Cover Page for Protocol

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16.1.1 Protocol and protocol amendments

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Redacted protocol
Includes redaction of personal identifiable information only.

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Protocol

NN7415-4310

explorer™4

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

Trial phase: 2

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List of abbreviations

ABI	ankle-brachial index
ABR	annualised bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under curve
BP	blood pressure
BU	Bethesda Unit
CCDS	company core data sheet
CLAE	clinical laboratory adverse event
C_{max}	maximum plasma concentration
CNS	central nervous system
concizumab B	the name concizumab is being used as an abbreviation for concizumab B. B is the formulation

CPoC	clinical proof of concept
CRF	case report form
CRO	contract research organisation
CRP	c-reactive protein
CT	computerized tomography
cTn	cardiac troponin
CTR	clinical trial report
DFU	direction for use
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
DRC	data request correction
DUN	dispensing unit number
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eITMF	electronic investigator trial master file
ELISA	enzyme-linked immunosorbent assay

EMA	european medicines agency
EOT	end of trial
ePRO	electronic patient reported outcome
eptacog alfa	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to rFVIIa,'NovoSeven®, and 'NiaStaseRT®'
ETP	endogenous thrombin potential
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendment Act
FIX	coagulation factor IX
FPFV	first patient first visit
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FVIII:C	plasma activity of factor VIII
FX	coagulation factor X
FX_a	activated coagulation factor X
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHN	global haemophilia network

HCP	host cell protein
IB	investigator's brochure
IC	informed consent
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	independent ethics committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
INN	International Non-Proprietary Names for Pharmaceutical Substances
IRB	institutional review board
ISTH	International Society on Thrombosis and Haemostasis
IT	information technology
i.v.	intravenous(-ly)
IWRS	interactive web response system
LBBB	left bundle branch block
LPFV	last patient first visit
LPLV	last patient last visit

mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NIMP	non investigational medicinal product
PCD	primary completion date
PD	pharmacodynamics
PEF	peak expiratory flow
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome
PT	prothrombin time
Q	Inter compartmental clearance
QA	quality assurance
Q4D	every 4^{th} day

eptacog alfa (rFVIIa)	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to 'NovoSeven®'
sABR	spontaneous annualised bleeding rate
SAE	serious adverse event
SAS	safety analysis set
sBE	spontaneous bleeding episodes
s.c.	subcutaneous(-ly)
SI	international system of units
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TAT	thrombin-antithrombin complex
TEAE	treatment emergent adverse events
TIA	transient ischemic attack
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TMM	trial materials manual
TVP	trial validation plan
UTN	Universal Trial Number

1 Summary

The main objective for the phase 2 trial NN7415-4310, explorer™4, is to assess the efficacy of concizumab administered s.c. once daily to prevent bleeding episodes in haemophilia A and B patients with inhibitors. Furthermore, this trial aims to assess the longer-term efficacy and safety of concizumab in haemophilia A and B patients with inhibitors and to establish the safety of treating breakthrough bleeding episodes with recombinant factor VIIa (rFVIIa) in these patients.

Objective(s) and endpoint(s)

Primary objective

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors.

Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

Primary endpoint

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

Key secondary endpoints

- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset
- Number of treatment emergent adverse events (TEAEs) during at least 24 weeks from treatment onset

Time frames for evaluation of Objectives/Endpoints

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of dosing treatment with trial product (or has withdrawn). In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial design

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. We expect 16 patients to complete treatment in concizumab arm (concizumab prophylaxis) and 8 patients in comparator arm (rFVIIa on demand). The dose regimen is selected based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Both on-demand and prophylaxis patients will be eligible for the trial.

For all patients treated with concizumab (concizumab arm and comparator arm extention part) a loading dose of 0,5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0,15 mg/kg. All patients in treatment with concizumab will in a non-bleeding state receive a single dose of 90 µg/kg eptacog alfa (rFVIIa) one week after dosing with concizumab. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at the site after 24h.

The total trial duration for the individual patient will be approximately 86-88 weeks, consisting of a 2-4 week screening period, a subsequent 76-week treatment period and an 8-week follow-up period. eptacog alfa (rFVIIa) for treatment of bleeding episodes during the trial will be provided by Novo Nordisk. The patient will not be provided with trial product or eptacog alfa (rFVIIa) after end of trial.

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn. The analysis of the main part of the trial aims to substantiate the clinical proof of concept (CPoC) that concizumab has the potential to prevent bleeding episodes in patients with haemophilia and inhibitors. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial population

Number of patients planned to be screened: 28
Number of patients planned to be started on trial product: 26
Number of patients expected to complete the trial: 24

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 the suitability for the trial
- Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
- Patients currently in need of treatment with bypassing agents

Key exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Known inherited or acquired bleeding disorder other than haemophilia
- Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX

Key Efficacy assessment

- Number of bleeding episodes during at least 24 weeks of treatment onset

Key Safety assessment

- Number of treatment emergent adverse events during at least 24 weeks of treatment onset

Trial products

The following products will be used in the trial:

- **Investigational Medicinal Products:**
  - concizumab B, 100mg/mL to be administered s.c. with NovoPen®4 and needles
  - eptacog alfa (rFVIIa), 5mg /vial and histidine (solvent). Reconstituted eptacog alfa (rFVIIa) is for intravenous administration and used in the trial at visit 3 and 9.1 for all patients with the purpose of investigating the safety of administering eptacog alfa (rFVIIa) to haemophilia patients
- **Non Investigational Medicinal Product**:
  - eptacog alfa (rFVIIa) 5 mg /vial and histidine (solvent). Reconstituted eptacog alfa is for intravenous administration and used in this trial for treatment of bleeding episodes

2 Flow chart

2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]													Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
PATIENT RELATED INFO/ASSESSMENTS																						
Informed consent/ Genotyping and Long-term storage consent	●																					
In/exclusion criteria	●	●[g]																				
Demography	●																					
Concomitant illness/Medical history	●																					
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Details of Haemophilia/Haemophilia treatment and bleed history	●																					
Withdrawal criteria/ Criteria for premature discontinuation of trial product		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Randomisation (IWRS)		●																				
EFFICACY																						
Bleeding episodes [h, i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Thrombin generation (central lab)	●	●	●[j, k]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Free TFPI (central lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
SAFETY																						
Physical examination	●	●	●[k]						●	●						●				●	●	●
Body measurements	●	●[m]	●[k, m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]		●[m]	●[m]
Vital signs	●	●[n]	●[k, n]	●	●	●	●	●	●[n]	●[n]	●	●	●	●	●	●	●	●	●	●	●	●	●
ECG	●																						
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Injection site reaction		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Urinalysis (local lab)	●																					
Haematology (local lab)	●	●	●[j, k]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Biochemistry (central lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVIII/ FIX activity (central lab)	●								●[l]											●[l]		
Coagulation parameters (central lab)	●	●		●	●	●	●	●	●[l]		●	●	●	●	●	●	●	●	●	●[l]	●	●
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			●[j, k]							●[j]												
FVIII/FIX inhibitors (central lab)	●								●[l]											●[l]		
Anti-concizumab antibodies (ADA) (special lab) [o]	●	●	●[k, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
Concizumab ELISA (special lab)		●	●[k, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVII ELISA (special lab)			●[j,k]							●[j]												
Total TFPI (special lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
TRIAL MATERIAL																						
IWRS call	●	●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●		●[k]			●			●	●		●		●		●	●	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]						●[d, s]	●											●	
Administration of trial product (eptacog alfa)			●[k, t]							●[t]												
Drug accountability (concizumab)			●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New dose of trial product [e, u]				●	●	●	●	●	●		●	●	●	●	●	●	●	●	●		●	
PRO questionnaires	●	●	●[k]	●	●	●	●	●	●			●								●		
REMINDERS																						
Human biological specimen for storage (central lab)	●																					●

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
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Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Handout ID card	●																					
Training [v]	●	●							●	●											●	
Compliance: eDiary			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of treatment																				●		
End of trial																						●

The cells marked in 'red' are only for the patients randomised to eptacog alfa (rFVIIa) arm.

2.2 Explanatory descriptions

Footer	Description
a	There is staggered recruitment for the 4 first patients in the trial on the concizumab arm.
b	Concizumab administration is performed at home except for visit 2 and visit 3 for patients randomised to concizumab and visit 9 and 9.1 for patients randomised to eptacog alfa. Sampling for Free TFPI, Anti-concizumab antibodies, Concizumab ELISA and Total TFPI are done prior to concizumab administration.
c	The duration of the visits will last according to patient's individual training need on concizumab administration, NovoPen®4, eDiary training etc. Visit 3 and visit 9.1 have a PK session of 24 hours and a safety follow up visit the following day.
d	Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment.
e	For patients being dose escalated on concizumab a phone call is recommended 1 week after first dose of concizumab.
f	Daily dosing preferably at the same time in the morning.
g	Evaluation of the laboratory results obtained from samples taken at screening.
h	Bleeding episodes occurring between visit 1 and visit 2 or at site should be registered in the eCRF. All bleeding episodes except for severe occurring after visit 2 at home should be registered in the eDiary. Severe bleeding episodes must be registered in the eCRF.
i	Eptacog alfa will be given to treat breakthrough bleeding episodes.
j	Sampling time schedule for thrombin generation, haematology, coagulation parameters and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.
k	ONLY for patients randomised to concizumab arm.
l	At visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.
m	Only body weight should be measured.
n	Vital signs should be evaluated before and after trial drug administration at visit 2 and visit 3 for concizumab arm and at visit 9 and visit 9.1 for patients in eptacog alfa arm switching to concizumab treatment.
o	In case clinical signs of e.g. hypersensitivity reactions or immune related events are seen, additional samples for ADAs may be taken. All antibody samples from the affected patient will be analysed on an ongoing basis. If antibodies are detected, additional blood samples will be taken and stored for characterisation of the antibodies.
p	Blood sampling for anti-concizumab antibodies and concizumab ELISA testing should only be collected for patients on concizumab.
q	If needed dispensing of eptacog alfa, histidine, trial injection kits and Direction For Use (DFU).
r	First treatment dose of concizumab is a loading dose and will be administered at visit 2 for the concizumab arm and visit 9 for the eptacog arm.
s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g., eptacog alfa, FEIBA®) for prophylaxis or treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2.

t	Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm.
u	Patient treated with concizumab should be dose escalated at next scheduled visit if he experiences ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab. If the investigator judges that next scheduled visit is too late an unscheduled visit should be performed for dose escalation.
v	Home treatment training must take place at visit 2 at the latest and whenever needed afterwards. Patients randomised to eptacog alfa will be re-trained in NovoPen®4 and s.c. administration at visit 9 and 9.1. If necessary training can be performed as needed at other visits. The eDiary will be provided to the patients at visit 2 if the patient feels capable in s.c. administration and using the eDiary. Further the patients will be trained in recognition of signs/symptoms of thrombosis.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [1], applicable regulatory requirements, in accordance with the Declaration of Helsinki [2] and ISO 14155 [3].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

The INN name of the active pharmaceutical ingredient is concizumab (synonyms used during early development are NNC0172-2021, anti-TFPI, NN7415 or mab2021). Throughout this document "concizumab" is used as the name of the trial drug.

3.1 Background information

3.1.1 Haemophilia

Haemophilia is an inherited bleeding disorder characterised by an increased bleeding tendency, typically in weight bearing joints. Haemophilia A is caused by a partial or complete deficiency of blood coagulation factor VIII (FVIII). In haemophilia B, it is factor IX (FIX) that is deficient. Inheritance is chromosome X-linked; therefore the disease mainly affects males. The incidence of haemophilia A and B on average is estimated to be about 1 in 5000 live male births [4]. According to the World Federation of Haemophilia global survey of 2014[5], about 178,500 persons are diagnosed with haemophilia worldwide. Of these, about 80% have haemophilia A.

Haemophilia is classified as "severe", "moderate" or "mild" according to the plasma activity of the affected coagulation factor [6]. 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 [7]. The haemostatic plug, if formed, in these patients 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 occurs spontaneously and is the most frequent symptoms 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 majority of children with severe haemophilia experience their first bleeding episode into a joint prior to age 4 year. Many children also bleed from other body sites before this age is reached [8]. For this reason, primary prophylaxis with regular FVIII or FIX injections in the non-bleeding state is the recommended treatment from early childhood.

In patients who have developed inhibitors towards FVIII or FIX, replacement therapy is rendered ineffective. Though prevalence studies and registry data indicate that the prevalence of inhibitors in the haemophiliac population overall has been reported to be between 5% and 7% [9], the prevalence

amongst patients with severe haemophilia (FVIII:C < 1%) is higher and has been reported to be up to 30% [9, 10]. These patients may be treated with bypassing agents, activated FVII (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) given as i.v. injections.

Current treatment options in haemophilia, replacement therapy or bypassing therapy, are hampered by the fact that these products must be given as i.v. injections. Furthermore, bypassing agents are characterized by relatively short half-lives, therefore prophylactic treatment is burdensome. It is also generally acknowledged that the efficacy profile of bypassing agents is inferior to replacement therapy. Consequently, delayed or sub-optimal treatment occurs in a significant number of patients with inhibitors. A new therapeutic agent that can be administered subcutaneously will represent a major improvement in the treatment of these patients in a prophylaxis setting.

3.1.2 Concizumab

The trial product, concizumab, is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype with a molecular weight of 149 kilo Dalton's. Like other antibodies, concizumab is composed of two light chains and two heavy chains linked together by disulfide bridges. To prevent formation of half-antibodies, the serine at position 241 in the heavy chain has been replaced with a proline (S241P (Kabat annotation)) [10]. The mechanism of action of concizumab is based on the concept of inhibiting the activity of a natural coagulation inhibitor, tissue factor pathway inhibitor (TFPI). TFPI is a potent inhibitor of the initiation phase of the coagulation process, i.e. the activation of (FX) to FXa by the tissue factor (TF)/factor VIIa (FVIIa) complex. TFPI first binds to and inhibits activated FXa and subsequently binds to and inhibits the TF/FVIIa complex, forming a TF/FVIIa/FXa/TFPI complex. Thus, concizumab prevents both inhibition of FXa and inhibition of FVIIa/TF by TFPI. In this manner, sufficient amounts of FXa to ensure effective haemostasis in the absence of a functional activated factor IX/activated factor VIII (FIXa/ FVIIIa) complex may be generated. This is a new concept that remains to be documented safe and efficacious in patients with haemophilia. More information about the physiological role of TFPI and the mode of action of concizumab is provided in the Investigator's Brochure.

Key differentiators of this new mode of action (MoA) and the key benefit of concizumab in patients with severe haemophilia A and B with inhibitors is reduced treatment burden due to subcutaneous administration potentially leading to better adherence, more patients on prophylactic treatment and ultimately better outcome.

Four clinical trials with concizumab have been completed thus far: the first human-dose trial (NN7415-3813, explorer™1) [11], a single dose trial in Japanese healthy subjects (NN7415-3981), two multiple dose trials (NN7415-3986, explorer™2) and (NN7415-4159, explorer™3). When the first cohort with 4 (four) healthy subjects in explorer™2 was completed, prior to the initiation of the 2nd cohort, the trial was halted, due to findings related to thrombosis in an ongoing 26-week toxicity study in primates. In this trial animal had concizumab plasma concentrations several hundred fold

above clinically relevant concentrations. Follow up investigations confirmed that the animal's condition was related to thrombosis in the lungs caused by exaggerated pharmacology at these high plasma concentrations. Before the initiation of the fourth phase 1 trial (NN7415-4159), explorer™3, a new 52 week non-clinical toxicology study was conducted in primates to investigate the findings in the previous study. The conclusion from this new non-clinical study was that the results from non-clinical studies support further clinical development of concizumab. Explorer™3 was a multiple dose clinical trial which aimed to investigate the safety, pharmacokinetics and pharmacodynamics of concizumab at five different dose levels in adult severe haemophilia A patients without inhibitors. In this trial multiple doses of concizumab were administered s.c. over a period of six weeks.

The explorer™3 trial was finalised following the completion of cohort 3 (0.8 mg/kg s.c. every 4 days for 6 weeks). Blinded preliminary safety and PK/PD data from the cohort was reviewed by the concizumab safety committee. Marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range. In addition, a substantial inter subject variation in pro-coagulant response to the drug was observed. Based on this, the Novo Nordisk safety committee (see Section 12.8.1) decided not to proceed to cohort 4 (1.1 mg/kg s.c. every 4 days for 6 weeks). No clinical consequences or serious adverse events were seen in the completed cohorts in explorer™3.

The PK results from explorer™3 showed exposure-response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL. Individual predicted PK profiles merged with recorded spontaneous and traumatic bleeding episodes are shown in Figure 3–1.

Figure 3–1 Individual predicted PK profiles based on data merged with recorded spontaneous (circles) and traumatic (triangles) bleeding episodes during the dosing period and follow-up period. All data originates from explorer™3 (N=24 patients). PK of concizumab is subdivided into three exposure levels of ≤ 20 ng/mL, 20-100 ng/mL, and > 100 ng/mL together with the number of contributing patients. LLOQ: lower limit of quantification.

[a] 'Time in trial' refers to the time that the patients spent on each concizumab exposure level, and the ≤ 20 ng/mL level therefore also includes the screening period (not shown on this figure).

A large difference between the peak and trough plasma concentrations of concizumab were observed as well, especially in the highest dose group (0.80 mg/kg) of explorer™3. In patients who received 0.25, 0.5 and 0.8 mg/kg doses a significant overlap in plasma concentrations of concizumab was seen due to high between-patient variability in concizumab.

Single doses of concizumab up to 9 mg/kg have been administered to haemophilia patients in the first human dose trial with concizumab, explorer™1. These doses resulted in plasma concentrations of concizumab that were significantly higher than the ones that are modelled to be reached in the highest escalated daily dose (0.25 mg/kg) of explorer™4.

In a drug–drug interaction study in monkeys (NN215431), three doses of up to 1 mg/kg of NovoSeven® were administered at 2h intervals, alone or in the presence of a steady state concentration of concizumab. No notable clinical observations were made, no treatment-related

adverse findings were seen, i.e. no thrombi or other signs of excessive coagulation. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation.

