] The spearman correlation between a patient's frailty for experiencing bleeds in the first and the second treatment period.

Combined power

Assuming that the confirmatory secondary endpoint is independent of the primary endpoint the combined power becomes at least 82%*79% = 65% for haemophilia A patients and at least 62% for haemophilia B patients.

Expected frequency and pattern of missing data

Since treatment options for haemophilia patients are limited and there is a general tendency to continue with the treatment regimen, the completion rate for this study is expected to be high with less than 15 % withdrawing or discontinuing treatment prematurely. The study will randomise 24 patients with haemophilia A and 36 with haemophilia B to account for potential withdrawals in particular in relation to other endpoints in this trial.

10.2 Definition of analysis sets

The following analysis sets are defined:

- Safety analysis set (SAS): All patients exposed to concizumab PPX or randomised to OnD.

- Full analysis set (FAS): All patients randomised to the new concizumab PPX dosing regimen or OnD after the treatment pause or allocated to arm 3 or 4 with the new concizumab PPX dosing regimen.

For both analysis sets, the specific treatment arms refer to the treatment arms the patients enter after restart.

10.3 Statistical analyses

The statistical analysis plan (SAP) was updated prior to the first patient restarting the trial to reflect the changes made in protocol amendment #4, and includes a more technical and detailed elaboration of the statistical analyses.

As described in Section 5, several evaluations will be made prior to the end of this trial. This section will describe the analyses of the primary and the secondary confirmatory endpoints at the confirmatory analyses cut-off focusing on the randomised arms as well the within-subject comparison in arm 4 of the confirmatory secondary endpoints.

The bleed rate is defined as the number of treated bleeds over the respective observation periods. As a general rule, a treated bleed is defined as any bleed where a factor-containing product is reported between the start and stop time of a bleed. Multiple bleeding locations occurring 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) starting within 72 hours after stopping treatment of a previous treated bleeding episode (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 bleeding episode occurs in the same location more than 72 hours after stopping treatment of a previous bleeding episode or re-bleed in the same location, the bleed is defined as a new bleeding episode.

The Type-I error for testing the two confirmatory hypotheses related to bleeds will be preserved by using hierarchical testing. The tests will be evaluated separately for the two patient populations, i) patients with haemophilia A and ii) patients with haemophilia B. The conclusion from the trial will be drawn for each of the two populations separately, i.e. the conclusion from one population does not influence the conclusion from the other population. Correction for multiplicity between the two populations is therefore not considered relevant. The type 1 error will be controlled for the two hypothesis within one population, as described below.

The overall significance level is 5%. If a hypothesis is confirmed, the significance level will be reallocated to the next hypothesis in the hierarchy and then that hypothesis will be tested at the 5% significance level. This process will be repeated until no further hypotheses can be confirmed.

The primary endpoint is analysed using negative binomial regression. Superiority of concizumab prophylaxis over no prophylaxis in the patient population will be concluded if the two-sided 95% confidence interval of the treatment ratio is below 1.

If superiority is concluded for the primary endpoint the confirmatory secondary hypothesis will be tested with a significant level of 5%. The confirmatory secondary hypothesis aims at comparing the

bleeding rate during concizumab treatment with the bleeding rate on the patients' previous prophylaxis.

10.3.1 Primary endpoint

The primary endpoint is defined in Section 4.3.1.

The estimand for the primary endpoint for patients with haemophilia A will be addressed comparing the number of treated bleeds between the randomised arms (arm 1 and 2) based on the FAS including information obtained from the restart of the trial to when the patient permanently discontinues treatment or completes the confirmatory analyses cut-off using negative binomial regression, where the patients' number of bleeds will be analysed with treatment and bleeding frequency (<9, ≥ 9 bleeding episodes during the past 24 weeks prior to screening) as factors, and logarithm of exposure time as offset. The estimated ratio of ABR between the treatment regimens (concizumab prophylaxis and no prophylaxis) with corresponding 95% confidence interval, p-value for the test for superiority and also estimates of the actual ABRs with corresponding 95% confidence intervals in each treatment arm will be presented. The primary analysis will also account for the different intercurrent events as described under the estimand.

The analysis of the primary endpoint for patients with haemophilia B will be done in a similar way as described for haemophilia A patients.

Sensitivity analysis

Several sensitivity analyses will be implemented by haemophilia type to further investigate the different assumptions that goes into the above estimand and statistical methodology. Note that some of these sensitivity analyses are implemented by altering the strategy for a given intercurrent event and hence addresses a slightly different estimand.

- In order to investigate the missing at random (MAR) assumption, a tipping point analysis will be implemented where patients that permanently discontinue treatment before 24 weeks for arm 1 or before 32 for arm 2 will be modelled with an increasing bleeding rate until the conclusion of superiority is changed. Those patients that permanently discontinues treatment before 24 weeks for arm 1 or before 32 weeks for arm 2 will have the offset period fixed at 24 or 32 weeks, respectively. Any patient that permanently discontinues treatment before the confirmatory analyses cut-off but after 24 weeks for arm 1 or after 32 weeks for arm 2 will not be considered to have missing data for the purpose of this tipping point analysis.
- In order to investigate the effect of excluding observed data a model where all intercurrent events will be handled by use of the treatment policy strategy will be fitted. The model will be similar to the primary analysis but where the patient's bleeds and observation time collected post permanent treatment discontinuation (the first intercurrent event) and collected during periods with use of factor products not related to treatment of a bleed (the third intercurrent event) will be used. This analysis will be performed using the FAS.
- In order to not rely on the model assumptions of the primary analysis a non-parametric Van Elteren test to compare the mean ABR in the two randomised groups will be done. This is done using the FAS including information obtained from the restart of the trial to when the patient permanently discontinues treatment or completes the confirmatory analyses cut-off.

- In order to investigate the impact of the initial randomisation prior to the clinical pause, the primary analyses will be re-run where patients from the initial randomisation are included. For patients randomised to on-demand all information from the point of the initial randomisation to the time of restart will be included. For patients randomised to the initial concizumab regimen all information collected from the time of randomisation until treatment discontinuation will be included.

Further sensitivity analyses can be specified in the SAP.

10.3.2 Secondary endpoints

10.3.2.1 Confirmatory secondary endpoints

The confirmatory secondary endpoint for haemophilia A patients is defined in Section 4.3.2.1.

Only the subset of patients from the FAS that entered the maintenance period in arm 4 and who were on a stable PPX regimen for at least 24 weeks in NN7415-4322 (explorer 6) will contribute to the analysis. The analysis will be done using a negative binomial regression, where the patients' number of bleeds will be analysed with exposure time as offset, treatment and bleeding frequency (<9, ≥9 bleeding episodes during the past 24 weeks prior to screening) as factors and within-subject repeated measurements will be incorporated using of an unstructured covariance structure. The estimated ratio of ABR between the treatment regimens (concizumab prophylaxis versus previous prophylaxis) with corresponding 95% confidence interval and also estimates of the actual ABRs with corresponding 95% confidence intervals in each treatment period will be presented. Non-inferiority will be confirmed if the upper limit of 95% confidence interval is below 2.0.

A similar approach will be used for haemophilia B patients.