For an assessment of benefits and risks of the trial, see Section 18.1.

For further information, please refer to the Investigator's Brochure.

3.2 Rationale for the trial

Four phase 1 clinical studies with concizumab have been finalised. Key safety and preliminary efficacy results from these phase 1 studies support further development of concizumab in haemophilia patients. Therefore, the main objective in the phase 2 of concizumab development is to assess efficacy and safety and provide data that will guide for the confirmatory phase 3 concizumab trials.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors

4.1.2 Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

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

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset

- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset
- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

Supportive secondary pharmacokinetic endpoints

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

Supportive secondary pharmacodynamic endpoints

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

4.2.3 Exploratory endpoints

4.2.3.1 Exploratory safety endpoints

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

4.2.3.2 Exploratory patient reported outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset

- Change in Hemo-TEM after 76 weeks from treatment onset
- Change in VERITAS-Pro® or VERITAS-PRN® after 24 weeks from treatment onset
- Change in VERITAS-Pro® or VERITAS-PRN® after 76 weeks from treatment onset
- Change in SF-36v2 after 24 weeks from treatment onset
- Change in SF-36v2 after 76 weeks from treatment onset
- Change in SDS after 24 weeks from treatment onset
- Change in SDS after 76 weeks from treatment onset
- Change in TSQM after 24 weeks from treatment onset
- Change in TSQM after 76 weeks from treatment onset
- Change in SIAQ-ISRQ after 24 weeks from treatment onset
- Change in SIAQ-ISRQ after 76 weeks from treatment onset
- Change in PGI-C after 24 weeks from treatment onset
- Change in PGI-C after 76 weeks from treatment onset

All endpoints referring to a time frame of either 24 weeks or of at least will be evaluated in the main part of the trial. All endpoints referring to a time frame of 76 weeks will be evaluated in the extension part of the trial.

5 Trial design

5.1 Type of trial

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. The selected dose regimen is based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Both on-demand and prophylaxis patients will be eligible for the trial.

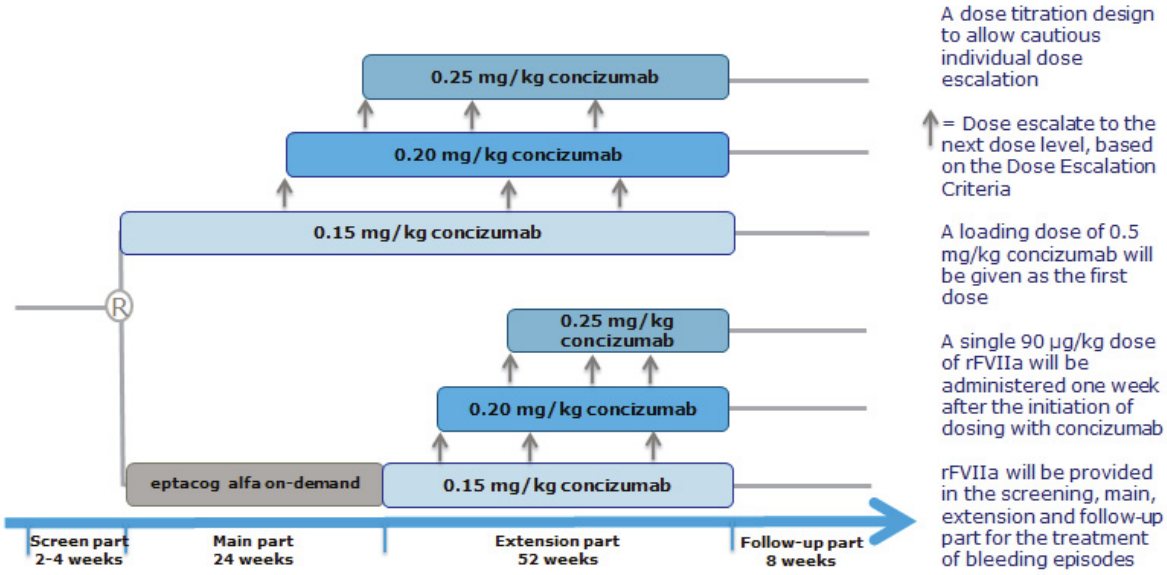

Figure 5–1 Schematic diagram of the trial design

The total trial duration for the individual patient will be approximately 86-88 weeks, including a 2-4 week screening period, a 76 week treatment period, and a follow-up period of 8 weeks, see Figure 5–1

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts up to 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn.

In the concizumab arm bleeding episodes occurring during the trial will be treated with eptacog alfa (rFVIIa). In all patients treated with concizumab a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state one week after dosing with concizumab has been initiated. The investigator will evaluate if there are any safety concerns 24 hours post eptacog alfa (rFVIIa) administration. Furthermore, the scheduled administration of eptacog alfa (rFVIIa) for the first 4 patients entering the trial with concizumab will be staggered.

In the comparator arm, in the main part, patients will receive eptacog alfa (rFVIIa) on-demand treatment. After completion of the main part, the patients will continue the trial in the extension part being treated with prophylactic concizumab 0.15 mg/kg (with potential dose escalation) s.c. daily administration.

Human biosamples (plasma, serum, and/or DNA for genotyping) will be collected in this trial for future exploratory analysis to pursue a deeper insight into the biology of TFPI, coagulation, and effect of concizumab on joint health. That may include coagulation parameters and markers of joint status and damage. Acceptance of storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for human biosamples to be stored for future exploratory analysis, see Section 8.1.1.

An independent data monitoring committee (DMC) will be established for this trial. The DMC will review all safety data from the ongoing trial with concizumab exposure, see Section 12.8.2.

5.1.1 Surgery

Minor surgery is allowed in this trial. Major surgery conducted earlier than one month (30 days) prior to trial start is allowed, see exclusion criteria no 6.

Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. Examples of minor surgery include implanting of central venous access devices (ports, CVC, pumps and other CVADs) in subcutaneous tissue, skin biopsies or simple dental procedures.

5.2 Rationale for trial design

Explorer™4 is a phase 2, clinical proof of concept (CPoC), and safety trial. The trial aims to substantiate CPoC that concizumab has the potential to prevent bleeding episodes in haemophilia patients with inhibitors. A dose escalation design will allow cautious dose escalation in order to identify an efficacious and safe concizumab dose for the individual patient. A comparator arm is included to assess if concizumab is superior to on-demand treatment. Furthermore, the trial will give a possibility to assess safety of co-administration of eptacog alfa (rFVIIa) to the patients exposed to the concizumab treatment.

The duration of 24 weeks for the main part of the trial is deemed necessary in order to obtain information on the annualised bleeding rate on concizumab prophylaxis. The duration of the extension part of the trial will be 52 weeks and provide further information on efficacy, i.e. annualised bleeding rate, and also provide additional safety data upon 76 weeks treatment with concizumab.

A total of 26 patients previously on prophylaxis (PPX) or on-demand (OD) treatment will be randomised into one of the two arms, with 16 patients in the concizumab arm and 8 patients in the comparator arm see Figure 5–1. Concizumab will be administered s.c. daily for patients randomised to the concizumab arm in the main and the extension part of the trial. For patients in the comparator arm in the extension part treatment will be changed from on-demand with rFVIIa to prophylaxis with concizumab.

The concizumab dose regimens will be starting with 0.15 mg/kg with the possibility to escalate to 0.20 mg/kg and 0.25 mg/kg based on bleeding frequency, see Section 5.3.3.

Daily dosing with concizumab 0.15 mg/kg aims to ensure steady-state levels of concizumab plasma concentrations above 100 ng/mL for the majority of the patients starting on this dose. The PK results from explorer™3 showed exposure response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL, see Figure 3–1 . The minority of patients which are predicted to have steady-state plasma concentrations below this threshold are expected to experience bleeding episodes and therefore will have the opportunity to be dose escalated to the dose of 0.2 mg/kg. A further dose escalation to 0.25 mg/kg per day is permitted, again based on the bleeding rate, see Section 5.3.3

Figure 5–2 Individual predicted concizumab concentration profiles for all concizumab-treated patients in explorer™2 (n=4 patients) and explorer™3 (n=18 patients). The horizontal lines indicate 100 ng/mL, and the shaded areas represent the full range (min-max) of the individual predicted profiles.[1]

Due to the high between patient variability in concizumab concentration observed in explorer™3, a significant overlap in plasma concentrations of concizumab in patients who received 0.25, 0.5 and 0.8 mg/kg doses was seen, see Figure 5–2. Therefore, choosing three doses that would lead to reasonably distinct mean plasma concentrations of concizumab, and thus different efficacy at each

[1] Plasma concentrations in the same range as those in explorer™3 are expected to be reached in this trial with daily dose administration. The starting dose for all patients will be 0.15 mg/kg daily. The plasma steady-state exposure for a typical subject at this dose level is predicted to fourfold lower compared to a typical subject on 0.8 mg/kg Q4D (cohort 3 of explorer3) in terms of both Cmax and AUC 0-24h. For 0.20 mg/kg daily and 0.25 mg/kg, the plasma steady-state exposure levels for a typical subject are predicted to be less than 40% and 70% respectively, compared to the typical subject exposure in the 3rd cohort of explorer™3 (AUC and Cmax). The maximum predicted plasma exposure levels (Cmax and AUC 0-24h) for the 0.15 mg/kg daily dose level is predicted to be more than 8 fold lower than for 0.80 mg/kg Q4D. For 0.20 mg/kg daily both Cmax and AUC 0-24h are predicted to be more than 3 times lower than for 0.80 mg/kg Q4D. For 0.25 mg/kg daily, the maximum Cmax and AUC 0-24h are predicted to be 35% lower than for 0.80 mg/kg Q4D.

dose level was not deemed possible. For this reason, a traditional parallel arm design was not chosen for the phase 2 trials. In contrast, the titration trial design allows patients to start on a low dose, which is expected to ensure prophylaxis but not marked changes in coagulation parameters, for the majority of patients. Escalation to the next dose level will only occur in the case of lack of efficacy (≥ 3 spontaneous bleeding episodes within the preceding 12 weeks). In addition, the PK of concizumab is heavily influenced by target mediated drug disposition, which means that small differences in concizumab dose ultimately leads to large differences in plasma concentrations. Therefore, daily dosing is proposed for the phase 2 trial, explorer™4. Daily dosing will allow for the increase in trough levels and thus better efficacy may be expected with a lower dose.

A loading dose of 0.5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0.15 mg/kg in order to ensure steady-state levels at the time of eptacog alfa (rFVIIa) administration. eptacog alfa (rFVIIa) will be administered one week after initiation of dosing with concizumab in a non-bleeding state to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment.

Embryonic exposure in pregnant female partners of men treated with concizumab is highly unlikely and there is no need for protocol requirements for use of contraception in phase 2 and 3 trials.

5.3 Treatment of patients

The following products will be administered in the trial.

Table 5–1 List of products provided by Novo Nordisk

Compound Name	Strength	Dosage form	Route of administration	Treatment period
concizumab B [a]	100 mg/mL	solution for s.c. injection in a 3 mL cartridge [b]	Subcutaneous administration using NovoPen®4	For prophylactic treatment in 76 weeks (for concizumab arm in the main part and extension part). For prophylactic treatment in 52 weeks (for comparator arm in the extension part).
eptacog alfa (rFVIIa) [a, c]	5 mg/vial	Powder for solution for i.v. injection	Intravenous administration	For treatment of breakthrough bleeding episodes at the discretion of the investigator (screening, main, extension and follow up part). [c] Administration of doses higher than
histidine solvent (5 mL)		Prefilled syringes for solution for i.v. injection		

				90µg/kg to patients exposed to concizumab is not allowed. For on-demand treatment at the discretion of the investigator in 24 weeks for comparator arm in the main part. In the concizumab arm and comparator arm after switching to concizumab in the extension part of the study a single 90µg/kg dose for initial safety assessments in a non-bleeding state. [a] Will be provided for as long as patients participate in the trial (screening, main, extension and follow up part)

[a] Investigational medicinal product (IMP)
[b] Not to be confused with the daily injected volume (~150 µL, depending on dose strength and body weight)
[c] Non-investigational medicinal product (NIMP)

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with national legislation and a copy of the label can be found in the Trial Materials Manual, see Section 9.

5.3.1 Concizumab arm

5.3.1.1 Concizumab prophylactic treatment (main and extension part)

Concizumab will be given s.c. once daily 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg). The dose escalation criteria are described, see Section 5.3.3. The first dose of concizumab will be given at the trial site under medical supervision.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 2 in order to ensure steady state levels at the time of the administration of eptacog alfa (rFVIIa) in a non-bleeding state at visit 3, see Section 5.3.4.

The patients will be trained in s.c. administration of concizumab with NovoPen®4 at the screening visit and at the first scheduled treatment visit.

5.3.2 Comparator arm (eptacog alfa (rFVIIa))

5.3.2.1 On-demand treatment (main part)

During the main part of the trial, patients will receive eptacog alfa (rFVIIa) for treatment of bleeding episodes, with a dose regimen at the discretion of the investigator.

5.3.2.2 Concizumab prophylactic treatment (extension part)

After completion of the main part, the patients will continue the trial in the extension part and will switch to prophylactic treatment with s.c. daily administration of concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) s.c. daily administration.

The same dose escalation criteria as described below (for the initial concizumab arm) will apply.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 9 in order to ensure steady state levels at the time of the administration of rFVIIa in a non-bleeding state at visit 9.1.

5.3.3 Dose escalation

The dose escalation criteria as described below will apply to all treatment arms.

Bleeding episodes will be assessed during the trial both at scheduled visit and also between visits. The first 2 weeks of the treatment with concizumab 0.15 mg/kg is considered as a run-in period. Hence, bleeding episodes occurring during first 2 weeks should not influence a dose escalation decision.

All spontaneous bleeding episodes (sBEs) are counted from 2 weeks after visit 2 (or visit 9 when switching from eptacog alfa (rFVIIa) to concizumab) (first treatment visit) until visit 16 (end of treatment visit), i.e. a total of 74 weeks. Dose escalation will be based on the number of spontaneous treated bleeding episodes in patients within preceding 12 weeks. However, before dose escalation can occur, to ensure the safety of the patients, the investigator must take into account the full clinical picture the patient is presenting with and all available laboratory results, including coagulation parameters.

Dose 0.15 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE). If yes, and if investigator deems it safe, the patient will be dose escalated from 0.15 to 0.20 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.20 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.20 mg/kg treatment period. If yes, and if investigator deems it safe, the patient will be dose escalated from 0.20 to 0.25 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.25 mg/kg:
Patients are not dose escalated further regardless of the number of sBEs.

The possibility of dose escalation at unscheduled visits is necessary in order to avoid bleeding episodes at inadequate dose level: e.g. if the dose escalation eliciting bleeding episode occurs soon after a scheduled visit, the patient will avoid to wait8 weeks for the next scheduled visit (in the extension part).

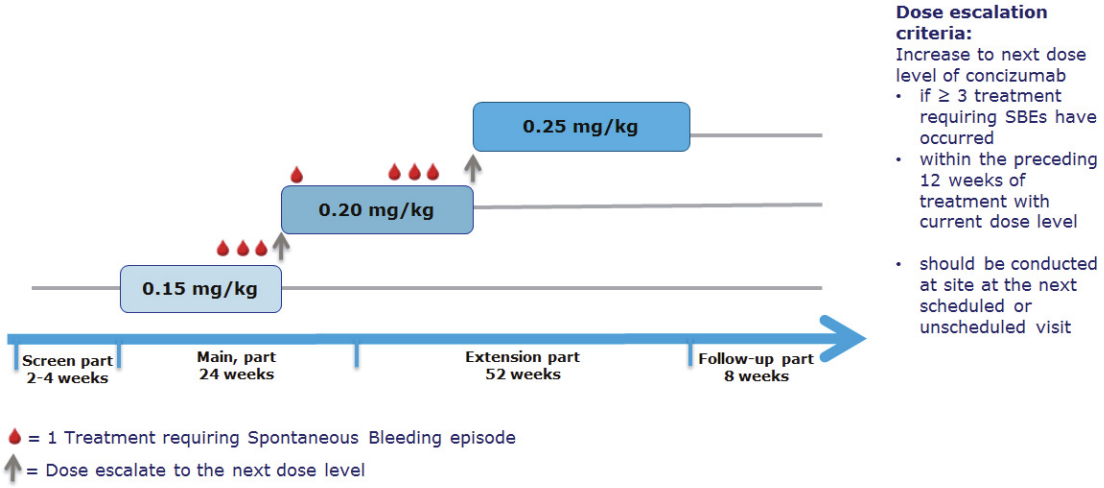

Figure 5–3 Dose escalation for one individual patient in the concizumab arm

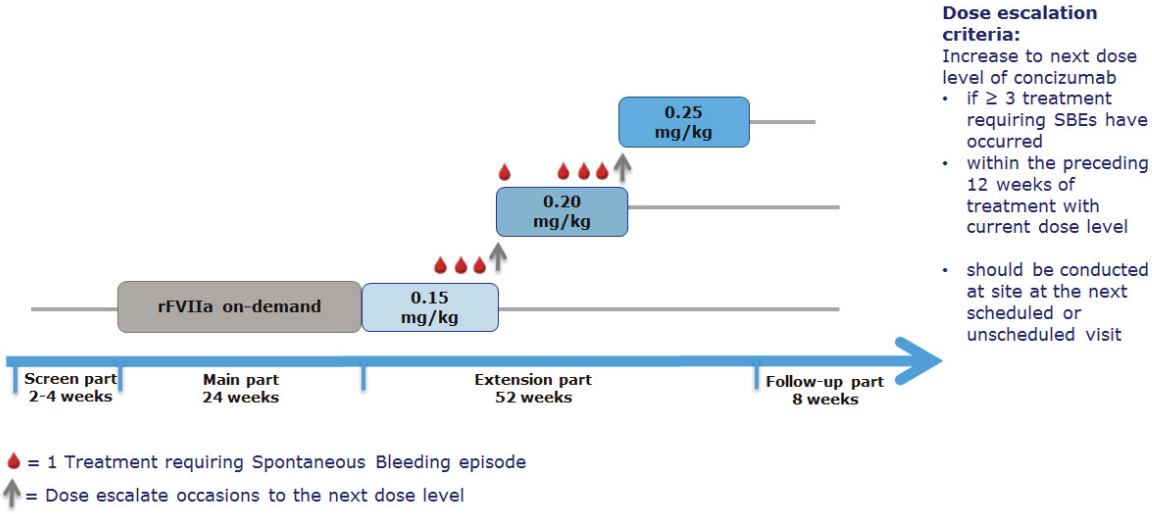

Figure 5–4 Dose escalation for one individual patient in the comparator arm

5.3.4 Co-administration of eptacog alfa (rFVIIa)

eptacog alfa (rFVIIa) will be used for treating breakthrough bleeding episodes in this trial; one week after initiation of dosing with concizumab, a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state at the trial site under medical supervision to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at site after 24h. Between 12h and 24h, the patient must either stay at the site or at a hotel or at home if he lives nearby to be able to continue visit 3 or 9.1 the day after. Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to concizumab arm will be staggered so that the period between eptacog alfa (rFVIIa) administrations from one patient to another is at least 48 hours. If no safety concerns are observed (for example signs and symptoms of thromboembolism, such as swelling, pain and redness of the leg, shortness of breath, and chest pain) by the investigator in the period between the administration of eptacog alfa (rFVIIa) and when the next daily concizumab dose is to be given, the investigator allows the individual patient to administer concizumab prophylactically at home and if needed, treat breakthrough bleeding episodes at home with eptacog alfa (rFVIIa). The patients will receive prophylactic doses of concizumab 0.15 mg/kg daily throughout the main part (24 weeks) and the extension part (52 weeks), unless dose escalation criteria are fulfilled, see Section 5.3.3.