Sensitivity analyses

The below sensitivity analyses will be implemented by haemophilia type to further investigate the underlying assumptions of the above statistical analyses. Note that as different strategies are implemented to address some of the intercurrent events, this analysis addresses a slightly different estimand:

- In order to investigate the missing at random (MAR) assumption, a tipping point analysis will be implemented where patients that permanently discontinue concizumab treatment after the dose is decreased, increased or confirmed and before 24 weeks of treatment have been observed will be modelled with an increasing bleeding rate until the conclusion of non-inferiority is changed. For those patients that permanently discontinues treatment before 24 weeks on maintenance dose, the offset period will be fixed at 24 weeks. For any patient that permanently discontinues treatment before the confirmatory analyses cut-off but after 24 weeks on maintenance dose will not be considered to have missing data for the purpose of this tipping point analysis.
- In order to investigate the effect of excluding observed data a model where all intercurrent events will be handled by use of the treatment policy strategy will be fitted. The model will be similar to the confirmatory secondary analysis but where the patient's bleeds and observation time collected post permanent treatment discontinuation (the first intercurrent event) and

collected during periods with use of factor products not related to treatment of a bleed (the third intercurrent event) will be used. This analysis will be performed using the FAS.

Further sensitivity analyses can be specified in the SAP.

10.3.2.2 Supportive secondary endpoints

Analyses of supportive secondary endpoints will be detailed in the SAP.

10.3.3 Exploratory endpoints

Analyses of exploratory endpoints will be detailed in the SAP.

10.3.4 Interim analyses

No formal interim analyses are planned.

As stated under Section 5.1 several evaluations are to be made during the conduct of the trial:

- at the confirmatory analyses cut-off
- at the 56-week 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.

10.3.5 Sequential safety analysis and safety monitoring

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

The DMC members will not have 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.

10.3.6 Explorative statistical analysis for pharmacogenetics and biomarkers

N/A

10.4 Pharmacokinetic and/or pharmacodynamic modelling

The concizumab concentration measurements obtained in this trial will be subject to exploratory PK modelling analysis performed by Quantitative Clinical Pharmacology, Novo Nordisk.

A previously developed PK model for concizumab will be applied to the PK data. If necessary, alternative models can be considered for an accurate description of the PK profile. Further exploratory population PK modelling can potentially be a joint analysis of data from multiple trials including investigation of covariate factors. Relevant PK endpoints will be derived from the model parameter estimates.

Selected PD measurements may be used for exploratory PK/PD analyses and if deemed feasible, population PK/PD and exposure-response modelling may be performed.

A more technical and detailed elaboration of the population PK, population PK/PD and exposure-response analyses will be given in a prospective modelling analysis plan.

The results of the final analyses will be reported separately from the CTR. If relevant, selected model-derived results may be summarised in the CTR.

11 References

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12 Appendices

Appendix 1 Abbreviations and Trademarks

ABI	ankle-brachial index
ABR	Annual Bleeding Rate
aPPC	activated prothrombin complex concentrate
ADA	anti drug antibodies
ADE	adverse device effect
AE	Adverse Event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
C_{max}	maximum concentration
C_{trough}	trough level concentration
CLAE	clinical laboratory adverse event
CRF	case report form
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
CNS	central nervous sstem
COVID-19	Coronavirus disease 2019
CT	computerised tomopraphy
CTR	clinical trial report
DFU	Direction For Use
DIC	Disseminated Intravascular Coagulation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease related event
DUN	dispensing unit number
DVT	deep vein thrombosis
ECG	Electrocardiogram
EOT	End of trial
ETP	Endogenous Thrombin potential
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPFV	first patient first visit

GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HA	Haemophilia A
HAwI	Haemophilia A with inhibitors
Haem-A-QoL	Haemophilia Quality of Life Quesionnaire for Audult
HB	Haemophilia B
HBwI	Haemophilia B with inhibitors
HCP	Host Cell Protein
Hemo-TEM	Haemophilia Treatment Experience Measure
H-PPQ	Haemophilia Patient Preference Questionnaire
IB	Investigators Broshure
IC	Immune Complex
ICH	International Council for Harmonisation
ICMJE	International of Committe Medicinal Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	Item response theory
IVD	in vitro diagnostic
IWRS	interactive web response system
LAR	legally acceptable representative
LLN	Lover limit of normal
LPFT	Last Patient First Treatment
MAR	missing at random
MI	Myocardial infarction
MIDF	monitor-initiated discrepancy form
MMRM	mixed-effect model for repeated measurements
MRA	Magnetic Resonance Angiography
MRI	Magnetic resonance imaging
MSE	Missing Score Evaluation
MVPA	Moderate to Vigorous Physical Activity
NI	Non-inferiority
NIS	Non-interventional Study
OD	On-demand
PCD	primary completion date
PD	Pharmacodynamic
PF	physical functioning

PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PPX	prophylaxis
PRO	patient-reported outcome
SADE	serious adverse device effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SUSAR	suspected unexpected serious adverse reaction
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inhibitor
TMA	Thrombotic Microangiopathy
ULN	upper limit of normal
URL	upper reference limit
USADE	unanticipated serious adverse device effect

Appendix 2 Clinical laboratory tests

- The tests detailed in Table 18 and Table 19 will be performed by central or designated special laboratories.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal values will be reported to the investigator.
- The investigator must review all laboratory results for concomitant illnesses and AEs except for results from Human biosamples.
- Laboratory samples will be destroyed no later than at finalisation of the clinical trial report except for samples as described in Appendix 9.
- Human biosamples for retention will be stored as described in Appendix 9.
  - All laboratory samples should be taken pre-dosing and as specified in the flowchart in Section 2.

Table 18 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Thrombin generation	Thrombin lag time Velocity index Endogenous thrombin potential Endogenous Thrombin Potential ratio Thrombin peak Time to peak
Concizumab ELISA IVD	Concizumab plasma concentration for dose adjustment
Concizumab ELISA	Concizumab plasma concentration
Free TFPI	Free TFPI

Table 19 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	Erythrocytes Haemoglobin Leucocytes Thrombocytes (platelets) Differential Leucocytes count: Lymphocytes, monocytes, neutrophils, Eosinophils and Basophiles
Biochemistry[a]	Alanine Aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate Aminotransferase (AST) Creatinine Bilirubin (total) C-reactive protein (CRP) Gamma-glutamyl transferase (GGT)
Urinalysis (screening only)	pH, glucose, protein, bilirubin, by dipstick
Antibodies	Anti-concizumab binding antibodies

Laboratory assessments	Parameters
	Anti-concizumab ab crossreacting w S241P Anti-concizumab ab crossreacting w IgG4 Anti-concizumab binding antibodies titre Anti-concizumab neutralising antibodies FVIII inhibitors (for HA) FIX inhibitors (for HB only)
Coagulation Factors	Factor VIII activity (for HA only) Factor IX activity (for HB only)
Coagulation parameters	Antithrombin Plasma D-Dimer Prothrombin Fragments 1 + 2 in Plasma Fibrinogen Activated Partial Thromboplastin Time Prothrombin Time INR Total TFPI
Human biological specimen for storage	Plasma Serum Whole Blood (for DNA genotyping)
Other tests	estimated Glomerular Filtration Rate (eGFR) test calculated by the central laboratory based on the creatinine value using the CKD-EPI equation
Notes: [a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in 8.1 and Appendix 5 (Hy's Law).	

All trial-required laboratory assessments will be performed by a central laboratory or designated special laboratories.

Laboratory sampling for patients from NN7415-4255 (explorer 5):

Only applicable for patients that were transferred prior to the treatment pause: Results from selected laboratory samples, from patients transferring from NN7415-4255 (explorer 5) taken at EOT, will be transferred to this trial.