In case safety concerns are raised by an investigator after eptacog alfa (rFVIIa) administration and these concerns meet the described criteria for putting enrolment of additional patients on hold, dosing in the individual patients will be halted and further recruitment in the trial will be halted, see

Section 12.7. In case safety concerns that do not meet the criteria for putting enrolment of additional patients on hold are observed by the investigator, dosing in that individual patient will be halted until further evaluation. In such cases, all available data will be assessed by the Data Monitoring Committee (DMC), see Section 12.8.2.

5.3.5 Treatment of bleeding episodes during the trial

Breakthrough bleeding episodes between visit 1 and visit 2 can be treated with any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) up to a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to first concizumab administration at visit 2. Novo Nordisk will provide eptacog alfa (rFVIIa) throughout the trial. The patient can treat himself and then he must call the site. The bleeding episode must be recorded in the eCRF.

Breakthrough bleeding episodes between visit 2-3 in the concizumab arm and visit 9-9.1 in the comparator arm must be treated with eptacog alfa (rFVIIa). Upon breakthrough bleeding episodes in this period the patient must first call the site. The investigator should instruct the patient about whether he should go to the site to receive treatment or if he can administer a single dose of eptacog alfa (rFVIIa) which is not higher than 90µg/kg without delay to treat the breakthrough bleeding episode. If the patient is instructed to administer the eptacog alfa (rFVIIa) dose at home, following the administration, the patient should immediately go to the site for further clinical evaluation. The bleeding episode must be recorded in the electronic Diary (eDiary).

Breakthrough bleeding episodes between visit 3 and visit 16 in the concizumab arm must be treated with eptacog alfa (rFVIIa). The patient can treat himself without delay but must inform the site that a bleeding episode has occurred. Doses of eptacog alfa (rFVIIa) that are lower than 90µg/kg may be used to treat breakthrough bleeding episodes at the discretion of the investigator. Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. If a single dose of eptacog alfa (rFVIIa) is not sufficient to stop a bleeding episode, the patient should inform the site and in agreement with the investigator may administer a second dose of eptacog alfa (rFVIIa) not higher than 90µg/kg 2-3h after the first dose has been administered. The same procedure should be repeated in case the second dose of eptacog alfa (rFVIIa) is not sufficient to stop the bleeding episode. If more than three 90µg/kg doses of eptacog alfa (rFVIIa) are needed to stop a bleeding episode, the patient should go to the site without delay. The definition and diagnostic criteria of DIC, acute myocardial infraction, stroke, deep vein thrombosis, pulmonary embolism and peripheral artery occlusion is provided in section 12.1.6. The bleeding episodes must be recorded in the eDiary.

Breakthrough bleeding episodes between visit 16 and visit 17 (follow-up part) may be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator. The patient can treat himself with eptacog alfa (rFVIIa) at home without delay. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The bleeding episodes must be recorded in the eDiary.

See Table 5–1 and Table 8–3.

5.3.6 Prohibited medication

- Treatment with anti-fibrinolytics (e.g. tranexamic acid, aminocaproic acid)
- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anticoagulants (DOACs)
- Home treatment (between visit 2 and visit 16) with activated prothrombin complex concentrates (FEIBA®)

5.4 Treatment after discontinuation of trial product

When discontinuing trial products (visit 16 or earlier), the patient should be switched to a suitable marketed product at the discretion of the investigator. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The patient will not be provided with concizumab or eptacog alfa (rFVIIa) after end of trial (EOT) (visit 17) by Novo Nordisk.

5.5 Rationale for treatment

Concizumab is a monoclonal antibody and as such offers the possibility of s.c. administration. S.c. administration of an effective prophylactic drug has potential to reduce the treatment burden compared to the currently approved prophylactic drugs which have to be administered i.v. Furthermore, the current treatment options for prophylaxis in inhibitor patients do not reduce the frequency of breakthrough bleeding episodes to the same extent as prophylaxis with replacement therapy in non-inhibitor patients. Concizumab may therefore show a better efficacy profile compared to current treatment options in haemophilia A and B patients with inhibitors.

The treatment period during at least 24 weeks (the main part of the trial) is considered necessary for providing robust data that allow demonstration of clinical proof of concept and to support decision making regarding a phase 3 confirmatory trial. Dosing for additional 52 weeks will provide valuable long term efficacy and safety data.

Breakthrough bleeding episodes occur in prophylactic regimens with both bypassing agents and replacement therapy. Therefore, it is expected that breakthrough bleeding episodes will occur during prophylaxis with concizumab even if clinical proof of concept is demonstrated. Consequently, eptacog alfa (rFVIIa) will be provided by Novo Nordisk in this trial for treatment of breakthrough bleeding episodes. In order to minimize the likelihood of any unforeseen adverse events associated with administration of eptacog alfa (rFVIIa) in these circumstances, administration of eptacog alfa (rFVIIa) in a controlled setting will be performed at visit 3 or 9.1.

Please refer to the Investigator's Brochure for further information.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 28

Number of patients planned to start on trial product: 26

Number of patients expected to complete the trial: 24

- Preferably 21 haemophilia A patients
- Preferably 3 haemophilia B patients

Discontinued patients will not be replaced.

6.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

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 the suitability for the trial
2. Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
3. For patients treated on-demand, a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening
4. Documented history of high-titer inhibitors towards FVIII or FIX, defined as ≥ 5 Bethesda Units
5. Patients currently in need of treatment with bypassing agents

6.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within the last 30 days or 5 half-lives (whichever is longer) from the last drug administration before screening
4. Any disorder which in the investigator's opinion, might jeopardise patient's safety or compliance with the protocol
5. Known inherited or acquired bleeding disorder other than haemophilia
6. Major surgery conducted within one month prior to the initiation of trial activities or major surgery planned to occur during the trial

7. Previous history of thromboembolic disease. Current clinical signs of thromboembolic disease or patients who in the judgement of the investigator are considered at high risk of thromboembolic events
8. Mental incapacity, unwillingness to cooperate or language barrier precluding adequate understanding and cooperation
9. Patients who, at screening, have a significant infection or known systemic inflammatory condition which requires systemic treatment according to the investigator's judgement
10. Hepatic dysfunction defined as elevated liver transaminases (ALT) >3 times the upper limit of normal laboratory reference ranges at screening
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m^2 for serum creatinine measured at screening for patients without evidence of renal damage
12. Platelet count ≤ $100x10^9$/L at screening
13. Fibrinogen level < the lower limit of normal
14. Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX
15. Antithrombin levels below the normal reference range at screening

6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation 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. Anaphylactic reaction
5. Thromboembolic event
6. Event of Disseminated Intravascular Coagulation
7. Loss of efficacy due to neutralizing antibodies

See Section 8.1.4 for procedures to be performed for patients discontinuing trial product prematurely.

6.5 Withdrawal from trial

The patient may withdraw consent at will at any time.
See section 8.1.5 for procedures to be performed for patients withdrawing consent.

6.6 Patient replacement

Patients who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

The most important reason for choosing the trial population, haemophilia with inhibitors, is that there is a significant unmet medical need in this patient population for

1. A more effective treatment and
2. A treatment which reduces treatment burden.

In addition to this, since most of these patients are likely to have been treated and therefore familiar with eptacog alfa (rFVIIa) on-demand treatment, this trial population is considered the most suitable for assessing the safety of administering eptacog alfa (rFVIIa) to patients in whom plasma TFPI levels are inhibited. Finally, the trial population reflects the patient population that will be selected in a potential subsequent phase 3 trial in which the efficacy and safety of concizumab are to be confirmed.

7 Milestones

Planned duration of recruitment period (FPFV-LPFV): 28 weeks

Planned FPFV:	16-Aug-2017
Planned FPFT:	30-Aug-2017
Planned LPFV:	28-Feb-2018
Planned LPLV:	23-Oct-2019

The total duration of concizumab treatment in this trial is 76 weeks for an individual patient randomised to concizumab prophylaxis treatment at visit 2.

The total duration of concizumab treatment in the trial is 52 weeks for an individual patient randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2.

EOT is defined as last patient last visit (LPLV).

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further patients may be screened and the IWRS will be closed for further screening. All patients screened during the recruitment period and found eligible for randomisation can be randomised in a 2:1 allocation to either the concizumab or the comparator arm within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, how-we-disclose-trial-information, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE), [12] the Food and Drug Administration Amendment Act (FDAAA), [13] European Commission Requirements, [14 15] 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.

Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this protocol LPFT (visit 2) + 24 weeks corresponding to visit 9. If the last patient is withdrawn early the PCD is the date when the last patient would have completed visit 9. The PCD determines the deadline for results disclosure at ClinicalTrials.gov according to FDAAA.[13]

8 Methods and assessments

Assessments to be performed at the scheduled and at the unscheduled visits in the trial are described in this section, Figure 8–1, Figure 8–2 and in Section 2.

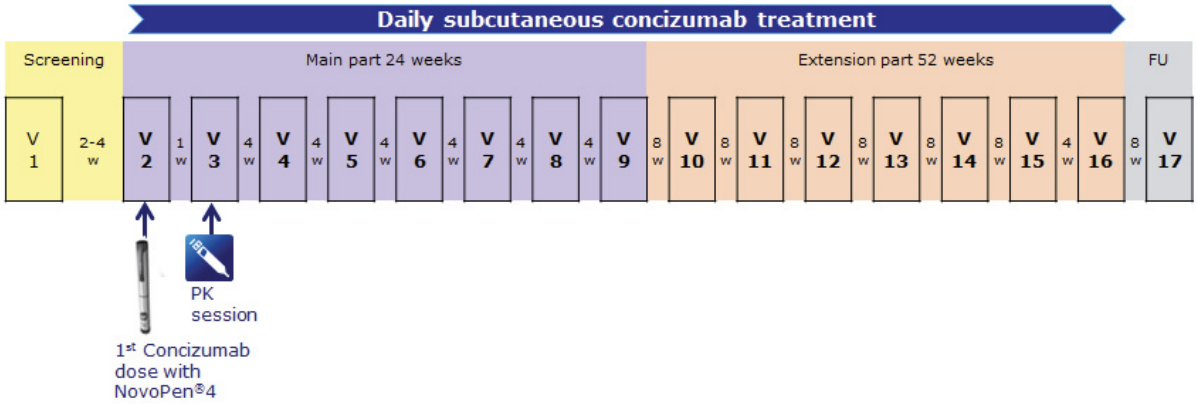

Figure 8–1 Visit schedule – concizumab arm.

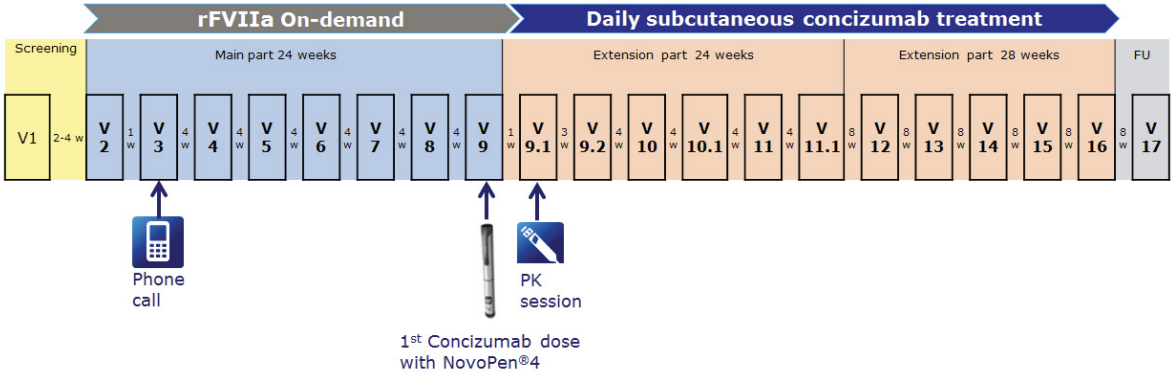

Figure 8–2 Visit schedule – eptacog alfa (rFVIIa) arm later switching to concizumab.

8.1 Visit procedures

For each patient the trial can consist of the following scheduled parts and visits depending upon which arm the patient is randomised to:

Screening Part:

- Visit 1 (screening visit)

Main Part:

- Visit 2 (Randomisation and 1st treatment visit with concizumab at site for patients randomised to the concizumab-arm)
- *Home treatment with concizumab daily*
- Visit 3 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site only for patients randomised to the concizumab-arm - phone visit for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 4 (Assessment visit, patients treat themselves at home)
- Visit 5 (Assessment visit, patients treat themselves at home)
- Visit 6 (Assessment visit, patients treat themselves at home)
- Visit 7 (Assessment visit, patients treat themselves at home)
- Visit 8 (Assessment visit, patients treat themselves at home)
- Visit 9 (Assessment visit, after the visit patients treat themselves at home – 1st treatment visit with concizumab at site for patients randomised to the eptacog alfa (rFVIIa) arm)

Extension Part:

- Visit 9.1 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 9.2 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 10 (Assessment visit, patients treat themselves at home)
- Visit 10.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 11 (Assessment visit, patients treat themselves at home)
- Visit 11.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on demand-arm)
- Visit 12 (Assessment visit, patients treat themselves at home)
- Visit 13 (Assessment visit, patients treat themselves at home)
- Visit 14 (Assessment visit, patients treat themselves at home)
- Visit 15 (Assessment visit, patients treat themselves at home)
- Visit 16 (Assessment visit, no treatment at home before the visit and End of Treatment)

Follow-up Part:

- Visit 17 (Assessment visit and End of Trial)

Unscheduled Part:

- Unscheduled visits can occur e.g. for dispensing of trial product, dose escalation or when an assessment of bleeding episodes is necessary at site or at the discretion of the investigator.

The duration of the visits (V1-V17) will depend on the assessments and the patient's individual training and/or discussion need on concizumab and eptacog alfa (rFVIIa) administration, NovoPen®4, usage of eDiary, completion of the PRO etc.

8.1.1 Informed consent, genotyping and long-term storage consent

Informed consent must be obtained before any trial related activity at visit 1, see Section 18.2.

The trial includes a separate informed consent for long-term storage of human biosamples, see Section 24.2.

Storage of human biosamples and/or genotyping is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for biological specimens and/or genotyping to be stored for future exploratory analysis.

8.1.2 Screening log, enrolment log, trial card and patient number

The investigator must keep a patients screening log, a patients identification code list and a patients enrolment log. Only patients who have signed the informed consent form should be included on the logs. The patients screening log and patients enrolment log may be combined in one log.

At screening, patients will be provided with a card stating that they are participating in a trial and given contact address(es) and telephone number(s) of relevant trial clinic staff. Patients should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each patient will be assigned a unique 6-digit patient number which will remain the same throughout the trial.

8.1.3 Screening failures and re-screening

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.

Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12. A screening failure session must be made in the IWRS. The case book must be signed in the eCRF.

Re-screening is NOT allowed if the patient has failed one of the inclusion or exclusion criteria; this includes re-sampling if the patient has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.1.4 Premature discontinuation of trial product

If a patient prematurely discontinues trial product, the investigator must undertake procedures similar to those for visit 9 (the last treatment in the main part) or visit 16 (the last treatment visit in the extension part) as soon as possible. The follow up visit (visit 17) must be performed 8 weeks (window minus 7 days) after last dose of trial drug.

The primary reason for premature 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.

Permanent premature discontinuation of treatment with trial product will lead to patient withdrawal from the trial.

8.1.5 Withdrawal from trial

If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for visit 9 (the last visit in the main part) or visit 16 (the last visit in the extension part) as soon as possible depending on where the patient is in the trial schedule.

The end-of-trial form must be completed, and 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 and the case book must be signed in the eCRF.

Although a patient is not obliged to give his reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.6 Review/ evaluation of clinical outcome

Novo Nordisk has constituted an internal concizumab safety committee and established an external DMC to perform ongoing safety surveillance of safety data relevant to concizumab, see Section 12.8.

Review of eDiary data and laboratory reports etc. must be documented either on the documents or in the patient's medical record.

If unclear entries or discrepancies in the eDiary or ePRO are identified and a clarification is needed, the patient must be asked for clarification and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

8.1.7 Visit 1 (Screening part)

Informed consent must be obtained before any trial related activity, see Section 18.2

All assessments to be performed at screening are listed in Section 2.