Appendix 3 Blood sampling in patients below 18 years of age

Blood sampling in adolescent patients aged 12−17 years must be performed according to local guidelines. The blood volume taken in patients below 18 years should not exceed 3% of the total volume during a 4-week period and should not exceed 1% at any single time point.[11]

In order to adhere to this guideline blood sampling in adolescent patients must be performed based on the patient's weight and blood volume, Table 20, the blood sample prioritisation list, Table 21 and the laboratory manual.

Table 20 shows the approximate blood volume in adolescents (12−17 years) weighing ≥25 kg and the maximum blood sampling volumes to be collected at one single time point and during a 4-week period. It is assumed that the blood volume is 80 ml pr. kg.

Table 20 Total blood volumes and maximum blood sampling volumes according to body weight (kg)

Body weight (kg)	Blood volume (ml) according to body weight (kg)	Maximum blood sampling volume at one single time point (ml)	Maximum blood sampling within 4 weeks (ml)
25 - 29	2000 - 2320	20.0 - 23.2	60.0 – 69.6
30 - 34	2400 - 2720	24.0 – 27.2	72.0 - 81.6
35 - 39	2800 - 3120	28.0 – 31.2	84.0 – 93.6
40 - 44	3200 - 3520	32.0 – 35.2	96.0 – 100.6
45 - 49	3600 - 3920	36.0 – 39.2	108.0 – 117.6
50 - 54	4000 - 4320	40.0 – 43.2	120.0 – 129.6
55 - 59	4400 - 4720	44.0 – 47.2	132.0 – 141.6
60 - 64	4800 - 5120	48.0 – 51.2	144.0 – 153.6
65 - 69	5200 - 5520	52.0 – 55.2	156.0 – 165.6
70 - 74	5600 - 5920	56.0 – 59.2	168.0 – 177.6
75 - 79	6000 - 6320	60.0 – 63.2	180.0 – 189.6
≥80	6400	64.0	192.0

Table 21 shows the blood sample prioritisation list that should be followed for adolescent patients. Blood samples should be drawn in the below mentioned order, highest priority sample assigned. If

deemed necessary by the investigator for safety reasons, the order may be changed. Please refer to the current version of the Laboratory Manual for further details.

Table 21 Blood sample prioritisation list

Priority	Laboratory parameter
1	Coagulation parameters
2	Haematology
3	Biochemistry
4	Concizumab ELISA
5	Concizumab Immunology
6	Free TFPI
7	TGA
8	Coagulation Factors (FVIII/FIX) and inhibitors
9	Human Biological Specimen for future research
10	Coagulation back-up

Appendix 4 Trial governance considerations

1) Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[21] and applicable ICH Good Clinical Practice (GCP) Guideline.[22]
    - Applicable laws and regulations
- The protocol, informed consent form, IB (as applicable) and other relevant documents (e.g. advertisements), must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial patients.
- Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
    - providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
    - ensuring submission of the clinical trial report (CTR) synopsis to the IRB/IEC.

2) Financial disclosure

Investigators and sub investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and one year after completion of the trial.
For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

3) Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the patient and/or the patient's LAR and answer all questions regarding the trial. This includes the use of an impartial witness where required according to local requirements.
- The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

- Patients must be informed that their participation is voluntary.
- Patients or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[22], Declaration of Helsinki[21] and the IRB/IEC or trial site.
- Whenever possible informed consent/assent must also be obtained by the minor/incapacitated patient. The informed consent/assent must be signed by patients below legal age according to local regulations.
- In addition to the information given to the patient's LAR, the minor/incapacitated patient must be given information according to his/her capacity to understand, always taking into consideration the minor's/patient's presumed willingness to participate in a clinical trial.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task of informing to a medically qualified person, in accordance with local requirements.
- Patients and/or their LAR must be re-consented to the most current version of the informed consent form(s) during their participation in the trial.
- For patients who were enrolled before the treatment pause, an addendum to the informed consent form must be signed by the patients and/or their LAR before reinitiating dosing with concizumab.
- A copy of the informed consent form(s) must be provided to the patient or the patient's LAR.
- If the minor reaches legal age while participating in the trial and has only signed an age specific informed consent/assent form, the patient has to re-consent to the informed consent form signed by the patient's LAR.

Long term Storage of human samples

- If allowed according to local law the patient will be asked to sign a separate consent form that addresses taken additional blood samples for Biomarkers and genetic testing (DNA) for long term storage of human samples and/or the use of samples for optional explanatory research. The objectives of the explanatory research must be explained to each patient.
- This separate informed consent form should be signed by the patient and/or patient's LAR if they consent to have additional sample taking for later biomarker and genotype analysis. The patient/ the patient's LAR has the option to abstain from this part while still participating in the trial.

4) Information to patients during trial

The site will be offered a communication package for the patient during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the patients. The written information will be translated and adjusted to local requirements and distributed to the patient at the discretion of the investigator. The patient may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the patient may receive other written information during the trial.

All written information to patients must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

5) Data protection

- Patients will be assigned a 6-digit unique identifier, a subject number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient and any biological material obtained from the patient will be identified by patient number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients as required by local, regional and national requirements.
- The patient must be informed that his personal trial related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the patient.
- The patient must be informed that his medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6) Committee structure

Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee.

Data monitoring committee

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the trial at predefined time points as well as ad hoc. This is done in order to protect the safety of the patients and to evaluate the benefit-risk balance. The DMC will have access to unblinded trial data, and will provide recommendations on trial continuation, modification or termination.
Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

7) Publication policy

The information obtained during the conduct of this trial is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.
The information obtained during this trial may be made available to other investigators who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information

obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial. One investigator will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator) on behalf of all participating investigators.

Communication of results
Novo Nordisk commits to communicate and disclose results of trials regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this trial will be patient to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Authorship
Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[23]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Site-specific publication(s) by investigator(s)
For a multicentre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript

is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the trial.

Investigator access to data and review of results
As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database.
Individual investigators will have their own research patients' data.

8) Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE)[24], the Food and Drug Administration Amendment Act (FDAAA)[25], European Commission Requirements[26-28] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint and is for this trial Last Patient First Treatment (LPFT) + 32 weeks corresponding to visit 10a. If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed visit 10a. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

9) Data quality assurance

Case Report Forms (CRFs)

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All patient data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory and diary data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporarily unavailable:
    - AE forms
    - Safety information forms
    - Technical complaint forms (also to be used to report complaints that are not patient related, e.g. discovered at trial site before allocation)
- Corrections to the eCRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the eCRF, the eCRF must be signed and dated again by the investigator.

- The investigator must ensure that data are recorded in the eCRF as soon as possible, preferably within 5 working days after the visit. Once data have been entered, it will be available to Novo Nordisk for data verification and validation purposes.

Monitoring

- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of patients are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to trial sites.

- Monitors will review the patient's medical records and other source data e.g. the diaries and paper PROs, to ensure consistency and/or identify omissions compared to the eCRF.

Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the trial database.

10) Source documents

All data entered in the eCRF must be verifiable in source documentation other than the eCRF.

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the trial site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

- It must be possible to verify patient's medical history related to haemophilia in source documents such as patient's medical record.
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each trial site. There will only be one source document defined at any time for any data element.

11) Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF and other patient data will be provided in an electronic readable format to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) must be retained by the trial site. If the provided electronic data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.
- Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice

12) Trial and site closure

Novo Nordisk reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of Novo Nordisk. If the trial is suspended or terminated, the investigator must inform the patients promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a trial site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of patients by the investigator
- discontinuation of further trial product development.

13) Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the trial site. If any tasks are delegated, the investigator

must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients.
A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents, including the patient identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of patients to a specific qualified physician who will be readily available to patients during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires) a new investigator will be appointed in consultation with Novo Nordisk.
The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

14) Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

15) Web-portal for document exchange

During the trial a web-portal will be used for document exchange between Novo Nordisk and the sites. The web-portal is not an archiving tool but could be used as a temporary archiving place during the trial as judged by the investigator.

Appendix 5 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial patient that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm. • Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the patient has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** • Hospitalisation signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Note:

- Hospitalisations for administrative, trial related, and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
- Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
    - suspicion of transmission of infectious agents via the trial product.
    - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x Upper Normal Limit (UNL) and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Description of AEs requiring additional data collection (via specific event form) and AESIs

AESIs

An AESI is an event, which in the evaluation of safety, has a special focus due to requirements from regulatory authorities.

In this trial, the following AEs fulfil the AESI criteria:

Thromboembolic events including but not limited to,

- disseminated intravascular coagulation (DIC) (A),
- thrombotic microangiopathy (TMA)(B)
- myocardial infarction (C),
- pulmonary embolism (D),
- stroke (E),
- deep vein thrombosis (F),
- other clinically significant thromboembolic events (G) and peripheral artery occlusion (see below H), see definitions below

In case of suspicion of thromboembolic events, further investigations and appropriate medical treatment should be initiated. Additionally, it is encouraged to perform a COVID-19 test in the case of a suspected thromboembolic event. If a thromboembolic event is diagnosed, COVID-19 testing must be performed.

A) Definition of disseminated intravascular coagulation (DIC), as defined below:

The definition of DIC in this trial should be made according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. Thus, a DIC diagnosis may be based on clinical signs and symptoms of a bleeding tendency or thrombotic tendency, organ dysfunction and the laboratory parameters criteria as listed below:

- Platelet count (>100 × 109/L = 0, <100 × 109/L = 1, <50 × 109/L = 2)
- Elevated D-dimer (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
- Fibrinogen level (>1 g/L = 0, <1 g/L = 1)
- Calculate score: ≥5 compatible with overt DIC

B) Definition of thrombotic microangiopathy, as defined below:
Thrombotic microangiopathies (TMA) are a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia and microthrombi leading to ischemic tissue injury that can affect e.g. the kidneys and the central nervous system.
TMA is a clinicopathologic diagnosis. The constellation of thrombocytopenia, anemia and red blood cell fragmentation (i.e. schistocytes) on the blood film is consistent with a diagnosis of TMA. The finding of concomitant anemia and thrombocytopenia should prompt a request for a peripheral blood film to look for red blood cell fragmentation.
If TMA is suspected the following laboratory assessment workup is suggested: standard hematology, hemolytic parameters (reticulocytes, hemoglobin, bilirubin, LDH, haptoglobin), Direct Anti-Globulin (DAT) test (also referred to as Coombs test), peripheral blood smear to look for schistocytes, creatinine, ADAMTS13 Antigen and ADAMTS13 Antibody.[29]

C) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction"[30]
Criteria for acute myocardial infarction - The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy

Criteria for prior myocardial infarction - Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

Recurrent myocardial infarction - Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, this is not counted as a new event for epidemiological purposes. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.

D) Definition of pulmonary embolism:
The "Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians" on diagnosis of venous thromboembolism recommends diagnostic imaging studies for patients with intermediate or high pre-test probability of pulmonary embolism.[31]

Accordingly, the definition of pulmonary embolism is the following: obstruction of a pulmonary artery or one of its branches, most frequently by detached fragments of thrombus from a leg or pelvic vein, diagnosed by at least one of the following:

- Positive findings in ventilation/perfusion scan
- Positive findings in a spiral (helical) computerised tomography (CT) or angiography
- Positive findings in a magnetic resonance imaging (MRI)
- Positive findings in a pulmonary angiography

E) Definition of stroke:
The definition of central nervous infarction is according to the American Heart Association/American Stroke Association Expert Consensus Document: "An Updated Definition of Stroke for the 21st Century".[32]

Accordingly, the term "stroke" should be broadly used to include all of the following:
Definition of central nervous system (CNS) infarction: CNS infarction is brain, spinal cord or retinal cell death attributable to ischemia, based on:

pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
clinical evidence of cerebral, spinal cord or retinal focal ischemic injury based on symptoms persisting 24 hours or until death, and other etiologies excluded
Note: CNS infarction includes haemorrhagic infarctions, types I and II; see "Haemorrhagic Infarction"

Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction. Note: Evidence of CNS infarction is defined above.

Definition of silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Definition of intracerebral haemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. Note: Intracerebral haemorrhage includes parenchymal haemorrhages after CNS infarction, types I and II - see "Haemorrhagic Infarction").

Definition of stroke caused by intracerebral haemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Definition of silent cerebral haemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

Definition of subarachnoid haemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

Definition of stroke caused by subarachnoid haemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Definition of stroke caused by cerebral venous thrombosis: Infarction or haemorrhage in the brain, spinal cord or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or haemorrhage do not qualify as stroke.

Definition of stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above.

Definition of a Transient Ischemic Attack: The definition of Transient Ischemic Attack is according to the American Heart Association/American Stroke Association. A Transient ischemic attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction.[33]

F) Definition of deep vein thrombosis:
The "Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians" on diagnosis of venous thromboembolism recommends ultrasound scanning for patients with intermediate or high pre-test probability of deep vein thrombosis (DVT) in the lower extremities.[31] Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

G) Definition of other clinically significant thromboembolic events:
Signs or suspicion of a clinically significant thromboembolic event (e.g. visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis). Superficial thrombophlebitis related to a central venous access device is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

H) Definition of peripheral artery occlusion:
Clinical signs of acute arterial occlusion verified by ankle-brachial index (ABI) test, Doppler and ultrasound (Duplex) imaging, computerised tomographic angiography, Magnetic Resonance Angiography (MRA) or conventional angiography. The 2011 American College of Cardiology Foundation/American Heart Association Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease could serve as a reference for the diagnosis of lower extremity peripheral artery disease

AEs requiring additional data collection
AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction is present, additional blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. See Section 9.4.8 for further guidance on additional laboratory testing to be performed. Attention should be given to clinical signs and symptoms of hypersensitivity reactions of type II and III. Common clinical signs and symptoms characteristic for these types of reactions may include, but are not limited to: fever/malaise, cutaneous eruptions, arthralgia, lymphadenopathy, itching, headaches and myalgia. Related laboratory findings may include but are not limited to: mild proteinuria or haematuria, leukopenia or leucocytosis, decreased complement levels or increased complement split products and transient elevations of serum creatinine levels.
In case of suspected severe systemic hypersensitivity reactions, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

Injection site reactions:
Any injection site reaction symptom must be reported on the AE form and the injection site reaction form, refer to Section 9.4.9.

Investigation of injection site reactions will be performed locally at all visits when patients are receiving treatment with concizumab PPX based on patient feedback and by following visual inspections of injection sites for concizumab administration. The affected area should be evaluated in cm or inches using a ruler. In the event of a local reaction, assessments will be performed until resolution as judged necessary by the investigator. Assessment of injection site reactions can be performed at any time, if deemed necessary by the investigator.

Medication error:
A medication error is an unintended failure in the trial drug process that leads to, or has the potential to lead to, harm to the patient, such as:

- Administration of wrong drug or use of wrong device.
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Accidental administration of a lower or higher dose than intended. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although they did not necessarily occur.

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the eCRF.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all patient identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to “SAE reporting via paper CRF” later in this section.

- Novo Nordisk products used as concomitant medication if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product should be assessed as:

- Probable - Good reason and sufficient documentation to assume a causal relationship.
- Possible - A causal relationship is conceivable and cannot be dismissed.
- Unlikely - The event is most likely related to aetiology other than the trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the IB for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving, and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the patient has not improved, and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.

- **Unknown:** This term is only applicable if the patient is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.
If a patient dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the eCRF.

SAE reporting via eCRF

- Relevant forms (AE and safety information form) must be completed in the eCRF.
- For reporting and sign-off timelines, see box below.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the eCRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below).
- The site will enter the SAE data into the eCRF as soon as it becomes available, see 9.3.1.
- After the trial is completed at a given site, the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after eCRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 4 in Section 9.3):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days.

Contact details for SAE reporting can be found in the investigator trial master file.

Appendix 6 Sports ratings by activity

As per US National Hemophilia Foundation brochure for haemophilia patients, PlayingItSafe.

Table of Activity Ratings

1 Low Risk | 1.5 Low to Moderate Risk | 2 Moderate Risk | 2.5 Moderate to High Risk | 3 High Risk

Activity	Category	Page
Aquatics	1	22
Archery	1	22
Baseball	1.5–2.5	22
Basketball	1.5–2.5	23
Bicycling	1.5–3	24
BMX Racing	3	25
Body Sculpting Class	1.5	30
Boot Camp Workout Class	2	31
Bounce Houses	2.5–3	25
Bowling	2	25
Boxing	3	26
Canoeing	1.5–2.5	42
Cardio Kickboxing Class	2	31
Cheerleading	1.5–2.5	28
Circuit Training	1.5	54
Dance	1–3	29
Diving, Competitive	2–3	30
Diving, Recreational	2	30
Elliptical Machine (Training Equipment)	1	26
Fishing	1–2	33
Football, Flag or Touch	2	34
Football, Tackle	3	34
Frisbee®	1–1.5	34
Frisbee®, Golf	1.5–2	35
Frisbee®, Ultimate	2–2.5	35
Golf	1	36
Gymnastics	2–3	36
High Intensity Functional Training (Incl. CrossFit®) Class	2–3	31
Hiking	1–1.5	37
Hockey, Field/Ice/Street	2.5–3	37
Horseback Riding	1.5–2.5	38
Indoor Cycling Class	1.5–2	32
Jet-Ski® (Personal Watercraft, PWC)	2–3	38
Jumping Rope	2	39
Kayaking	1.5–2.5	42
Lacrosse	3	40
Martial Arts, Tai Chi	1	41
Martial Arts, Traditional and Mixed	2–3	40
Motorcycle/Motocross (ATV, Dirt Bikes)	3	41

Activity	Category	Page
Mountain Biking	2.5	42
Pilates	1.5–2	44
Power Lifting	3	44
Racquetball	2.5	44
River Rafting	2	43
Rock Climbing, Indoor or Challenge/Ropes Course	1.5–2	45
Rock Climbing, Outdoor	2–3	45
Rodeo	3	46
Rowing	1.5	43
Rowing Machine (Training Equipment)	1.5	27
Rugby	3	46
Running/Jogging	2	47
Scooters, Motorized	2–2.5	48
Scooters, Nonmotorized	1.5–2.5	48
Scuba Diving	2–2.5	49
Skateboarding	1.5–2.5	50
Skating, Ice	1.5–2.5	49
Skating, Inline and Roller	1.5–2.5	50
Skiing, Cross-Country	2	50
Skiing, Downhill	2.5	51
Skiing, Water	2–2.5	51
Ski Machine (Training Equipment)	1.5	27
Snorkeling	1	52
Snowboarding	2.5	52
Snowmobiling	3	53
Soccer	2–3	53
Softball	1.5–2.5	22
Stationary Bike (Training Equipment)	1	27
Stepper (Training Equipment)	1–1.5	28
Strength Training/ Resistance Training/ Weight Lifting	1.5	54
Surfing	2–2.5	54
Swimming	1	55
Tee-Ball	1.5	22
Tennis	2	55
Track and Field	2–2.5	56
Trampoline	2.5–3	56
Treadmill (Training Equipment)	1.5	28
Volleyball	2–2.5	57
Walking	1	58
Water Polo	2.5	58
Wrestling	3	59
Yoga	1.5–2	59
Zumba® Class	1.5–2	33

Appendix 7 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

Technical complaint definition
• A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself. • Technical complaints include the definition of device deficiency, please refer to Appendix 8

Examples of technical complaints:

- Problems with the physical or chemical appearance of trial products (e.g. discoloration, particles or contamination).
- Problems with packaging material including labelling.
- Problems related to medical devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle).
- Problems related to concizumab-ELISA (e.g. uncertain results).

Time period for detecting technical complaints
All technical complaints, which occur from the time of receipt of the product at trial site until the time of the last usage of the product, must be collected for products predefined on the technical complaint form.

Reporting of technical complaints to Novo Nordisk
Contact details (fax, e-mail and address) for Customer Complaint Center – refer to Attachment I Technical complaints must be reported on a separate technical complaint form: • For concizumab pen-injector: One technical complaint form must be completed for each affected DUN • For concizumab-ELISA: One technical complaint form must be completed for each onset For medical device under investigation (concizumab-ELISA), evaluate on the technical complaint form if the technical complaint could have led to an SAE. If the technical complaint on a medical device under investigation could have led to an SAE, a device deficiency that could have led to an SAE form must be completed as described in Appendix 8.

Timelines for reporting of technical complaints to Novo Nordisk
The investigator must complete the technical complaint form in the eCRF within: • 24 hours if could have led to an SAE (for concizumab-ELISA) • 24 hours if related to an SAE • 5 calendar days for all other technical complaints If the eCRF is unavailable or when reporting a technical complaint that is not patient related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

Follow-up of technical complaints
The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form

Collection, storage and shipment of technical complaint samples – not applicable for concizumab-ELISA
The investigator must collect the technical complaint sample and all associated parts that were packed in the same DUN and notify the monitor within 5 calendar days of obtaining the sample at trial site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together. Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

Reporting of technical complaints for Novo Nordisk products not included in technical complaint form
Technical complaints on Novo Nordisk products not included in the technical complaint form should be reported to local Novo Nordisk affiliate with a reference to trial ID.

Appendix 8 AEs, ADEs, SAEs, SADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

Definition of AE and adverse device effects

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in trial patients, users, or other persons, whether or not related to the medical device under investigation and whether anticipated or unanticipated. This definition includes events related to the medical device under investigation or comparator and events related to the procedures involved. For users or other persons, this definition is restricted to events related to medical devices under investigation or comparators.

An adverse device effect (ADE) is an AE related to the use of a medical device under investigation. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device under investigation as well as any event resulting from use error or from intentional misuse of the medical device under investigation or comparator if the comparator is a medical device. See the current edition of the investigator's brochure and any updates hereof for the anticipated ADEs.