After informed consent is given, patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- Hemo-TEM,
- VERITAS-Pro® or VERITAS-PRN®

Assessment results from physical examination and body measurements, as well as measurements of vital signs, urinalysis and ECG and details of any contemporary adverse events, must be entered into the eCRF.

A screening confirmation call must be performed in the IWRS, at the day of the visit.

The investigator must review all information obtained from the screening procedures. If a patient does not meet all inclusion criteria or meets one or more of the exclusion criteria for the trial the patient does not qualify to be enrolled.

For bleeding episodes that occur in the period from Screening visit (Visit1) to randomisation visit (Visit 2), information about the bleeding episode is to be entered in the eCRF at visit 2.

Patients will be provided with eptacog alfa (rFVIIa), trial injection kits and direction for use (DFU) to cover the potential eptacog alfa (rFVIIa) treatment after the screening part of the trial and investigator will ensure that the patients are capable of treating themselves with eptacog alfa (rFVIIa).

Dispensing of eptacog alfa (rFVIIa) should be performed in IWRS.

The patient must be instructed to call the site if any bleeding episodes, questions or issues arise after he has left the site.

8.1.8 Training of patients at visit 1, visit 2 and visit 9

During visit 1 and visit 2 and visit 9 (comparator arm) patients must be trained in self-administration of concizumab in the home setting using NovoPen®4. The dose of concizumab to be administered must be communicated to the patient at visit 2 (if they are randomised to concizumab) or at visit 9 (if they are randomised to eptacog alfa (rFVIIa) and switching to concizumab at visit 9). Furthermore, patients must be instructed and trained in the importance of reporting all the home treatments with concizumab, details of the bleeding episodes and the eptacog alfa (rFVIIa)

treatments associated with these bleeding episodes in the eDiary. The patient should call the site if bleeding episodes occur between visit 1 and 2 for the site to register in the eCRF.

Patients should be trained on how to recognize signs of thromboembolic events, so that the patient contacts the site without delay.

The site and patient can arrange for additional training whenever needed during the remaining time of the trial.

8.1.9 Treatment period at home

Home treatment is defined as self-administration of trial product, performed independently by the patient, preferably in the morning. Home treatment starts after visit 2 (concizumab arm) or when the patient is comfortable self-administrating trial product subcutaneously (concizumab) and intravenously (eptacog alfa (rFVIIa)).

8.1.10 Staggered recruitment

Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to the concizumab arm will be staggered until the 4th patient randomised to the concizumab arm has completed visit 3 without any safety concerns raised by the investigator. Until this time point, enrolled patients will not be randomised until the previous patient randomised to concizumab has completed visit 3 without any safety concerns raised by the investigator. Novo Nordisk will as sponsor control and communicate the staggered recruitment process.

8.1.11 Treatment period – Main part

8.1.11.1 Visit 2 (Randomisation)

Visit 2 should be scheduled 14 to 28 days after visit 1. The date of visit 2 will be considered as trial day 1.

It is important to verify the in/exclusion criteria again and review central laboratory tests from screening.

The patients must be in a non-bleeding state and should not have received any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) for treatment of bleeding episodes within a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to the potential first concizumab administration (depending on the treatment arm). After visit 2 only treatment with eptacog alfa (rFVIIa) for bleeding episodes is allowed.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments listed in 2, must be performed before potential administration of concizumab (depending on the treatment arm). Vital signs must be assessed both before (within 1 hour) and after concizumab administration. Pre-dose blood sampling must take place no more than 1 hour before concizumab administration.

Assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

A randomisation and dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the Trial Materials Manual (TMM) on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

For patients randomised to the concizumab arm, the first treatment with the loading dose of concizumab will be given.

The time point at which the completion of the first dose takes place corresponds to 'Time on treatment' = 0 and must be recorded in the eCRF.

The patient must be observed at the trial site for at least 2 hours after the administration of the first dose of concizumab.

At the visit the patient will be provided with trial product concizumab and/or eptacog alfa (rFVIIa) and trial injection kits and an eDiary device to be able to conduct and report home treatment and bleeding episodes until next scheduled visit.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for eptacog alfa (rFVIIa), if applicable according to section 9.4.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site. If the patient on concizumab needs to treat a bleeding episode with eptacog alfa (rFVIIa) at home, then he must visit the site immediately after.

8.1.11.2 Visit 3 (Phone call for eptacog alfa (rFVIIa) on-demand arm and PK visit for concizumab arm)

eptacog alfa (rFVIIa) on-demand arm:

Visit 3 for eptacog alfa (rFVIIa) on-demand arm is a phone call scheduled 7 days after visit 2 (with a visit window of +1 day).

All relevant assessments listed in Section 2, must be discussed.

Assessment results from concomitant medication and details of adverse events must be entered into the eCRF.

concizumab arm:

Visit 3 is to be scheduled 7 days after visit 2 (with a visit window of +1 day) and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- PGI-C
- Hemo-TEM

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) dosing.

eptacog alfa (rFVIIa) should be administered to the trial patients at the site under the surveillance of medically trained trial site staff. Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.

Samples for thrombin generation, haematology, coagulation parameters and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

The investigator must ensure all assessments are performed as described in Section 2, Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF before next dose with concizumab is given the day after.

Recruitment of the first four patients will be staggered according to section 8.1.9.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.11.3 Visit 4, 5, 6, 7 and 8

Patients should treat themselves at home according to their individual dosing schedule regardless of when visits 4, 5, 6, 7 and 8 are scheduled.

Visits 4, 5, 6, 7 and 8 are to be scheduled on trial day 29 (4 weeks), day 57 (8 weeks), day 85 (12 weeks), day 113 (16 weeks) and day 141 (20 weeks) respectively with a visit window of ±7days.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM

All assessments are to be performed according to Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 8 patients should be reminded that treatment with concizumab (concizumab arm) must take place after the blood sampling at visit 9.

8.1.11.4 Visit 9

Visit 9 is to be scheduled on trial day 169 (24 weeks) with a visit window of ±7days.

Patients randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2 will now be switched to concizumab treatment. At this visit the first treatment (loading dose) with concizumab will take place.

Treatment with concizumab must take place after the blood sampling for both the patients on the concizumab arm as well as patients on the eptacog alfa (rFVIIa on-demand) arm.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are to be performed according to Section 2, and the assessment results from physical examination, concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through the available access to collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in Section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12 Treatment period – Extension part

8.1.12.1 Visit 9.1 (PK visit and ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.1 is to be scheduled on trial day 176 (25 weeks) with a visit window of +1 day and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) dosing.

eptacog alfa (rFVIIa) should be administered at the site under the surveillance of medically trained trial site staff. Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

Samples for thrombin generation, haematology, coagulation parameters and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9 h (± 10 min) and 12h (±20 min) and 24h (±20 min).

Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF before the next dose of concizumab is given the day after.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.2 Visit 9.2 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.2 is to be scheduled on trial day 197 (28 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's

current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.3 Visit 10

Visits 10 is to be scheduled on trial day 225 (32 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1.

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.4 Visit 10.1 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 10.1 is to be scheduled on trial day 253 (36 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.5 Visit 11

Visit 11 is to be scheduled on trial day 281 (40 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.6 Visit 11.1 (ONLY patients previously on the rFVIIa on-demand arm)

Visit 11.1 is to be scheduled on trial day 309 (44 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules

described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.7 Visit 12, 13, 14 and 15

Visits 12, 13, 14 and 15 are to be scheduled on trial day 337 (48 weeks), 393(56 weeks), day 449 (64 weeks) and day 505 (72 weeks) respectively with a visit window of ±7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 15 patients should be reminded that treatment with concizumab must take place after the blood sampling at visit 16.

8.1.12.8 Visit 16

Visit 16 is to be scheduled on trial day 533 (76 weeks) with a visit window of ±7days. Further visit 16 should be scheduled to be conducted at the last day of treatment with concizumab.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary.

In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat eventual bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period.

If necessary, a dispensing call must be performed in the IWRS. At the visit the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes) arise after he has left the site.

8.1.13 Visit 17 (End of trial) - Follow-up part

Visit 17 is to be scheduled on trial day 589 (84 weeks) with a visit window of minus 7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, physical examination, body measurements (weight only), vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data. Patients should be asked if their female partner has become pregnant, see Section 12.5.1.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

End-of-Trial information must be entered in the End-of-Trial form in the eCRF.

Completion or treatment discontinuation (if the trial is not completed) session should be performed in IWRS, see Section 10.

8.1.14 Unscheduled Visit

Unscheduled visits can be performed at any time during the trial as listed in Section 2. The purpose of the unscheduled visit must be documented in the eCRF.

During unscheduled visits assessments and blood sampling must be performed according to Section 2. Assessment results must be recorded in the eCRF. Assessments and blood sampling can be omitted if the only reason for the unscheduled visit is dispensing of trial product.

If trial product administration or dispensing is required, dispensing of trial product must be performed via IWRS.

The following forms can be found in the unscheduled visit in the eCRF:

- Bleeding episodes
- Dosing with eptacog alfa (rFVIIa), concizumab including dose escalation, see Section 5.3.3.
- Surgery

- Local, special and central laboratory (re-)sampling/results
- Body measurements

8.2 Patient related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history other than haemophilia

A **concomitant illness** is any illness, other than haemophilia, 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 first exposure to trial product. All concomitant illnesses should be reported in the concomitant illness forms in the eCRF except information on haemophilia with inhibitors which is to be reported in the haemophilia medical history section of the eCRF.

Medical history is a medical event, other than haemophilia, which the patient has experienced in the past. Only relevant medical history should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the patient's medical history in source documents such as patient's medical record, see Section 6.2 and 6.3.

If a patient is not from the investigators own practice; the investigator must make a reasonable effort to obtain a copy of the patient's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the concizumab and eptacog alfa (rFVIIa), which is taken during the trial, including the screening and follow-up period.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Details of Haemophilia, Haemophilia treatment and bleed history

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

- Diagnosis of haemophilia (date)
  - Classification of haemophilia type (haemophilia A/B)
  - Severity of haemophilia (severe, moderate or mild)
  - Aetiology of haemophilia (congenital or acquired)
- Family history of
  - Haemophilia (Y/N)
  - Inhibitors (Y/N)
  - Prothrombotic disorders (Y/N)
  - Thromboembolism (Y/N)
- Inhibitor tests taken (Y/N)
  - Date (dd-mmm-yyyy)
  - Result (BU)
- Cut-off for positive inhibitor result
- Deficiency factor level

The following information on bleeding episodes one year prior to screening should be recorded in the eCRF:

- Type of treatment
  - 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
- Dosing frequency during prophylaxis
- Approximate dose to treat a bleeding episode

- Approximate number of doses to treat a bleeding episode
- Target joint listing (definition: a target joint is a joint in which 3 or more spontaneous bleeding episodes have occurred within a consecutive 6-month period)
    - Location
    - Position (left/right)
    - Number of bleeding episodes

8.3 Efficacy assessments

8.3.1 Bleeding episodes

All bleeding episodes treated with eptacog alfa (rFVIIa) and symptoms related to the underlying disease must be captured in the eDiary by the patient or in the eCRF by the investigator. The trial site should be informed of the details of all bleeding episodes, including those that are treated outside of the trial site.

All information captured during visits to the trial site will be collected in the eCRF.

When home treatment is initiated at visit 2 all bleeding episodes and injections with concizumab and eptacog alfa (rFVIIa) injection occurring outside the trial site should be entered in the eDiary by the patient, Section 13.3.

The completed eDiary is considered source data.

For reporting of bleeding episodes as AEs/SAEs, please refer to Section 12. In case of life-threatening bleeding episode, it should always be reported as an SAE, see Section 12.1.2.

The following must be recorded for any bleeding episode, including bleeding episodes that do not require treatment with eptacog alfa (rFVIIa):

- Start date and time
- Stop date and time (see Table 8–1)
- Anatomical location
    - Position (left/right)
- Cause (see Table 8–2)
    - spontaneous
    - traumatic
    - post-surgical
- Severity (see Table 8–3)
    - mild/moderate, severe
        - classification and recording of severe bleeding episodes is the responsibility of the investigator
- Treatment, if any

- eptacog alfa (rFVIIa) administration or other product administration
  - dose, date, stop time
- other medicinal treatments related to the bleeding episode (pain relieving medication, non-medical therapy etc.)
  - record as concomitant medication (section 8.2.3)

- Symptoms during bleeding episode(s)
  - Pain
  - 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 if fatal, life threatening or evaluated as related to trial product, see Section 12.1.1 and 12.1.2.

Table 8–1 Definition of stop of bleeding episode

Stop time is:	When the patient experiences/observes signs of cessation of the active bleeding episode 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 8–2 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 8–3 Definition of bleeding episode severity and treatment recommendation

Category	Definition	Treatment recommendation
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeding episodes (joint, muscular bleeding episodes without compartment syndrome), mucosal- or subcutaneous bleeding episodes Mild/moderate bleeding episodes may occur in other anatomical locations	Mild/moderate bleeding episodes: • patient must call the site between visit 1-2 and visit 3-16 (see 2-3 and 9-9.1 below) • patient must call the site between visit 2-3 or visit 9-9.1 (eptacog alfa arm) and if treated at home, go to the site immediately after • patient can treat themselves at home between visit 16 and visit 17
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeding episodes; muscle bleeding episodes with compartment syndrome; bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeding episodes may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes	Severe bleeding episodes must be treated immediately
Instruction for patients	The patient must be instructed to contact the site immediately if in doubt regarding treatment of a bleeding episode and to discuss what other actions may need to be taken	

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.

Dosing for bleeding episodes with eptacog alfa (rFVIIa) should be documented in the eCRF (visit 1 to visit 2) and eDiary (visit 2 to visit 17). After visit 2 bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see section 13.3.

Investigator must instruct the patient not to perform preventive treatment with eptacog alfa (rFVIIa) after bleeding stop as defined in Table 8–1.

Investigator must instruct the patient to use eptacog alfa (rFVIIa) as rescue medication to treat bleeding episode between visit 2 and visit 16, see Section 5.3.5.

Furthermore investigator must instruct the patient to contact the site when a bleeding episode occurs. It is the responsibility of the investigator to instruct the patient about the timelines for timely completion of the eDiary.

Furthermore the investigator must review the bleeding and treatment data collected by the eDiary according to Section 13.3.

For in-between visit administrations of trial drug, patients will self-administer concizumab (and eptacog alfa (rFVIIa) as rescue medication) and will record treatment in the eDiary, which will be reviewed during periodic calls to/contact with the patient and at each visit by trial site staff and the sponsor staff.

8.4 Safety assessments

8.4.1 Physical examination

Performed as standard physical examination and include the following.

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

The investigator must evaluate the results of the examination and classify them 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 Medical History (Section 8.2.2)
- If observed after screening: report an AE/SAE (Section 12)

Measurements will be reported in the eCRF.

8.4.2 Body measurements

- Height (cm), at screening
- Body weight (kg), (with one decimal)

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

Measurements will be reported in the eCRF.

8.4.3 Vital Signs

Before measurement of vital signs the patient should preferably rest comfortably for at least five minutes and all measurements should, if possible, be performed using the same method and in a sitting position throughout the trial.

Measurements at visits must be performed prior to any trial product administration unless otherwise specified.

- Body temperature (°C)
- Systolic and diastolic blood pressure, sitting (BP) (mmHg)
- Pulse, sitting (beats/min)
- Respiratory rate

Exception: At visits 2 and visit 3 (for patients randomised to concizumab) and at visit 9 and visit 9.1 (for patients initiating concizumab treatment at visit 9), the measurements are also performed after concizumab administration.

The investigator must evaluate the vital signs 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, section 8.2.2
  - If observed after screening: report an AE/SAE, section 12

Measurements will be reported in the eCRF.

8.4.4 Electrocardiogram

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 Medical History, section 8.2.2
  - If observed after screening: report an AE/SAE, section 12

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.

8.4.5 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.5.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product involved
- Classification of medication error
- Whether the patient experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.5.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

Injection site reaction

Investigation of injection site reactions will be performed locally at all visits after visit 2 until visit 16 based on patient feedback and by following visual inspections of injection sites for concizumab administration:

Symptoms e.g.

- Pain
- Numbness
- Itching
- Burning

Signs e.g.

- Redness (mm x mm)
- Induration (mm x mm)
- Swelling
- Dimpling
- Macula
- Haematoma
- Bleeding
- Other (visual reactions)

Any injection site reaction symptom (evaluated at visit 2-16) should be recorded in the AE form and the injection site reaction form, see Section 12.1.5.

A separate AE should be recorded for each injection site reaction symptom. The affected area should also be evaluated for redness and induration in mm using a ruler. To ensure all local injection site assessments are performed at the injection site, the area around the site will be marked with a pen prior to injection.

In the event of a local reaction, additional visual assessments (as described above) 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.

Hypersensitivity reaction

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

All events of hypersensitivity reactions must be reported and the following information must be obtained if available on the hypersensitivity reaction form:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed, see Section 8.5.2.7
- Treatment given for the reaction
- Previous history of similar reactions
- Association with the trial product(s)
- Relevant risk factors associated with the event
- Storage condition of the trial product
- Total number of doses, from first day on trial product, up to the time of this event

8.5 Laboratory assessments

An approximate total blood volume of 725 mL will be taken from each patient on the concizumab arm and 625 mL from each patient on the eptacog alfa (rFVIIa) arm.

A laboratory manual will be provided for detailed description of obtaining and processing blood samples.

All laboratory blood samples collected for this trial except for haematology samples at all visits and coagulation parameters at visits 3 and 9.1 are to be shipped for analysis at central laboratories or further distribution to special laboratories. Haematology samples (all visits) and coagulation parameters (visit 3 and 9.1) are to be analysed locally. Ports cannot be used for blood sampling.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Laboratory reports listing results from centrally analysed samples will be made available for the investigator. Investigator must review and evaluate the results and report AEs for results which are clinically significant. Laboratory reports will where possible indicate normal ranges.

Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: FVIII/FIX activity, FVIII/FIX inhibitor

test, Thrombin generation, Free TFPI (TFPI not bound to concizumab), concizumab concentration in plasma, anti-concizumab antibodies, Total TFPI and FVII antigen concentration.