Definition of SAE, serious adverse device effect and unanticipated serious adverse device effect

An SAE is an AE that fulfils at least one of the following criteria:

1. Results in death
2. Leads to serious deterioration in the health of the patient, user or other person that either results in:
    a. A life-threatening illness or injury. The term 'life-threatening' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
    b. Persistent or significant disability/incapacity: A permanent impairment of a body structure or a body function including chronic diseases.
    c. In-patient or prolonged hospitalisation, planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
    d. Important medical event: Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. Congenital anomaly/birth defect: Results in foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment.

Serious adverse device effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

Unanticipated serious adverse device effect

A unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment analysis report (see Section 3.3).

Anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Definition of serious health threat

A serious health threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in trial participants, users or other persons, and that requires prompt remedial action for other participants, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Definition of device deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and the inadequacy of the information supplied by the manufacturer, including labelling.

This definition includes device deficiencies related to the medical device under investigation. Device deficiency is part of technical complaint definition, please refer to Appendix 7.

Recording and follow-up of AE and/or SAE and device deficiencies

AE, SAE and device deficiency recording

When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, will be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest.

The investigator will then record all relevant AE/SAE/device deficiency information in the patient's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.

For device deficiencies, it is very important that the investigator describes any corrective actions taken to prevent recurrence of the event.

Assessment of severity

The investigator will make an assessment of severity for each AE/SAE/device deficiency reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the criteria described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between medical device under investigation, the procedure and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine relationship.

Relationship between an AE/SAE and the medical device under investigation and the procedure should be assessed as:

- Causal: when relationship is beyond any doubt
- Probable: when relationship seems relevant and/or the event cannot be explained by another cause
- Possible: when relationship is weak but cannot be ruled out
- Not related: when relationship can be excluded

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the use of the medical device under investigation, will be considered and investigated.

The investigator will also consult the investigator's brochure in his/her assessment.

For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality for AE or SAE.

There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial report to Novo Nordisk. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.

The investigator may change his/her opinion of causality in light of follow-up information and send an AE/SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the patient is expected to recover from the event. This term may be applicable in case of chronic conditions, cancer of AEs ongoing at time of death (where death is due to another AE). Note: for SAEs, this term is only applicable if the patient has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: the patient has recovered from the condition but with lasting effect due to disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: the condition of the patient has not improved, and the symptoms are unchanged, or the outcome is no known.
  Note: this term may be applicable in case of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the patient died from a condition related to the reported AE. Outcome of other reported AEs in a patient before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the patient is lost to follow-up.

Follow-up of AE/SAE/device deficiency

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to Novo Nordisk within 24 hours of receipt of the information.

Reporting of SAEs, Serious Device Deficiencies that could have led to an SAE and serious health threats

Relevant CRFs (AE and safety information forms, device deficiency that could have led to an SAE form) must be forwarded to Novo Nordisk in accordance with Appendix 4 (Data protection).

Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE, device deficiency that could have led to an SAE and safety information form within the designated reporting time frames:

- AE and device deficiency that could have led to an SAE form within 24 hours

- Safety information form within 5 calendar days
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.

A suspicion of a serious health threat must be indicated in the SAE form or in the device deficiency that could have led to an SAE form.

For device deficiency that could have led to an SAE, a technical complaint form must also be completed, refer to Appendix 7.

Appendix 9 Retention of human biosamples

The trial will involve collection of human biosamples to be stored in a central archive.

1) Biosamples for future research (Biomarkers and Genetics)

1.2 ml citrated plasma, 1.0 ml serum and /or 2.0 ml whole blood (DNA for genotyping) will be obtained from patients/LARs who have consented to this part of the trial.

Biomarkers
As new biomarkers related to the disease and/or safety, efficacy or mechanism of action of concizumab may evolve during the conduct of the trial, the analyses of the stored biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

Only Novo Nordisk staff and biorepository personnel will have access to the stored samples. For all retained samples the patient's identity will remain confidential and the samples will be identified only by subject number, visit number and or date and trial identification number. No direct identification of the patient will be stored together with the samples. The biosamples may be transferred to other countries.

In the event that the collected biosamples (blood) will be used in the future, the investigator will become directly informed by Novo Nordisk about the results, if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of patient specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk. Potentially, observations of neoplastic diseases, serious hereditary diseases, other un-treatable diseases or any other abnormal findings could be part of the observations. Patients can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.

Use/Analysis of DNA
Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

DNA samples will be used for research related to trial product or indication and related diseases. Genetic research may consist of the analysis of one or more candidate genes, or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analysed as part of a multi-trial assessment of genetic factors involved in the response to trial product or product treatments of this class to understand trial disease or related conditions.

2) Antibodies and PK/PD samples

Antibodies and PK/PD samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons. Remaining blood from the samples already collected may be used for further development of Anti-drug antibody and PK/PD assays and will not be reported in this trial. Residual samples may also be used to generate reagents for in study validation or control of future assay performance inside or outside this trial. Selected samples would be pooled, and not be traceable to any individual. Pooling would not be done if it prevented retention of sufficient sample material for possible further characterisation of antibody responses in this trial.

3) Storage and destruction

The samples will be stored at Novo Nordisk and/or at a central bio-repository after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

Appendix 10 Country-specific requirements

Algeria: Legal age of majority is 19 years old. Biogenic testing and biobanking not allowed.

France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I,IX, Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical the research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the faults of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research."

India: In India, Novo Nordisk will provide or reimburse the patients treatment for bleeds during the entire trial including the screening and follow-up parts.

Israel: With reference to Sections 9.7.1, 9.7.2 and Appendix 9: No patients from Israel will participate in the optional biobank part of the trial, and no genetic testing will be performed.

Japan: The legal age in Japan is 20 or above. The head of the trial site or the trial product storage manager assigned by the head of the trial site (a pharmacist in principle) is responsible for control and accountability of the trial products.

Mexico: Should the subject his/her family members parents or legal representative decide to withdraw the consent for participation in the trial, the subject will be entitled to receive appropriate, free of charge medical care and/or trial drug during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the subject participation in the research occurred.

Russia: The trial should be conducted in compliance with the protocol and Ministry of Healthcare of Russian Federation‘ order # 200n from April 01, 2016 “Approval of rules of good clinical practice”.

South Africa: Genetic testing and biobanking not allowed.

South Korea: The legal age is above or equal to 19 years. In South Korea, Novo Nordisk will provide or reimburse the patients treatment for bleeds during the entire trial including the screening and follow-up parts. In addition, Novo Nordisk will provide or reimburse patients on-demand treatment if patients are randomised to arm 1.

Turkey: In Turkey Novo Nordisk will provide or reimburse the patients treatment for bleeds during the entire trial including the screening and follow-up parts. In addition, Novo Nordisk will provide or reimburse patients on-demand treatment if patients are randomised to arm 1.

Rotational thrombelastometry (ROTEM) Sub-Study: Applicable for site [redacted] (Germany), site [redacted] (Spain), site [redacted] (Sweden) and site [redacted] (UK).

Four sites in four countries will participate in a ROTEM sub-study in either protocols NN7415-4307 (explorer 8) and/or NN7415-4311 (explorer 7). The purpose of this sub-study is to evaluate the use of ROTEM parameters as possible marker for evaluation of concizumab.

ROTEM enables the evaluation of haemostatic potential in whole blood, providing multiple parameters to describe clot formation and strength. ROTEM evaluation has the potential of being used to evaluate the haemostatic effect of treatment with concizumab in patients with haemophilia. The ROTEM evaluation will be added to the trial at four sites.

The selected trial sites have extensive experience with ROTEM evaluation, as well as a thorough understanding of concizumab treatment from clinical trials. The number of sites will be limited to reduce assay variation, as ROTEM is known to show a high degree of user-dependent variation in the evaluation of patients with haemophilia.

The ROTEM parameters will be compared to PK parameter and thrombin generation parameter from the two clinical trials, NN7415-4307 (explorer 8) and NN7415-4311 (explorer 7), and thus sampling for ROTEM evaluation will take place at the same time as sampling for thrombin generation for subject treated with concizumab. As the ROTEM assay is for research purpose only, the evaluation of the ROTEM parameters will be exploratory only, and not be part of the formal statistical evaluation as per protocol.

Sampling for ROTEM will take place in the main part at each visit where Thrombin Generation sampling takes place (please see flowchart Section 2). In addition, thrombin generation sampling will be added to timepoint 3 hours, please see Table 22 below. This means that ROTEM sampling will be take place at pre-dose, 3 hours, and 6 hours (when a PK profile is taken).

The collection will involve an additional blood collection tube of 2 ml per time point for the PK profile (V2a and V9a), and 2 ml at the other visits where thrombin generation is taken in the main part for arms 2−4 (32 weeks). The total additional sampling for subjects agreeing to take part will be 30 ml.

For patients that are currently in the trial and is restarting concizumab treatment at visit 2a, ROTEM sampling will be repeated. These patients will not have a PK profile at visit 2a but ROTEM samples will be taken in the main part at each visit where Thrombin Generation sampling takes place and at visit 9a. The total volume for sampling for these subjects will be higher depending on how many samples that were taken prior to the treatment pause (maximum 60 ml).

The details of the ROTEM assay method will be outlined in a separate laboratory manual, applicable for only the selected sites participating in the ROTEM sub-study and covered by this amendment.

Table 22 Pharmacokinetic (PK)/ Pharmacodynamic (PD) sampling flowchart

	Visit 2a and Visit 9a (PK/PD profile only applicable for patients on concizumab treatment from visit 2a)				
PK sampling timepoint (hours)[a]	**Pre-dose**	**3 hours**	**6 hours**	**9 hours**	**24 hours**
Sampling window	-1 − 0 hours	±30 min	±30 min	±1 hour	±3 hours
PK ASSESSMENTS					
Concizumab ELISA	X	X	X	X	X
Free TFPI	X	X	X	X	X
Thrombin generation	X	X	X		X
ROTEM samples	X	X	X		

Note: [a]If the patient has already completed the PK profile at visit 2 before the treatment pause, the PK profile will not be repeated at visit 2a. Then the patient will only have the ROTEM sampling performed at visit 9a and at the other visits where thrombin generation is assessed in the main part of the trial.

All patients participating in the ROTEM sub-study must signed a separate informed consent form.

Applicable for site [redacted] (Spain) only: Participants must be aged ≥18 years at the time of signing the informed consent.

Applicable for the other sites: If participations below 18 years are included in the ROTEM sub-study, the site must ensure that the blood volumes listed in Appendix 3 are adhered to. The sampling for ROTEM is lowest priority.

Appendix 11 Breakthrough bleed treatment guidance

The investigator must instruct the patient on how to treat breakthrough bleeds.

The investigator must ensure that patients are instructed to contact the site before administering breakthrough bleed treatment to ensure that treatment is administered when and as applicable.

Treatment of mild or moderate breakthrough bleeds with factor products

In case a patient experiences a mild or moderate treatment-requiring bleed, the investigator should instruct the patient to treat the bleed taking the guidance on doses and dose intervals in Table 23 into consideration.

For treatment of bleeds with FEIBA®, the dose must not exceed a single dose of 50 U/kg, and not exceed 100 U/kg within 24 hours. The first treatment should be at the hospital, with observation if the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with FEIBA® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 50 U/kg. If an additional dose is needed because a single dose was insufficient to treat the bleed the patient must some to the site.

For treatment of bleeds with ByClot®, the dose must not exceed 60 µg/kg, and not exceed 90 µg/kg within 24 hours. Additional dose can be given at an interval of 8 hours or longer. The first treatment should be at the hospital, with observation of the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with ByClot® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 60 µg/kg. If an additional dose is needed because a single dose was insufficient to treat the bleed, the patient must come to the site.

Table 23 Guidance on management of mild and moderate bleeds during concizumab PPX

	FVIII SHL	FVIII EHL	FIX SHL	FIX EHL	rFVIIa	aPCC	ByClot®
Contact centre (PI)	The patient must contact the centre before initiating treatment of a bleeding episode. If more doses are needed, the patient should contact the centre before each dose.						
First dose[a]	20 IU/kg	20 IU/kg	30 IU/kg	30 IU/kg	90 µg/kg	Single dose must not exceed 50 U/kg, and not exceed 100 U/kg within 24 hours	Single dose must not exceed 60 µg/kg ByClot®, and not exceed 90 µg/kg ByClot® within 24 hours
Second dose	20 IU/kg	20 IU/kg	30 IU/kg	At investigator's discretion	90 µg/kg	At investigator's discretion	Additional dose can be given at an interval of 8 hours or longer
Dose interval	Time between first and second dose must not be shorter than stated in local labelling[b]						
Anti-fibrinolytics	Local/topical use is allowed. Use of single systemic doses is allowed after careful benefit-risk evaluation					Not recommended	Not recommended

Notes: [a]Lowest dose in accordance with local labelling. [b]The interval between the two doses could be increased based on clinical case-by-case judgment keeping in mind that early breakthrough bleed control remains crucial.
Abbreviations: SHL=standard half-life, EHL=extended half-life

Severe and life-threatening bleeding episodes

From a patient safety perspective, specific recommendations for the management of severe and life-threatening bleeding episodes (see definition in Table 10 in the protocol) are not considered feasible as such management often poses several complex clinical challenges that need to be addressed case by case by the treating physicians hereby tailoring and securing the optimal treatment, which in some cases may be high factor replacement doses for extended periods of time. In the rare event of a severe (life-threatening) bleed the patient should be in immediate and close contact to the investigator and be treated with relevant doses of factor containing products at the discretion of the investigator.

Investigator−patient interactions and training

It is important that patients are trained in the management of bleeds. New and updated training material for both site staff and patients has been developed, see overview in Table 24.

Table 24 Overview of documents for investigator and patient training.

Investigators & Site Staff	Patients
Patient bleed treatment plan Guidance for management of bleeds.	Updated Informed Consent Forms Updated Patient Handbook Trial ID patient card – key instructions to the patient on how to proceed when suspecting a bleed.

Patient-specific bleed treatment plan

Investigative sites are encouraged to create a patient-specific plan for breakthrough bleed treatment such that all involved investigators are aligned in the treatment instructions to the patient when the patient contacts the site.

Patient education on management of bleeds

Adequate management of breakthrough bleeds is important for the patient's safety and overall disease outcome, and to the outcome of the trial. The investigator must educate the patient on adequate management of bleeds before (re-)start of concizumab treatment (i.e., visit 2a (arms 2−4) or visit 9a (arm 1)). The training conversation with the patient must be documented in the patient medical records and should as a minimum cover the below points:

- Introduce management of bleeds during concizumab prophylaxis as described in Sections 5.2.3 and 9.2.3
- Explain need for a cautious treatment approach while avoiding undertreatment
- Provide rationale to the patient for a close patient to site contact
- Instruct patients to contact site before every bleed treatment dose
- Discuss practicalities of contacts to the investigational site i.e. when, how and whom to contact
- Describe to the patient the difference between traumatic and spontaneous bleed
- Discuss severe bleeds and surgical procedures with the patient
- Explain what products the patient should use for treatment of bleeds and how
- Touch on dose levels and intervals between dosing
- Explain how to record bleeds and bleed treatment in the eDiary
- Introduce the patient information material and explain how to use it.