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 and report these according to Section 8.2.3 and Section 12.

Only laboratory samples specified in the protocol must 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 except for biomarkers and anti-drug antibodies (anti-concizumab IgE antibodies and anti-concizumab antibodies).

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and human biosamples, if applicable, will be stored as described in Section 24.2. The investigator may not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV.

8.5.1 Laboratory assessments for efficacy

8.5.1.1 Thrombin generation

The Thrombin Generation Assay (TGA) will be collected at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

The TGA is included as an exploratory PD assessment.

The generation of thrombin is a fundamental part of the haemostatic system, and is a key measurable parameter of the formation of a clot under bleeding or thrombotic conditions. The thrombin burst is crucial for the formation of a stable fibrin clot.

The Calibrated Automated Thrombogram (CAT) method (used by Thrombinoscope BV) will be used to measure thrombin generation (TG). This method uses a slow acting fluorogenic substrate that allows continuous measurement of thrombin generation in double centrifuged citrated plasma.

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.

The thrombin generation endpoints are defined but not limited to:

- The Endogenous Thrombin Potential (ETP) – the area under the curve
- Peak thrombin generation
- Velocity Index

8.5.1.2 Free TFPI

Free TFPI (TFPI not bound to concizumab) will be collected at all visits, pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm).

The free TFPI assay is an enzyme immunoassay measuring levels of free TFPI from [redacted] (named and referred to [redacted] TOTAL TFPI) and will be used for PD assessments.

8.5.2 Laboratory assessments for safety

8.5.2.1 Urinalysis

- pH
- Protein
- Glucose
- Bilirubin

This is a semi qualitative measurement which will be performed (locally) at the screening visit by the site by using the appropriate reagent strips for urinalysis. The results will be recorded in the eCRF.

The investigator must evaluate the results and record the outcome as:

- Normal or abnormal
- If abnormal the investigator must:
    - Record if the result is clinically significant? (Yes/No)
    - If observed before or at screening: record as concomitant illness (section 8.2.2)

8.5.2.2 Haematology

Haematology samples are to be sampled and analysed locally at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa), 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

- Haemoglobin
- Erythrocytes (cell count)
- Thrombocytes (platelet count)

- Leucocytes (cell count)
- Differential leucocytes cell count
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils

The investigator must evaluate the results and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Haematology results are to be entered into the eCRF.

8.5.2.3 Biochemistry

Biochemistry samples are to be sampled and analysed centrally at all visits.

- Creatinine
- Albumin
- Bilirubin; total, direct, indirect
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma glutamyltransferase (GGT)
- Alkaline phosphatase
- C-reactive protein (CRP)

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

8.5.2.4 FVIII/FIX activity

FVIII/FIX activity is to be sampled and analysed centrally at visit 1, visit 9 and visit 16.

- FVIII activity level (IU/mL) or
- FIX activity level (IU/mL)

8.5.2.5 Coagulation parameters

Coagulation parameters will be performed centrally at all visits with the exception of visit 3 and visit 9.1 where the PT, APTT, and Fibrinogen will be performed locally.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa) at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (±10 min) and 12h (±20 min) and 24h (± 20 min) locally.

- Fibrinogen – centrally and locally
- Prothrombin time (incl. INR) (PT) centrally and locally
- D-dimer – only centrally
- Prothrombin fragment 1+2 – only centrally
- Activated partial thromboplastin time (APTT) – centrally and locally
- Antithrombin (AT) activity – only centrally

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Coagulation parameters analysed locally are to be entered into the eCRF.

8.5.2.6 FVIII/FIX inhibitors

FVIII/FIX inhibitor level will be measured by the Nijmegen method at visit 1, visit 9 and visit 16.

- FVIII inhibitors (BU) or
- FIX inhibitors (BU)

8.5.2.7 Anti-concizumab antibodies

Samples for the determination of anti-drug antibodies collected during the treatment period must be drawn at all visits and prior to administering concizumab at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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. Confirmed positive samples will be characterised for binding to IgG backbone, CDR region or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a modified TFPI functionality assay (neutralising ADA assay). All antibody assays are validated according to international guidelines and recommendations.

The following analyses will be available:

- Anti-concizumab antibodies assay
- Specificity assay (Anti-concizumab antibodies cross reacting with IgG4 backbone, CDR region or S241P mutation)
- Anti-concizumab neutralising antibodies assay

The samples will be analysed in batches during the trial and results will be available to the data monitoring committee approximately every third month after the first patient has been dosed. Neutralising antibodies will be analysed and reported at the EOT. A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit. The ADA positive patients will be called for additional visits, e.g. every 4 to 6 weeks, for safety assessment and blood sampling for ADA and PD markers (free TFPI and Thrombin generation). The ADA positive patients will be followed no longer than one year after End-of-Trial.

Hypersensitivity

If suspicion of a hypersensitivity reaction occurs, patients should be instructed to contact the site staff as soon as possible for further guidance, see Section 12.1.5.

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 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 months post 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.

Results from the following additional tests will be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS database and included in the narratives, if measured.

Test to be performed in case of severe hypersensitivity

- Anti-concizumab IgE antibodies
- Anti-concizumab antibodies (additional to scheduled time points)

Additional testing may be performed if deemed relevant e.g.

- Anti-Host Cell Proteins (HCP) antibodies
- Anti-HCP IgE antibodies
- Basophil activation results
- Prick test/intra-dermal test
- Complement test results

Furthermore, it is recommended locally to test for

- Tryptase (total and/or mature tryptase)

8.5.2.8 Concizumab ELISA

Concizumab ELISA will be collected at all visits except at screening only for the concizumab arm. Samples will be collected pre-dose at visit 2 and 3 for concizumab arm and visit 9 and 9.1 for eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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 correlates 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.

8.5.2.9 FVII ELISA

FVII ELISA will be collected at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) pre-dose eptacog alfa (rFVIIa) and post-dose at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa (rFVIIa) administration.

FVII in plasma will be quantified using a validated enzyme-linked immunosorbent assay (ELISA). The FVII ELISA will detect the total sum of FVII in a sample, including endogenous FVII, eptacog alfa (rFVIIa) and FVII in complex with other molecules e.g. antithrombin. The ELISA has been validated for measuring FVII in human citrated plasma samples. Validation follows current guidelines for bioanalytical method validation. Bioanalytical data will be reported in a bioanalytical report.

8.5.2.10 Total TFPI

Total TFPI ELISA will be collected at all visits. Samples will be collected pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

The total TFPI level (free and concizumab bound) will be included as an exploratory biomarker assessment.

The assay is an ELISA, where TFPI is captured by a polyclonal anti-TFPI antibody, distanced from the binding site of concizumab; meaning that both free TFPI and concizumab bound TFPI will be captured. Detection will be obtained with a monoclonal antibody against TFPI, which does not bind to the concizumab epitope.

Data will be reported in ng/mL TFPI.

8.5.3 Human Biosamples

If patient permission is obtained plasma, serum and/or DNA for genotyping samples are to be taken for long term retention, see Section 2. The blood samples can be stored up to 15 years, for future potential exploratory purposes please refer to section 24.2.

Antibody samples storage and retention, see Section 24.2.1. The investigator is not able to review the results of antibody measurements in relation to AEs as these are analysed after LPLV. Plasma and serum is taken at visit 1 and 17. DNA for genotyping is only taken at visit 1.

8.6 Other assessments

8.6.1 Patient reported outcomes

A newly developed disease-specific electronic PRO (ePRO) the Hemophilia Treatment Experience Measure (Hemo-TEM) - is being validated in this trial. In order to assess the psychometric properties of Hemo-TEM, other questionnaires will be provided; see further appendix 1.

The following ePRO questionnaires will be used in the trial:

- Hemophilia Treatment Experience Measure (Hemo-TEM)
- Validated Hemophilia Regimen Treatment Adherence Scale - Prophylaxis (VERITAS-Pro®) or Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®) [16]
- 36-Item Short Form Health Survey (SF-36v2) (4 week recall) [17]
- Patient's Global Impression of Change (PGI-C)
- Sheehan Disability Scale (SDS) [18]
- Treatment Satisfaction Questionnaire for Medication (TSQM, version II) [19] [20] [21]
- Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)[22]

The ePROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, VERITAS-Pro® or VERITAS-PRN®)
- visit 2 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 3 (PGI-C, Hemo-TEM)
- visit 4 (PGI-C, Hemo-TEM)
- visit 5 (PGI-C, Hemo-TEM)
- visit 6 (PGI-C, Hemo-TEM)
- visit 7 (PGI-C, Hemo-TEM)
- visit 8 (PGI-C, Hemo-TEM)
- visit 9 (PGI-C, Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 10 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 16 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)

At visit 1: before any visit-related activities all patients should complete Hemo-TEM and VERITAS-Pro® (if the patient at baseline receives prophylactic treatment) or VERITAS-PRN® (if the patient at baseline receives on-demand treatment).

At visit 2: before any visit-related activities all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 3-8: before any visit-related activities the patient should complete the PGI-C before the Hemo-Tem. These are the rules that apply:.

- If the patient responds "1" to question 1 in the PGI-C, the patient should also complete the Hemo-TEM. In this case the patient should not fill in the PGI-C any more in the trial and the Hemo-TEM only again at visits 9, 10 and 16.
- If the patient responds "0" or "2" to question 1 in the PGI-C, the patient should not complete any other questionnaires at this visit, but should repeat the procedure at next visit.

Exception: Patients randomised to eptacog alfa (rFVIIa) on-demand should not complete the ePRO at visit 3 as this is a phone visit.

At visit 9 if the patient has responded "0" or "2" in the PGI-C at all previous visits, the patient should complete PGI-C. All patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 10 and 16 all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

The investigator must check the ePROs for potential AEs and SAEs. The completed ePROs should be transmitted at each visit to the PRO database by the Investigator.

8.6.2 Training

The patients must be trained in how to handle bleeding episodes and how to recognize the signs and symptoms of thrombosis. The training must be documented in the medical record.

8.6.2.1 Concizumab and NovoPen®4

Direction for use (DFUs) will be available as a hand out for patients at visit 2. Training in NovoPen®4 can start at screening (visit 1) and s.c administration of concizumab using the NovoPen®4 can start at the first dose at the trial site (visit 2). Patients must be instructed that injections are to be performed subcutaneously, not intravenously. Concizumab and NovoPen®4 will be dispensed to the patients at visit 2. Training must be performed at site until patients feel comfortable using the device or performing the treatment. The training must be documented in the medical records.

Detailed instructions can be found in the DFUs .

8.6.2.2 eptacog alfa (rFVIIa)

A direction for use (DFU) will be available as hand out for patients at visit 1. Training must be performed at site until patients feel comfortable performing the treatment. The training must be documented in the medical records.

The following should be emphasised for eptacog alfa (rFVIIa):

- eptacog alfa (rFVIIa) should be slowly injected intravenously over 2 to 5 minutes

Detailed instructions can be found in the DFU

8.6.2.3 eDiary

Training on the use of the eDiary can start at visit 1. The eDiary will be provided to the patients at visit 2.

Training must be repeated at the site until patients feel comfortable using the device. The training must be documented in the medical records.

During the home treatment period the patient must ensure that all home treatments of concizumab, details of bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes are captured in the eDiary as instructed and trained by investigator or delegated staff.

It will be the responsibility of the investigator or delegated staff to assess the eDiary data throughout the conduct of the trial and to ensure data entry compliance (timely entry, no duplicate data, no missing data etc.) and retraining if necessary.

For patients completing the trial or in case of withdrawal, the eDiary will be collected at the EOT.

8.6.3 Surgery

Minor surgery can be performed within this trial at the investigator's discretion according to local guidelines. Definition of minor surgery, see Section 5.1.1. Major surgery is not allowed, see exclusion criteria no 6.

For minor surgery the following should be recorded in the eCRF:

- Date, stop time and dose of preventive treatment with eptacog alfa (rFVIIa) before surgery, if this was deemed necessary by the investigator
- Indication for surgery
- Location of surgery
- Date of surgery
- Start and stop time of surgery

8.7 Patient 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.

8.8 Treatment compliance

Treatment compliance will be monitored and documented through timely review of eDiary data and drug accountability.

Concizumab will be administered at the trial site at visit 2 for the concizumab arm supervised by medically trained trial staff and administration at home can be initiated after visit 2 if the patient feels comfortable with the s.c. administration. Administration of eptacog alfa (rFVIIa) for bleeding episodes will be administered at the trial site by a medically trained trial staff or at home by the patient, see Section 8.3.1.

Drug accountability will be performed and will be used to assess patient compliance together with the patients' adherence to trial procedures.

Compliance check includes a cross check between records in EDC/eDiary (number of administrations and bleeding episodes) and the used/returned cartridges/vials.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the TMM.

The trial product, concizumab B, appears as clear to slightly opalescent and colourless to slightly yellow. The trial product must not be used if it contains visible particles or discoloration.

The reconstituted eptacog alfa (rFVIIa) solution appears clear and colourless. Do not use the reconstituted solution if it contains visible particles or if it is discoloured.

Trial products must not be dispensed to any person not included in the trial.

9.1 Trial products

The following trial products will be provided by Novo Nordisk, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
concizumab B (IMP)	100 mg/mL	Solution for injection	s.c. injection	3 mL cartridge
eptacog alfa (IMP [a] and NIMP [b])	5 mg/vial	Powder for solution for injection	i.v. injection	Vial
histidine 5 mL	N/A	Solvent for solution for injection	i.v. injection	prefilled syringe

[a] Investigational Medicinal Product (IMP) given as IMP for a single dose at visit 3 and 9.1.
[b] Non-Investigational Medicinal Product (NIMP) given as NIMP for bleeding episodes

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with the EMA directive on medical devices annex I [23] and similar national legislation. A description of how to use the device is given in the DFU.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13 [24], local regulations and trial requirements.

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 enrolment and randomisation.

The investigator must document that DFUs are given to the patient orally and in writing at the first dispensing visit (see Section 2).

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time [a]
concizumab B 100 mg/mL	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store at room temperature (below 30°C) Do not refrigerate Protect from light	Use within 4 weeks (28 days)
eptacog alfa 5mg	Store between 2°C-25°C Do not freeze Protect from light	For single use Do not freeze Protect from light To be used immediately after reconstitution	If not used immediately, store in refrigerator (2°C-8°C) for up to 3 hours
histidine 5 mL	Store between 2°C-25°C Do not freeze Protect from light	For single use	N/A

[a] In-use time for concizumab starts when first dose is administered from an individual cartridge and for eptacog alfa (rFVIIa) when the product is reconstituted

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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 must take appropriate action to ensure correct storage.

Investigator must instruct the patient to use and store trial product according to the label.

9.4 Drug accountability and destruction

Drug accountability of all trial products (concizumab and eptacog alfa (rFVIIa) received at site is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial product during the trial as instructed by the investigator, except for histidine which should be discarded at home and not accounted for.

All cartridges (concizumab) and vials (eptacog alfa (rFVIIa)) must be accounted for as used, partly used or unused.

The investigator will perform drug accountability using the IWRS Drug Accountability module.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial product including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Destruction of concizumab and eptacog alfa (rFVIIa) can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

For Japan only: Responsibility for storage and drug accountability of the trial drug product at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug product at the trial sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug product in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary supplies

Novo Nordisk will provide the auxiliaries for this trial:

- For concizumab administration: NovoPen®4, needles and DFUs
- For eptacog alfa (rFVIIa) reconstitution and administration: Trial Injection Kit and DFU

Only needles and trial injection kit provided by Novo Nordisk must be used for administration of trial product.

For further guidance please see the TMM.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

Randomisation will be handed by the IWRS.

All patients included in the screening period and eligible for the trial will enter the trial and be randomised at visit 2 in a 2:1 allocation to either concizumab prophylaxis arm or eptacog alfa (rFVIIa) on-demand arm.

11.2 Breaking of blinded codes

Not applicable for this trial.

12 Adverse events, and technical complaints

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality 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.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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
- Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. All bleeding episodes and other findings related to underlying disease will be captured in the eCRF/eDiary.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the patient's daily activities
  - **Moderate** – marked symptoms, moderate interference with the patient's daily activities
  - **Severe** – considerable interference with the patient's daily activities; unacceptable
- **Causality**

Relationship between an AE and the relevant trial product(s):

- **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

- **Final 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 fatal outcome must be reported as an SAE
  - **Unknown** - This term is only applicable if the patient is lost to follow-up

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death
- A life-threatening [a] experience
- In-patient hospitalisation [b] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity [c]
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening [a] or require hospitalisation [b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE [d]

a. The term "life threatening" in the definition of SAE 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 was more severe.

[b.] The term "hospitalisation" is used when a patient:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a patient's ability to conduct normal life functions (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE 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 ALT or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug

  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- 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

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.5.1

12.1.5 Adverse events 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.

In this trial the following AEs require the completion of specific event forms in the eCRF:

- Injection site reaction, see Section 8.4.5.2
- Hypersensitivity type reactions, incl. anaphylactic reactions, see Section 8.4.5.2

Injection site reactions:
Any injection site reaction symptom must be recorded on the AE form and the injection site reaction form.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction are present, blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. In the event of an immediate systemic hypersensitivity reaction to the trial product, it is recommended to also test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary ~1 week after the immediate severe hypersensitivity reaction due to individual to individual variation in tryptase baseline concentration. Tryptase concentrations (if measured) must be interpreted and considered in the context of a complete workup of each patient.

Special 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 type 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 cases where there is a suspicion of hypersensitivity reaction that requires systemic treatment, additional sampling for the purpose of measuring ADA will be performed.

Definition of anaphylaxis [25]
Anaphylaxis is highly likely when **any one of the following 3 criteria** is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
    a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

- **Two or more of the following** that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours): Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP.

If a patient fulfils any of the three criteria of anaphylaxis outlined above, the patient should receive epinephrine/adrenalin immediately. Dose regimen should be according to hospital operating procedure, and the patient should be transferred to an emergency department or intensive care unit, if clinically warranted.