Investigator's responsibilities regarding patient information material

The investigator must hand out all approved supportive material to the patient for him to bring home. The purpose of the patient information material is to help the patient remember trial instructions and procedures, as well as to serve as documentation.

Furthermore, the investigator has the following responsibilities:

- Provide information to the patient in accordance with the latest version of the informed consent form, particularly Section 5 'What are the possible side effects or harms of taking part?'.
- Hand out the Patient Handbook to the patient and ensure that the patient is familiar with the content of the current version of the Patient Handbook to an extent that allows the patient to comply with the trial procedures. The Patient Handbook is developed as a tool for patients describing the trial and the connected trial procedures in layman terms, and it is recommended to put emphasis on following sections:
    - Bleeds
    - Treatment of bleeds
    - Thromboembolic events
    - Electronic Diary
- Hand out the Trial ID patient card, which carries key instructions to the patient on how to proceed when suspecting a bleed.

Investigator's responsibilities concerning reporting of bleeding episodes

Patients must report all bleeding episodes and bleed treatment in eDiaries when bleeds and treatment occur away from the investigational site. When occurring at the investigational site, circumstances of the bleed and the bleed treatment will be reported in the eCRF.

- Whenever recording a bleed in the eDiary, patients will receive a reminder on the eDiary device to contact investigator
- Investigator must report in the eCRF or eDiary-portal StudyWorks whether a patient-investigator contact was established before treating the bleed. The investigator must also report treatment type for each treatment
- Investigator is requested to perform a rating of the severity of each bleeding episode reported and report the severity in StudyWorks or in the eCRF as applicable

Appendix 12 Flowcharts applicable for patients enrolled before the treatment pause and who have permanently discontinued treatment prior to restart

The below flowchart is only applicable for those patients enrolled in the trial before the treatment pause and who have permanently discontinued from treatment prior to restart. Patients who enrolled in the trial or reinitiated treatment after the treatment pause must follow the flowcharts in Section 2.

	Main Part									Extension Part																		
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 9.1**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**	**Visit 27**
Visit	1[a]	2[b]	3[c]	4	5	6	7	8	9[b]	9.1[d]	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of Visit (Weeks)	-3	0	1	4	8	12	16	20	24	25	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±3	±3	±3	±3	±3	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
SUBJECT RELATED INFORMATION AND ASSESSMENTS																												
Informed consent	X																											
In/exclusion Criteria	X	X																										
Demography	X																											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant illness	X																											
Medical history	X																											
Details of Haemophila[l]	X																											
Haemophilia treatment and bleed history[l]	X	X																										
Target Joints	X								X																			
Treatment discontinuation criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation		X																										
EFFICACY																												
Bleeding episode		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Main Part									Extension Part																		
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 9.1**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**	**Visit 27**
Visit	1[a]	2[b]	3[c]	4	5	6	7	8	9[b]	9.1[d]	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of Visit (Weeks)	-3	0	1	4	8	12	16	20	24	25	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±3	±3	±3	±3	±3	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Body measurements[e]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Thrombin generation		X[b]	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sport activity		X						X																			X	
Concizumab ELISA[f]		X[b]	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Free TFPI		X[b]	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAFETY																												
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reaction		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[l]	X																											
Coagulation Parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation factors	X																											
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X																											
Physical examination	X	X							X					X						X							X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-concizumab antibodies	X	X		X	X	X	X	X	X			X		X			X			X			X				X	X
FVIII/FIX inhibitors	X																											
Total TFPI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OTHER ASSESSMENTS																												
PRO questionnaires																												
SF-36 v2 Health Survey		X		X	X		X		X																		X	

	Main Part									Extension Part																		
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 9.1**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**	**Visit 27**
Visit	1[a]	2[b]	3[c]	4	5	6	7	8	9[b]	9.1[d]	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Timing of Visit (Weeks)	-3	0	1	4	8	12	16	20	24	25	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167
Visit Window (Days)	±0	±0	±1	±3	±3	±3	±3	±3	±3	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Patient preference questionnaire				X					X																			
PROMIS Short Form Upper Extremity		X		X	X		X		X																		X	
PROMIS Numeric Rating Scale - Pain Intensity		X		X	X		X		X																		X	
Haemophilia Treatment Experience Measure		X							X																			
Haem-A-QoL[g]	X			X	X		X		X																		X	
PGI-S on physical functioning		X		X	X		X		X																			
PGI-C on physical functioning				X	X		X		X																			
TRIAL MATERIAL																												
Administration of trial product (on site)		X							X																			
Dispensing visit		X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug accountability		X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
REMINDERS																												
Human biological specimen for storage[l]	X[j]					X			X					X							X						X	
actiGraph dispensing/collection	X[h]						X[h]		X[h]																			
Hand out of Direction for Use		X[k]							X[d]																			
Hand out patient ID card and patient material	X																											
End of Treatment																											X	
End of trial																												X

Footnote
a) Only for patients from phase 2 (NN7415-4255, explorer 5): Visits 1 and 2 must be on same day. Patients will receive their first dose in this trial on the combined visit 1/visit 2 day. Assessments applicable for both visits 1 and 2 should only be performed once. Some assessments will also be transferred directly from phase 2, see section 9.
b) For patients having concizumab dosing at visit 2 there will be a 24-hour PK-session at visits 2 and 9. Please see details for PK sampling in section 2.1. For on-demand patients (arm 1) only the pre-dose sample will be taken.
c) Phone visit is allowed for patients enrolled from NN7415-4255 (explorer 5), arm 3, and patients randomised to arm 1 (on-demand patient).
d) Only for patients randomised to the on-demand treatment
e) Weight only, except at visit 1 where height is measured
f) Sample is taken pre-dose. Patients must not inject before the sample is taken.
g) Only for patients above ≥ 17 years old
h) Patients from phase 2, NN7415-4255 (explorer 5) should not use the actiGraph tracker. For patients coming from NN7415-4322 (explorer 6), actiGraph tracker should only be dispensed at visit 7. New patients should have the tracker at visits 1 and visit 7. See section 9.2.5 for further details.
i) A separate Informed Consent Form must be signed before any samples are taken. See section 9.7 for further details.
j) Whole blood for DNA is only taken at screening.
k) Only for patients receiving concizumab at visit 2.
l) Only for patients is arms 1,2 and 4 who did not participate in NN74154255 (explorer 5) and NN7415-4322 (explorer 6).

Pharmacokinetic (PK)/ Pharmacodynamic (PD) sampling flowchart

	Visit 2 and Visit 9 (PK/PD profile only applicable for patients on concizumab treatment from visit 2)				
PK sampling timepoint (hours)	**Pre-dose**	**3 hours***	**6 hours***	**9 hours***	**24 hours**
Sampling window	-1- 0 hours	±30 min	±30 min	±1 hour	±3 hours
PK ASSESSMENTS					
Concizumab Elisa	X	X	X	X	X
Free TFPI	X	X	X	X	X
Thrombin generation	X		X		X

*Patients coming from NN7415-4255 (explorer 5) should only have PK/PD sampling, pre-dose and after 24 hours at visit 2.
At visit 9 all patients (arms 2, 3 and 4) should have a full PK profile.