Events not fulfilling the criteria for an anaphylactic reaction and other allergic reactions must be treated at the discretion of the treating physician. If according to the investigators judgement, hypersensitivity type reactions that require systemic treatment are suspected, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

12.1.6 Adverse Events of special interest

An adverse event of special interest (AESI) is an event, which in the evaluation of safety, has a special focus. In this trial, the following AEs fulfil the AESI criteria:

- Thromboembolic events including but not limited to,
    - disseminated intravascular coagulation (DIC) (A),
    - clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction (B),
    - pulmonary embolism (C),
    - stroke (D),
    - deep vein thrombosis (E),
    - other clinically significant thromboembolic events (F) and peripheral artery occlusion (see below G), see definitions below

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

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 × 10^9/L = 0, <100 × 10^9/L = 1, <50 × 10^9/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) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction" [26]
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.

C) 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 (27).

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

D) 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" (28).

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:

- 1. pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
- 2. 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 [(29)].

E) 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 DVT in the lower extremities[27]. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

F) 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 is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

G) 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, 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 [30].

12.1.7 Technical complaints

A technical complaint is any written, electronic or oral communication that alledges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until the end of the post-treatment follow-up period (visit 17). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the patient must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or patient, must be reported by the investigator and evaluated. All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

AESIs regardless of the seriousness must be reported using the AE form and safety information form.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

- **Non-serious AEs fulfilling the AESI criteria:** The AE form and safety information form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

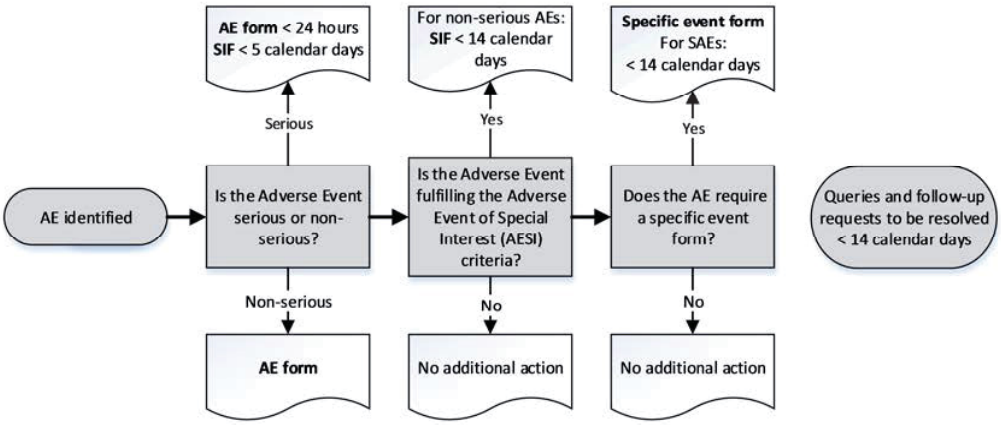

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto.

When eptacog alfa (rFVIIa), NovoSeven® is used as IMP, expectedness should be performed according to the Company Core Data Sheet (CCDS).

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP [1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP [1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (eptacog alfa (rFVIIa)) or 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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AEs fulfilling the AESI criteria:** Non-serious AE fulfilling the AESI criteria must be followed as specified for non-serious AEs. Follow-up information on AESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the AESI criteria.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a patient after the patient has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Concizumab B 100 mg/mL, solution for injection in a 3 mL cartridge
- NovoPen®4
- Novo Nordisk needles
- Eptacog alfa (rFVIIa) 5 mg/vial, powder for solution for injection in a vial
- Histidine 5 mL, solvent for solution for injection in a prefilled syringe
- Novo Nordisk trial injection kit

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, AESI and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

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 Centre, 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.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Centre, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female partners of male patients

Male patients must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period (from visit 1 to dosing with concizumab at visit 2 or visit 9 depending on the arm). At the last scheduled visit (visit 17), male patients must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male patient and assess if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the patient's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax.

1. **Reporting of pregnancy information**
   Information from the male patient has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

   Initial reporting and follow-up information must be reported within **14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

- Paper AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE

SAEs:

- Paper AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Dose limiting toxicities of concizumab have not been investigated in clinical trials.

There have been no reports about overdosing of concizumab and therefore no experience with overdose and overdose reactions exists. In case of a concizumab overdose, symptomatic medical treatment according to the clinical condition should be applied. No antidote exists in case of concizumab overdose.

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors.

Treatment should be as appropriate and in accordance with hospital practice and guidelines.

12.7 Rules for putting enrolment on hold

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee.

- Significant thromboembolic event*
- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product

* Superficial thrombophlebitis or venous thrombosis associated with indwelling catheters is not considered a significant thromboembolic event unless evaluated as such by the investigator

If two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements, or if trends in AEs, clinical observations or laboratory parameters raise concerns about the safety of continued treatment, the safety committee (see Section 12.8.1) will decide if further dosing of any patients in the clinical trial programme should be continued, paused or discontinued.

12.8 Committees related to safety

12.8.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal concizumab safety committee to perform ongoing safety surveillance of safety data relevant to concizumab. The safety committee is a cross functional group within Novo Nordisk.

12.8.2 Data monitoring committee

The 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 in order to protect the safety

of the patients and to evaluate the benefit-risk balance. The DMC will have access to the data, and will provide recommendations on trial continuation, modification or termination.

In case there is any safety concern, data will be compiled and the DMC will review these data. Their recommendation will go to the Novo Nordisk Safety committee for final decision of what next step is in this trial.

The DMC members will only have direct contact with the Novo Nordisk Global Safety department through the safety surveillance representatives, and will have no direct interaction with those in trial management. The DMC recommendations should be addressed directly to the Novo Nordisk Global Safety department and the internal Novo Nordisk safety committee for concizumab. It is the responsibility of the Novo Nordisk internal safety committee for concizumab to take action(s) for patient safety based on the DMC recommendations.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms
- AE forms
- Safety information forms

The paper version of the technical complaint form, AE form, and safety information form must only be used to ensure timely reporting when/if the electronic CRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable)

indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

13.3 Electronic diary

Novo Nordisk will provide the patient with an eDiary for electronic recording of details of their home treatment, bleeding episodes and treatment of bleeding episodes (i.e. use of eptacog alfa (rFVIIa)).
The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

Patients will be instructed in the use of the eDiary by the investigator or delegated person before entering of any data. The eDiary will be dispensed to the patient at visit 2. After visit 2 and onwards, data will be entered by the patient in the eDiary device during home treatment.

The eDiary will be returned by the patient at the EOT visit.

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

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.

Investigator review of eDiary data

It is the responsibility of the Investigator or delegated staff to review the eDiary data reported by the patient. As a minimum it must be verified that the eDiary data is complete, consistent and according to the requirements defined in this protocol. This also includes that the number of doses reported in the eDiary is reviewed against the number of vials/cartridge accounted for as used by the patient. Upon review the Investigator must document that the review has taken place and any actions required e.g. retraining of the patient or decision to amend or correct the data reported by the patient.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. Monitoring visits should be scheduled as frequently as needed to support the first 6 patients recruited in the trial. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site. This only applies to sites with scheduled, ongoing and/or discontinued patients.

The monitor must be given direct access to all source 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 or text message).

All data must be verifiable in source documentation other than the eCRF. eDiary data is entered by the patient and will also be treated as source data.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

For historical data such as medical history, details of haemophilia and haemophilia treatment history, a reasonable effort must be made by the investigator, considering local requirements, to obtain this information from external sources, if not known by the patient. It is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document. This means that for laboratory results (e.g. biochemistry and haematology) a signed printout of the electronic results must be available.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The monitor will ensure that the eCRFs are completed and paper CRFs (if any) collected, that ePROs and eDiaries are completed and reviewed by the investigator at the relevant scheduled visits and needed action has been taken and documented, if any.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Inclusion and exclusion criteria
- Screen failure reason if possible
- Date patient left the trial
- Data relating to AEs if applicable
- Demography, see section 8.2.1
- Date of visit

Monitors will review the patient's medical records and other source data (e.g. the eDiaries and ePROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of patient data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide all laboratory reports to the investigator for filing at the trial site. The laboratory report must be signed and dated by the investigator or delegated person and stored at the trial site as source data.

The patient and any biological material obtained from the patient will be identified by patient number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

Novo Nordisk will use the Global Haemophilia Network Investigator Portal to distribute and share trial-related documents and information with the participating sites. After trial completion, Novo Nordisk will supply each trial site with long-life CDs or other relevant archiving containing the electronic Investigator Trial Master File (eITMF) for each trial site. These CDs or other relevant archiving will contain site-specific trial documentation as well as trial specific news and other relevant trial information, including audit trail on documents and site staff users. The GHN Portal software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1 31]

Novo Nordisk will provide electronic tablets for reporting of all PROs questionnaires described in section 8.6.1 and in Appendix 1. In case the electronic tablet is revoked the questionnaires will be available in paper.

The eDiary and ePRO software and hardware implementation are compliant with the requirements of FDA 21
CFR Part 11 and ICH E6 (EU directive for personal data protection).[1 31] After trial completion, each trial site will be supplied with long-life CDs. These CDs will contain site-specific patient records including the patient's eDiaries and audit trail including any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 15 years or as required by local data retention laws for trial data.

17 Statistical considerations

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Please refer to Figure 17–1 for further information.

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

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. Further, the endpoints will not include re-bleed. A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping, the treatment is defined as a new bleeding episode.

Clinical proof of concept

The statistical analysis of the collected data aims to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia patients with inhibitors. The objective will be assessed when the last of the 24 patients has completed 24 weeks of dosing (or has withdrawn before that).

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

The referred comparisons will be made using a negative binomial model with log of exposure time in main part as offset and regimen as factor (concizumab vs. on-demand). For each criterion, evidence of effect will be concluded if the 95% confidence interval of the treatment ratio is below 1.

Clinical arguments for the hierarchical test approach

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

17.1 Sample size calculation

The estimand will be defined as the "if all patients had adhered" estimand.

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

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

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

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm. It is expected that the treatment duration of the main part allowing for escalation time for some patients is on average 6 months in the below calculations.

When evaluating the power of the negative binomial analysis referred above, annual bleeding rates of 24 and 6 are assumed for the on-demand patients and the end dose concizumab regimen, respectively. Assuming further over-dispersion of 7, the power for concluding superiority of the concizumab regimen becomes approximately 80%. The power under varying values of true ABR and over-dispersion for the primary CPoC criterion are shown below in Table 17–1.

Table 17–1 Power in superiority comparison between concizumab prophylaxis and on-demand treatment under different assumptions of ABR for concizumab and over-dispersion (assuming on-demand ABR=24).

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

For the secondary CPoC criterion that includes data prior to potential dose escalation, it is expected that the treatment duration of the main part is on average 8 months with an average ABR of 7.6 for the concizumab regimen. This yields a marginal power of approximately 70% for the secondary CPoC criterion.

In prior Novo Nordisk trials conducted in haemophilia patients, the typical 1-year over-dispersion for non-inhibitor patients on prophylaxis with FVIII or FIX has been in the range 4-8, implying 24 weeks over-dispersion of 3-5 (e.g. in NN7008-3543, NN7088-3859 and NN7999-3747). In the NN7128-1907 trial in inhibitor patients, larger 1-year over-dispersion values of approximately 21 and 18, respectively, were observed during an initial 3-month on-demand period and a subsequent 3-month prophylaxis period. It is expected that the variation in the current trial will be smaller, partly due to the longer duration of the trial and partly due to an expected more homogenous patient population. Another published trial including inhibitor patients, comparing prophylaxis using FEIBA® with on-demand treatment, showed 6-month over-dispersion of 4-5 [32]. On that background, an over-dispersion of 7 over the 24 weeks in main part of the current trial is deemed realistic.

17.2 Definition of analysis sets

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

17.3 Primary endpoint

The primary endpoint is the number of bleeding episodes during at least 24 weeks from treatment onset.

The endpoint will be analysed when the main part of trial has been completed.

17.3.1 Estimand and primary statistical analysis

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

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

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

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time in main part as offset and regimen as factor, providing an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is "missing at random", i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

17.3.2 Sensitivity analysis

To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis will be performed where patients having discontinued before finalization of the main part are assumed to have a worse outcome compared to what was observed during the main part of the trial. This will be done by adding a value Δ to the observed bleeding episodes in the main part of the trial before analysing the data. The offset is maintained as being the exposure during the main part since it is not possible to identify the amount of missing observation time.The degree of worsening, $\Delta_{i,}$ will gradually be increased to evaluate at which point concizumab prophylaxis no longer is superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis will be considered robust if the tipping point is above what is considered clinically plausible.

17.3.3 Additional analysis

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

administration, peak thrombin generation (nM) , Endogenous thrombin potential ($nM^{x}min$) and velocity index (nM/min).

17.4 Supportive secondary endpoints

17.4.1 Supportive secondary efficacy endpoints

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

The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset will be addressed in terms of the same estimand as for the primary endpoint. The estimand will be estimated using the same negative binomial regression model as for the primary endpoint.

Furthermore, an additional evaluation will be made, where actual concizumab dose is included as factors in the model.

The remaining supportive secondary efficacy endpoints will be summarised descriptively by treatment regimen. In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed using a negative binomial model with log of trial duration as offset, providing estimates of the ABR with confidence interval for that particular regimen.

17.4.2 Supportive secondary safety endpoints

- Number of TEAEs during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence rate of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset
- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset

- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

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

TEAE is defined as an event that has onset from the first exposure to treatment until the last visit in the trial. Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All adverse events will further be listed.

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

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

17.4.3 Supportive secondary pharmacokinetic endpoints

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

The pharmacokinetic endpoints will be summarised and listed.

17.4.4 Supportive secondary pharmacodynamic endpoints

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

The PD endpoints will be summarized and listed.

17.4.5 Exploratory endpoints

17.4.5.1 Exploratory safety endpoints

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

Adverse events related to technical complaints will be listed and summarised

17.4.5.2 Exploratory patient reported-outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset
- Change in Hemo-TEM after 76 weeks from treatment onset
- Change in VERITAS-Pro® or VERITAS-PRN® after 24 weeks from treatment onset
- Change in VERITAS-Pro® or VERITAS-PRN® after 76 weeks from treatment onset
- Change in SF-36v2 after 24 weeks from treatment onset
- Change in SF-36v2 after 76 weeks from treatment onset
- Change in SDS after 24 weeks from treatment onset
- Change in SDS after 76 weeks from treatment onset
- Change in TSQM after 24 weeks from treatment onset
- Change in TSQM after 76 weeks from treatment onset
- Change in SIAQ-ISRQ after 24 weeks from treatment onset
- Change in SIAQ-ISRQ after 76 weeks from treatment onset
- Change in PGI-C after 24 weeks from treatment onset
- Change in PGI-C after 76 weeks from treatment onset

VERITAS-Pro® or VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

The PRO endpoints will be summarised using descriptive statistics and the remaining questionnaires (Hemo-TEM, PGI-C, SIAQ-ISRQ) will be summarised and listed using descriptive statistics.

17.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. Main part is defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual CTRs might in such case be issued. A CTR describing results

from the main and the extension part will be written when the last patient has either completed or withdrawn from the trial. All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 17–1.

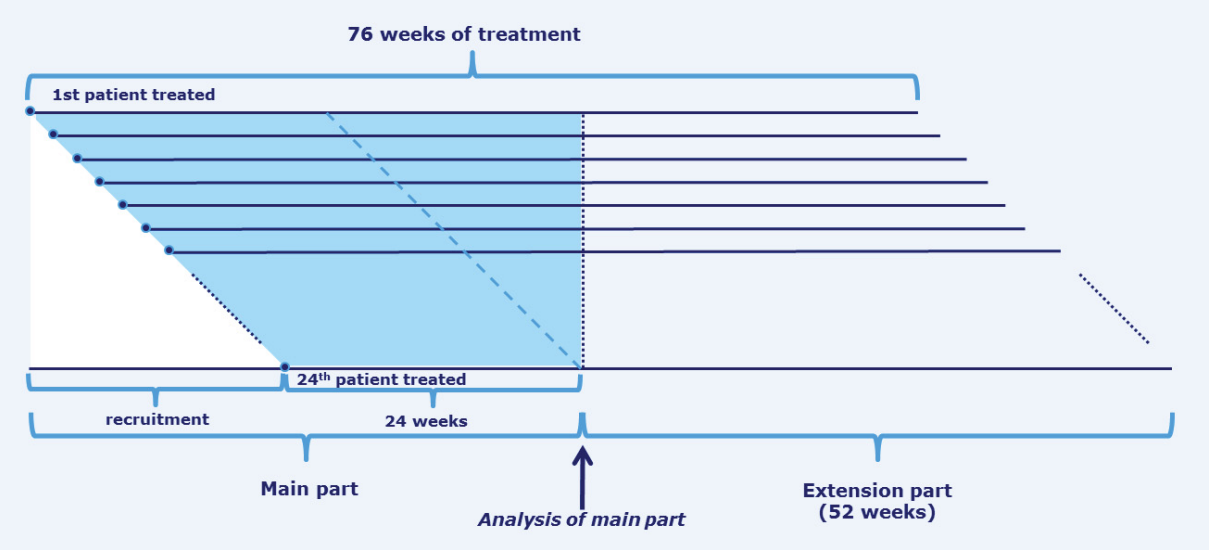

Figure 17–1 Definition of main and extension part

18 Ethics

18.1 Benefit-risk assessment of the trial

Benefits

Results from a multiple dose phase 1 trial where concizumab was dosed for approximately 6 weeks showed a trend towards efficacy in a limited number of patients who reached concizumab plasma concentrations above 100 ng/mL, see Section 3.1.2. Based on these results, it is expected that the majority of the patients randomised to the concizumab treatment with 0.15 mg/kg daily dose will be protected from bleeding episodes. Patients who experience excessive bleeding episodes on the lowest dose will have a possibility to be escalated to a higher dose where bleeding preventive efficacy of concizumab treatment is expected to improve. For haemophilia patients with inhibitors and who are treated on-demand, expected improved efficacy is considered to be a major benefit in participating in this trial. Also, concizumab is administered s.c. and might reduce the burden of frequent i.v. injections associated with current treatment options in haemophilia patients with inhibitors.

Information gained from this trial will contribute to gaining regulatory approval for a product that is anticipated to offer clinical advantages over currently available products.

Risks

No risks have been recognised as identified risks by review of safety data from the activities in the clinical development so far. However, the nonclinical toxicity studies have identified thromboembolic events as a potential risk when treating non-human primates with concizumab at high exposures.

As observed for other pro-coagulant compounds, there is a potential safety risk of thrombosis and vascular ischemia with reaching very high concizumab plasma concentrations. In non-clinical toxicity studies with concizumab, thrombi were observed at high doses. However, a no observed adverse effect level (NOAEL) for concizumab has been identified in non-haemophilic animals at plasma concentrations several folds higher than the currently anticipated effective plasma concentration (mean area under curve [AUC] and C_{max}) based on PK modelling.

In a drug–drug interaction study in monkeys, three doses of up to 1 mg/kg of NovoSeven® were administered at 2-h intervals, alone or in the presence of a steady state concentration of concizumab. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation. No notable clinical observations were made.

In clinical trials, except for one case of superficial thrombophlebitis in a healthy volunteer who received a single dose of 1mg/kg, no other thromboembolic events were observed. A phase 1

multiple dose trial was finalised in haemophilia A patients (0.8 mg/kg s.c. every 4 days for 6 weeks). In this clinical trial, marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range in patients with high plasma concentrations of concizumab. These changes were not judged as clinically significant by the investigators and were not followed by thromboembolic AEs or an increase in the number of bleeding episodes in the explorer™3 trial.

A potential risk identified in non-clinical studies is vascular vessel wall changes due to immune complex deposition causing localized vascular vessel wall changes such as hypertrophy and inflammatory cell infiltration. Concizumab is a foreign protein to animals and it is generally recognized that animal studies are limited in their ability to predict human immune responses to a therapeutic protein product. The concentrations of concizumab in plasma in animals in the non-clinical studies have reached levels far above the anticipated effective concentration. Humans are expected to have a very low immunogenic response towards a humanised mAb. The antibodies towards concizumab have not been observed so far in clinical trials. Furthermore, even if antibodies towards concizumab occur, the risk for the rate of immune complex formation exceeding the clearance capacity is considered low. Please refer to the Investigator's Brochure for further information.

If antibodies against concizumab develop, they might also inhibit the function of the administered drug. The consequence of this could be that the patient may not be able to benefit from the drug in the future. Antibody development against concizumab is not expected to reduce the effect of other treatment options.

Theoretical risks include bleeding due to consumption of coagulation factors and adverse reactions due to potentiation of inflammatory reactions or tissue damage due to impairment of tissue repair mechanisms [33 34] . TFPI is an important inhibitor of TF which, in addition to its role in haemostasis, is implicated in tissue repair processes and in a variety of physiological and pathophysiological states where repair mechanisms are activated. These include sepsis, DIC, inflammation, atherosclerosis, cancer and crush injuries [35 36, 37].

There may be a risk of allergic reactions, including severe (anaphylactic) reactions, in connection with concizumab administration. Severe allergic reactions may potentially be life-threatening and thus, the trial products will be administered to the trial patients at the site under the surveillance of medically trained trial site staff in the beginning of the trial.

Overall the anticipated benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP [1] and the requirements in the Declaration of Helsinki [2].

Before any trial-related activity, the investigator must give the patient verbal and written information about the trial and the procedures involved in a form that the patient can read and understand.

The patients must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the patient before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

Only applicable for Japan: As a minor is unable to provide legally binding consent, informed consent must be sought from the parent(s)/LAR(s) on the child's behalf prior to enrolling a child in the trial, according to local requirements.

18.3 Data handling

If the patient withdraws from the trial or is lost to follow up, then the patient's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to patients during 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

19 Protocol compliance

19.1 Protocol deviations

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.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The below process will be in place to prevent missing data in this trial.

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 is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. 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).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

An Investigator Portal (Global Haemophilia Network [GHN]) will be used as primary media for exchange and handling of investigator trial master file documents between Novo Nordisk and the site and for electronic storage of these documents during trial conduct.

Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- SmPC or similar labelling of eptacog alfa (rFVIIa)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- Description of research facility obtained (applicable for sites outside the US)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

For local laboratory parameters the following will be collected:

- Laboratory normal ranges
- Laboratory certification, QA scheme or similar documentation
- Laboratory assay methods (only non-standard assays) and/or analytical methods

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP [1] applicable regulatory requirements and the Declaration of Helsinki [2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 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.

At least investigator must be trained in the current protocol version at a Novo Nordisk Investigator meeting or by the most recent version of the web training. It is recommended that all site staff completes the web protocol training.

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 will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [38].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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 subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure how-we-disclose-trial-information.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. 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.

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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors [38](sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Patients' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

Only applicable for Spain: 25 years retention according to the Spanish Royal Decree 1090/2015.

The files from the trial site/institution must be retained for 15 years after EOT as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

This trial will involve collection of human biosamples at visit 1 (screening visit) and at visit 17 (EOT) and these samples are to be stored maximum 15 years from EOT. In addition, samples which have been drawn as back-up samples during the conduct of the trial and have not been analysed will be captured and stored under the same conditions.

Storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and

participate, while refusing permission for biological specimens to be stored for future exploratory analysis.

- Human biosamples will be stored at the central laboratory
- 1.0 mL citrated plasma, 1.2 mL serum and/or 2.0 mL whole blood (DNA for genotyping) will be obtained
- The intended use of the stored human biosamples e.g.: 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 human biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- Human biosamples may be transferred to third parties e.g. research consortia
- The human biosamples will be transferred and stored after the EOT at a designated central laboratory
- Confidentiality and personal data protection will be ensured during storage after the EOT
- The human biosamples may be transferred to other countries (not applicable if local regulations prohibit export of human biosamples)
- The human biosamples will be destroyed at the latest 15 years from EOT
- The patient may request the stored human biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used
- Novo Nordisk and laboratory will have access to the stored human biosamples
- Potential consequences for the patient and their relatives: In the event that the collected human biosamples (plasma, serum and/or DNA for genotyping) 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 human biosamples obtained from their own body, see Section 5.1.

24.2.1 Antibody samples

Antibody samples will be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

The retained antibody samples may be used 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 assays, and will not be reported in this trial. The samples will be stored at a central bio-repository after EOT and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from EOT after which they will be destroyed.

The patients' identity will remain confidential and the antibody samples will be identified only by patient number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Patients can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC (not applicable for Japan).

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the patients.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

26 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.

Novo Nordisk accepts liability in accordance with:

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. II Nr. 105/2015

Only applicable for 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 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 or the fault 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"

Only applicable for Poland: Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal pf Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigators are covered by the Insurance Policy issued according to applicable Polish law.

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Protocol

NN7415-4310

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

Trial phase: 2

Includes: Protocol Version 1 (15 March 2017); Protocol Amendment no 1 (05 May 2017) for all participating countries.

Protocol originator

[redacted], Senior International Trial Manager
Biopharm Trial Ops 1

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List of abbreviations

ABI	ankle-brachial index
ABR	annualised bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under curve
BP	blood pressure
BU	Bethesda Unit
CCDS	company core data sheet
CLAE	clinical laboratory adverse event
C_{max}	maximum plasma concentration
CNS	central nervous system
concizumab B	the name concizumab is being used as an abbreviation for concizumab B. B is the formulation

CPoC	clinical proof of concept
CRF	case report form
CRO	contract research organisation
CRP	c-reactive protein
CT	computerized tomography
cTn	cardiac troponin
CTR	clinical trial report
DFU	direction for use
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
DRC	data request correction
DUN	dispensing unit number
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eITMF	electronic investigator trial master file
ELISA	enzyme-linked immunosorbent assay

EMA	european medicines agency
EOT	end of trial
ePRO	electronic patient reported outcome
eptacog alfa	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to rFVIIa,'NovoSeven®, and 'NiaStaseRT®'
ETP	endogenous thrombin potential
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendment Act
FIX	coagulation factor IX
FPFV	first patient first visit
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FVIII:C	plasma activity of factor VIII
FX	coagulation factor X
FX_a	activated coagulation factor X
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHN	global haemophilia network

HCP	host cell protein
IB	investigator's brochure
IC	informed consent
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	independent ethics committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
INN	International Non-Proprietary Names for Pharmaceutical Substances
IRB	institutional review board
ISTH	International Society on Thrombosis and Haemostasis
IT	information technology
i.v.	intravenous(-ly)
IWRS	interactive web response system
LBBB	left bundle branch block
LPFV	last patient first visit
LPLV	last patient last visit

mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NIMP	non investigational medicinal product
PCD	primary completion date
PD	pharmacodynamics
PEF	peak expiratory flow
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome
PT	prothrombin time
Q	Inter compartmental clearance
QA	quality assurance
Q4D	every 4^{th} day

eptacog alfa (rFVIIa)	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to 'NovoSeven®'
sABR	spontaneous annualised bleeding rate
SAE	serious adverse event
SAS	safety analysis set
sBE	spontaneous bleeding episodes
s.c.	subcutaneous(-ly)
SI	international system of units
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TAT	thrombin-antithrombin complex
TEAE	treatment emergent adverse events
TIA	transient ischemic attack
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TMM	trial materials manual
TVP	trial validation plan
UTN	Universal Trial Number

1 Summary

The main objective for the phase 2 trial NN7415-4310, explorer™4, is to assess the efficacy of concizumab administered s.c. once daily to prevent bleeding episodes in haemophilia A and B patients with inhibitors. Furthermore, this trial aims to assess the longer-term efficacy and safety of concizumab in haemophilia A and B patients with inhibitors and to establish the safety of treating breakthrough bleeding episodes with recombinant factor VIIa (rFVIIa) in these patients.

Objective(s) and endpoint(s)

Primary objective

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors.

Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

Primary endpoint

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

Key secondary endpoints

- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset
- Number of treatment emergent adverse events (TEAEs) during at least 24 weeks from treatment onset

Time frames for evaluation of Objectives/Endpoints

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of dosing treatment with trial product (or has withdrawn). In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial design

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. We expect 16 patients to complete treatment in concizumab arm (concizumab prophylaxis) and 8 patients in comparator arm (rFVIIa on demand). The dose regimen is selected based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

For all patients treated with concizumab (concizumab arm and comparator arm extention part) a loading dose of 0,5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0,15 mg/kg. All patients in treatment with concizumab will in a non-bleeding state receive a single dose of 90 µg/kg eptacog alfa (rFVIIa) one week after dosing with concizumab. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at the site after 24h.

The total trial duration for the individual patient will be approximately 86-88 weeks, consisting of a 2-4 week screening period, a subsequent 76-week treatment period and an 8-week follow-up period. eptacog alfa (rFVIIa) for treatment of bleeding episodes during the trial will be provided by Novo Nordisk. The patient will not be provided with trial product or eptacog alfa (rFVIIa) after end of trial.

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn. The analysis of the main part of the trial aims to substantiate the clinical proof of concept (CPoC) that concizumab has the potential to prevent bleeding episodes in patients with haemophilia and inhibitors. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial population

Number of patients planned to be screened: 28
Number of patients planned to be started on trial product: 26
Number of patients expected to complete the trial: 24

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 the suitability for the trial
- Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
- Patients currently in need of treatment with bypassing agents

Key exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Known inherited or acquired bleeding disorder other than haemophilia
- Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX

Key Efficacy assessment

- Number of bleeding episodes during at least 24 weeks of treatment onset

Key Safety assessment

- Number of treatment emergent adverse events during at least 24 weeks of treatment onset

Trial products

The following products will be used in the trial:

- **Investigational Medicinal Products:**
  - concizumab B, 100mg/mL to be administered s.c. with NovoPen®4 and needles
  - eptacog alfa (rFVIIa), 5mg /vial and histidine (solvent). Reconstituted eptacog alfa (rFVIIa) is for intravenous administration and used in the trial at visit 3 and 9.1 for all patients with the purpose of investigating the safety of administering eptacog alfa (rFVIIa) to haemophilia patients
- **Non Investigational Medicinal Product**:
  - eptacog alfa (rFVIIa) 5 mg /vial and histidine (solvent). Reconstituted eptacog alfa is for intravenous administration and used in this trial for treatment of bleeding episodes

2 Flow chart

2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]													Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
PATIENT RELATED INFO/ASSESSMENTS																						
Informed consent/ Genotyping and Long-term storage consent	●																					
In/exclusion criteria	●	●[g]																				
Demography	●																					
Concomitant illness/Medical history	●																					
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Details of Haemophilia/Haemophilia treatment and bleed history	●																					
Withdrawal criteria/ Criteria for premature discontinuation of trial product		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Randomisation (IWRS)		●																				
EFFICACY																						
Bleeding episodes [h, i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Thrombin generation (central lab)	●	●	●[j, k]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Free TFPI (central lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
SAFETY																						
Physical examination	●	●	●[k]						●	●						●				●	●	●
Body measurements	●	●[m]	●[k, m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]		●[m]	●[m]
Vital signs	●	●[n]	●[k, n]	●	●	●	●	●	●[n]	●[n]	●	●	●	●	●	●	●	●	●	●	●	●	●
ECG	●																						
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Injection site reaction		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Urinalysis (local lab)	●																					
Haematology (local lab)	●	●	●[j, k]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Biochemistry (central lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVIII/ FIX activity (central lab)	●								●[l]											●[l]		
Coagulation parameters (central lab)	●	●		●	●	●	●	●	●[l]		●	●	●	●	●	●	●	●	●	●[l]	●	●
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			●[j, k]							●[j]												
FVIII/FIX inhibitors (central lab)	●								●[l]											●[l]		
Anti-concizumab antibodies (ADA) (special lab) [o]	●	●	●[k, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
Concizumab ELISA (special lab)		●	●[k, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVII ELISA (special lab)			●[j,k]							●[j]												
Total TFPI (special lab)	●	●	●[k]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
TRIAL MATERIAL																						
IWRS call	●	●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●	●[w]	●[k]			●			●	●		●		●		●	●	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]						●[d, s]	●											●	
Administration of trial product (eptacog alfa)			●[k, t]							●[t]												
Drug accountability (concizumab)			●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New dose of trial product [e, u]				●	●	●	●	●	●		●	●	●	●	●	●	●	●	●		●	
PRO questionnaires	●	●	●[k]	●	●	●	●	●	●			●								●		
REMINDERS																						
Human biological specimen for storage (central lab)	●																					●

explorer™4 trial periods	Screening	Treatment main [a,b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176	197	225	253	281	309	337	393	449	505	533	When applicable	589
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Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Handout ID card	●																					
Training [v]	●	●							●	●											●	
Compliance: eDiary			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of treatment																				●		
End of trial																						●

The cells marked in 'red' are only for the patients randomised to eptacog alfa (rFVIIa) arm.

2.2 Explanatory descriptions

Footer	Description
a	There is staggered recruitment for the 4 first patients in the trial on the concizumab arm.
b	Concizumab administration is performed at home except for visit 2 and visit 3 for patients randomised to concizumab and visit 9 and 9.1 for patients randomised to eptacog alfa. Sampling for Free TFPI, Anti-concizumab antibodies, Concizumab ELISA and Total TFPI are done prior to concizumab administration.
c	The duration of the visits will last according to patient's individual training need on concizumab administration, NovoPen®4, eDiary training etc. Visit 3 and visit 9.1 have a PK session of 24 hours and a safety follow up visit the following day.
d	Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment.
e	For patients being dose escalated on concizumab a phone call is recommended 1 week after first dose of concizumab.
f	Daily dosing preferably at the same time in the morning.
g	Evaluation of the laboratory results obtained from samples taken at screening.
h	Bleeding episodes occurring between visit 1 and visit 2 or at site should be registered in the eCRF. All bleeding episodes except for severe occurring after visit 2 at home should be registered in the eDiary. Severe bleeding episodes must be registered in the eCRF.
i	Eptacog alfa will be given to treat breakthrough bleeding episodes.
j	Sampling time schedule for thrombin generation, haematology, coagulation parameters and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.
k	ONLY for patients randomised to concizumab arm.
l	At visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.
m	Only body weight should be measured.
n	Vital signs should be evaluated before and after trial drug administration at visit 2 and visit 3 for concizumab arm and at visit 9 and visit 9.1 for patients in eptacog alfa arm switching to concizumab treatment.
o	In case clinical signs of e.g. hypersensitivity reactions or immune related events are seen, additional samples for ADAs may be taken. All antibody samples from the affected patient will be analysed on an ongoing basis. If antibodies are detected, additional blood samples will be taken and stored for characterisation of the antibodies.
p	Blood sampling for anti-concizumab antibodies and concizumab ELISA testing should only be collected for patients on concizumab.
q	If needed dispensing of eptacog alfa, histidine, trial injection kits and Direction For Use (DFU).
r	First treatment dose of concizumab is a loading dose and will be administered at visit 2 for the concizumab arm and visit 9 for the eptacog arm.
s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g., eptacog alfa, FEIBA®) for treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2.

t	Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm.
u	Patient treated with concizumab should be dose escalated at next scheduled visit if he experiences ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab. If the investigator judges that next scheduled visit is too late an unscheduled visit should be performed for dose escalation.
v	Home treatment training must take place at visit 2 at the latest and whenever needed afterwards. Patients randomised to eptacog alfa will be re-trained in NovoPen®4 and s.c. administration at visit 9 and 9.1. If necessary training can be performed as needed at other visits. The eDiary will be provided to the patients at visit 2 if the patient feels capable in s.c. administration and using the eDiary. Further the patients will be trained in recognition of signs/symptoms of thrombosis.
w	Only for patients randomised to on-demand arm.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [1], applicable regulatory requirements, in accordance with the Declaration of Helsinki [2] and ISO 14155 [3].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

The INN name of the active pharmaceutical ingredient is concizumab (synonyms used during early development are NNC0172-2021, anti-TFPI, NN7415 or mab2021). Throughout this document "concizumab" is used as the name of the trial drug.

3.1 Background information

3.1.1 Haemophilia

Haemophilia is an inherited bleeding disorder characterised by an increased bleeding tendency, typically in weight bearing joints. Haemophilia A is caused by a partial or complete deficiency of blood coagulation factor VIII (FVIII). In haemophilia B, it is factor IX (FIX) that is deficient. Inheritance is chromosome X-linked; therefore the disease mainly affects males. The incidence of haemophilia A and B on average is estimated to be about 1 in 5000 live male births [4]. According to the World Federation of Haemophilia global survey of 2014[5], about 178,500 persons are diagnosed with haemophilia worldwide. Of these, about 80% have haemophilia A.

Haemophilia is classified as "severe", "moderate" or "mild" according to the plasma activity of the affected coagulation factor [6]. 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 [7]. The haemostatic plug, if formed, in these patients 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 occurs spontaneously and is the most frequent symptoms 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 majority of children with severe haemophilia experience their first bleeding episode into a joint prior to age 4 year. Many children also bleed from other body sites before this age is reached [8]. For this reason, primary prophylaxis with regular FVIII or FIX injections in the non-bleeding state is the recommended treatment from early childhood.

In patients who have developed inhibitors towards FVIII or FIX, replacement therapy is rendered ineffective. Though prevalence studies and registry data indicate that the prevalence of inhibitors in the haemophiliac population overall has been reported to be between 5% and 7% [9], the prevalence

amongst patients with severe haemophilia (FVIII:C < 1%) is higher and has been reported to be up to 30% [9, 10]. These patients may be treated with bypassing agents, activated FVII (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) given as i.v. injections.

Current treatment options in haemophilia, replacement therapy or bypassing therapy, are hampered by the fact that these products must be given as i.v. injections. Furthermore, bypassing agents are characterized by relatively short half-lives, therefore prophylactic treatment is burdensome. It is also generally acknowledged that the efficacy profile of bypassing agents is inferior to replacement therapy. Consequently, delayed or sub-optimal treatment occurs in a significant number of patients with inhibitors. A new therapeutic agent that can be administered subcutaneously will represent a major improvement in the treatment of these patients in a prophylaxis setting.

3.1.2 Concizumab

The trial product, concizumab, is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype with a molecular weight of 149 kilo Dalton's. Like other antibodies, concizumab is composed of two light chains and two heavy chains linked together by disulfide bridges. To prevent formation of half-antibodies, the serine at position 241 in the heavy chain has been replaced with a proline (S241P (Kabat annotation)) [10]. The mechanism of action of concizumab is based on the concept of inhibiting the activity of a natural coagulation inhibitor, tissue factor pathway inhibitor (TFPI). TFPI is a potent inhibitor of the initiation phase of the coagulation process, i.e. the activation of (FX) to FXa by the tissue factor (TF)/factor VIIa (FVIIa) complex. TFPI first binds to and inhibits activated FXa and subsequently binds to and inhibits the TF/FVIIa complex, forming a TF/FVIIa/FXa/TFPI complex. Thus, concizumab prevents both inhibition of FXa and inhibition of FVIIa/TF by TFPI. In this manner, sufficient amounts of FXa to ensure effective haemostasis in the absence of a functional activated factor IX/activated factor VIII (FIXa/ FVIIIa) complex may be generated. This is a new concept that remains to be documented safe and efficacious in patients with haemophilia. More information about the physiological role of TFPI and the mode of action of concizumab is provided in the Investigator's Brochure.

Key differentiators of this new mode of action (MoA) and the key benefit of concizumab in patients with severe haemophilia A and B with inhibitors is reduced treatment burden due to subcutaneous administration potentially leading to better adherence, more patients on prophylactic treatment and ultimately better outcome.

Four clinical trials with concizumab have been completed thus far: the first human-dose trial (NN7415-3813, explorer™1) [11], a single dose trial in Japanese healthy subjects (NN7415-3981), two multiple dose trials (NN7415-3986, explorer™2) and (NN7415-4159, explorer™3). When the first cohort with 4 (four) healthy subjects in explorer™2 was completed, prior to the initiation of the 2nd cohort, the trial was halted, due to findings related to thrombosis in an ongoing 26-week toxicity study in primates. In this trial animal had concizumab plasma concentrations several hundred fold

above clinically relevant concentrations. Follow up investigations confirmed that the animal's condition was related to thrombosis in the lungs caused by exaggerated pharmacology at these high plasma concentrations. Before the initiation of the fourth phase 1 trial (NN7415-4159), explorer™3, a new 52 week non-clinical toxicology study was conducted in primates to investigate the findings in the previous study. The conclusion from this new non-clinical study was that the results from non-clinical studies support further clinical development of concizumab. Explorer™3 was a multiple dose clinical trial which aimed to investigate the safety, pharmacokinetics and pharmacodynamics of concizumab at five different dose levels in adult severe haemophilia A patients without inhibitors. In this trial multiple doses of concizumab were administered s.c. over a period of six weeks.

The explorer™3 trial was finalised following the completion of cohort 3 (0.8 mg/kg s.c. every 4 days for 6 weeks). Blinded preliminary safety and PK/PD data from the cohort was reviewed by the concizumab safety committee. Marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range. In addition, a substantial inter subject variation in pro-coagulant response to the drug was observed. Based on this, the Novo Nordisk safety committee (see Section 12.8.1) decided not to proceed to cohort 4 (1.1 mg/kg s.c. every 4 days for 6 weeks). No clinical consequences or serious adverse events were seen in the completed cohorts in explorer™3.

The PK results from explorer™3 showed exposure-response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL. Individual predicted PK profiles merged with recorded spontaneous and traumatic bleeding episodes are shown in Figure 3–1.

Figure 3–1 Individual predicted PK profiles based on data merged with recorded spontaneous (circles) and traumatic (triangles) bleeding episodes during the dosing period and follow-up period. All data originates from explorer™3 (N=24 patients). PK of concizumab is subdivided into three exposure levels of ≤ 20 ng/mL, 20-100 ng/mL, and > 100 ng/mL together with the number of contributing patients. LLOQ: lower limit of quantification.

[a] 'Time in trial' refers to the time that the patients spent on each concizumab exposure level, and the ≤ 20 ng/mL level therefore also includes the screening period (not shown on this figure).

A large difference between the peak and trough plasma concentrations of concizumab were observed as well, especially in the highest dose group (0.80 mg/kg) of explorer™3. In patients who received 0.25, 0.5 and 0.8 mg/kg doses a significant overlap in plasma concentrations of concizumab was seen due to high between-patient variability in concizumab.

Single doses of concizumab up to 9 mg/kg have been administered to haemophilia patients in the first human dose trial with concizumab, explorer™1. These doses resulted in plasma concentrations of concizumab that were significantly higher than the ones that are modelled to be reached in the highest escalated daily dose (0.25 mg/kg) of explorer™4.

In a drug–drug interaction study in monkeys (NN215431), three doses of up to 1 mg/kg of NovoSeven® were administered at 2h intervals, alone or in the presence of a steady state concentration of concizumab. No notable clinical observations were made, no treatment-related

adverse findings were seen, i.e. no thrombi or other signs of excessive coagulation. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation.

For an assessment of benefits and risks of the trial, see Section 18.1.

For further information, please refer to the Investigator's Brochure.

3.2 Rationale for the trial

Four phase 1 clinical studies with concizumab have been finalised. Key safety and preliminary efficacy results from these phase 1 studies support further development of concizumab in haemophilia patients. Therefore, the main objective in the phase 2 of concizumab development is to assess efficacy and safety and provide data that will guide for the confirmatory phase 3 concizumab trials.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors

4.1.2 Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

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

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset

- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset
- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

Supportive secondary pharmacokinetic endpoints

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

Supportive secondary pharmacodynamic endpoints

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

4.2.3 Exploratory endpoints

4.2.3.1 Exploratory safety endpoints

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

4.2.3.2 Exploratory patient reported outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset

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

All endpoints referring to a time frame of either 24 weeks or of at least will be evaluated in the main part of the trial. All endpoints referring to a time frame of 76 weeks will be evaluated in the extension part of the trial.

5 Trial design

5.1 Type of trial

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. The selected dose regimen is based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

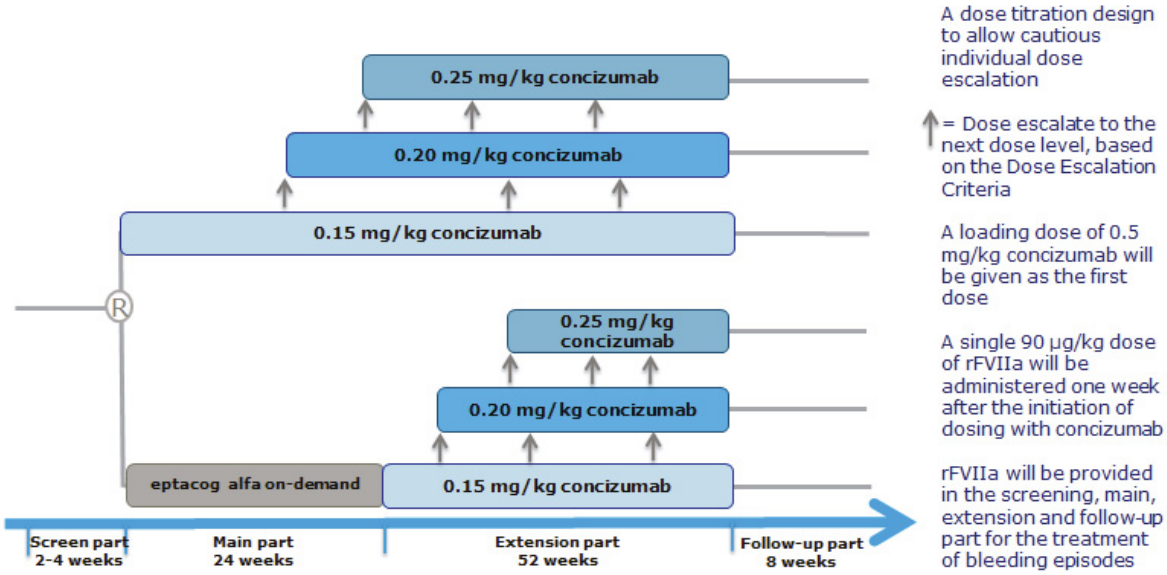


Figure 5–1 Schematic diagram of the trial design

The total trial duration for the individual patient will be approximately 86-88 weeks, including a 2-4 week screening period, a 76 week treatment period, and a follow-up period of 8 weeks, see Figure 5–1

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts up to 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn.

In the concizumab arm bleeding episodes occurring during the trial will be treated with eptacog alfa (rFVIIa). In all patients treated with concizumab a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state one week after dosing with concizumab has been initiated. The investigator will evaluate if there are any safety concerns 24 hours post eptacog alfa (rFVIIa) administration. Furthermore, the scheduled administration of eptacog alfa (rFVIIa) for the first 4 patients entering the trial with concizumab will be staggered.

In the comparator arm, in the main part, patients will receive eptacog alfa (rFVIIa) on-demand treatment. After completion of the main part, the patients will continue the trial in the extension part being treated with prophylactic concizumab 0.15 mg/kg (with potential dose escalation) s.c. daily administration.

Human biosamples (plasma, serum, and/or DNA for genotyping) will be collected in this trial for future exploratory analysis to pursue a deeper insight into the biology of TFPI, coagulation, and effect of concizumab on joint health. That may include coagulation parameters and markers of joint status and damage. Acceptance of storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for human biosamples to be stored for future exploratory analysis, see Section 8.1.1.

An independent data monitoring committee (DMC) will be established for this trial. The DMC will review all safety data from the ongoing trial with concizumab exposure, see Section 12.8.2.

5.1.1 Surgery

Minor surgery is allowed in this trial. Major surgery conducted earlier than one month (30 days) prior to trial start is allowed, see exclusion criteria no 6.

Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. Examples of minor surgery include implanting of central venous access devices (ports, CVC, pumps and other CVADs) in subcutaneous tissue, skin biopsies or simple dental procedures.

5.2 Rationale for trial design

Explorer™4 is a phase 2, clinical proof of concept (CPoC), and safety trial. The trial aims to substantiate CPoC that concizumab has the potential to prevent bleeding episodes in haemophilia patients with inhibitors. A dose escalation design will allow cautious dose escalation in order to identify an efficacious and safe concizumab dose for the individual patient. A comparator arm is included to assess if concizumab is superior to on-demand treatment. Furthermore, the trial will give a possibility to assess safety of co-administration of eptacog alfa (rFVIIa) to the patients exposed to the concizumab treatment.

The duration of 24 weeks for the main part of the trial is deemed necessary in order to obtain information on the annualised bleeding rate on concizumab prophylaxis. The duration of the extension part of the trial will be 52 weeks and provide further information on efficacy, i.e. annualised bleeding rate, and also provide additional safety data upon 76 weeks treatment with concizumab.

A total of 26 patients previously on-demand (OD) treatment will be randomised into one of the two arms, with 16 patients in the concizumab arm and 8 patients in the comparator arm see Figure 5–1. Concizumab will be administered s.c. daily for patients randomised to the concizumab arm in the main and the extension part of the trial. For patients in the comparator arm in the extension part treatment will be changed from on-demand with rFVIIa to prophylaxis with concizumab.

The concizumab dose regimens will be starting with 0.15 mg/kg with the possibility to escalate to 0.20 mg/kg and 0.25 mg/kg based on bleeding frequency, see Section 5.3.3.

Daily dosing with concizumab 0.15 mg/kg aims to ensure steady-state levels of concizumab plasma concentrations above 100 ng/mL for the majority of the patients starting on this dose. The PK results from explorer™3 showed exposure response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL, see Figure 3–1 . The minority of patients which are predicted to have steady-state plasma concentrations below this threshold are expected to experience bleeding episodes and therefore will have the opportunity to be dose escalated to the dose of 0.2 mg/kg. A further dose escalation to 0.25 mg/kg per day is permitted, again based on the bleeding rate, see Section 5.3.3.

Figure 5–2 Individual predicted concizumab concentration profiles for all concizumab-treated patients in explorer™2 (n=4 patients) and explorer™3 (n=18 patients). The horizontal lines indicate 100 ng/mL, and the shaded areas represent the full range (min-max) of the individual predicted profiles.[1]

Due to the high between patient variability in concizumab concentration observed in explorer™3, a significant overlap in plasma concentrations of concizumab in patients who received 0.25, 0.5 and 0.8 mg/kg doses was seen, see Figure 5–2. Therefore, choosing three doses that would lead to reasonably distinct mean plasma concentrations of concizumab, and thus different efficacy at each

[1] Plasma concentrations in the same range as those in explorer™3 are expected to be reached in this trial with daily dose administration. The starting dose for all patients will be 0.15 mg/kg daily. The plasma steady-state exposure for a typical subject at this dose level is predicted to fourfold lower compared to a typical subject on 0.8 mg/kg Q4D (cohort 3 of explorer3) in terms of both Cmax and AUC 0-24h. For 0.20 mg/kg daily and 0.25 mg/kg, the plasma steady-state exposure levels for a typical subject are predicted to be less than 40% and 70% respectively, compared to the typical subject exposure in the 3rd cohort of explorer™3 (AUC and Cmax). The maximum predicted plasma exposure levels (Cmax and AUC 0-24h) for the 0.15 mg/kg daily dose level is predicted to be more than 8 fold lower than for 0.80 mg/kg Q4D. For 0.20 mg/kg daily both Cmax and AUC 0-24h are predicted to be more than 3 times lower than for 0.80 mg/kg Q4D. For 0.25 mg/kg daily, the maximum Cmax and AUC 0-24h are predicted to be 35% lower than for 0.80 mg/kg Q4D.

dose level was not deemed possible. For this reason, a traditional parallel arm design was not chosen for the phase 2 trials. In contrast, the titration trial design allows patients to start on a low dose, which is expected to ensure prophylaxis but not marked changes in coagulation parameters, for the majority of patients. Escalation to the next dose level will only occur in the case of lack of efficacy (≥ 3 spontaneous bleeding episodes within the preceding 12 weeks). In addition, the PK of concizumab is heavily influenced by target mediated drug disposition, which means that small differences in concizumab dose ultimately leads to large differences in plasma concentrations. Therefore, daily dosing is proposed for the phase 2 trial, explorer™4. Daily dosing will allow for the increase in trough levels and thus better efficacy may be expected with a lower dose.

A loading dose of 0.5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0.15 mg/kg in order to ensure steady-state levels at the time of eptacog alfa (rFVIIa) administration. eptacog alfa (rFVIIa) will be administered one week after initiation of dosing with concizumab in a non-bleeding state to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment.

Embryonic exposure in pregnant female partners of men treated with concizumab is highly unlikely and there is no need for protocol requirements for use of contraception in phase 2 and 3 trials.

5.3 Treatment of patients

The following products will be administered in the trial.

Table 5–1 List of products provided by Novo Nordisk

Compound Name	Strength	Dosage form	Route of administration	Treatment period
concizumab B [a]	100 mg/mL	solution for s.c. injection in a 3 mL cartridge [b]	Subcutaneous administration using NovoPen®4	For prophylactic treatment in 76 weeks (for concizumab arm in the main part and extension part). For prophylactic treatment in 52 weeks (for comparator arm in the extension part).
eptacog alfa (rFVIIa) [a, c]	5 mg/vial	Powder for solution for i.v. injection	Intravenous administration	For treatment of breakthrough bleeding episodes at the discretion of the investigator (screening, main, extension and follow up part). [c] Administration of doses higher than
histidine solvent (5 mL)		Prefilled syringes for solution for i.v. injection		

				90µg/kg to patients exposed to concizumab is not allowed. For on-demand treatment at the discretion of the investigator in 24 weeks for comparator arm in the main part. In the concizumab arm and comparator arm after switching to concizumab in the extension part of the study a single 90µg/kg dose for initial safety assessments in a non-bleeding state. [a] Will be provided for as long as patients participate in the trial (screening, main, extension and follow up part)

[a] Investigational medicinal product (IMP)
[b] Not to be confused with the daily injected volume (~150 µL, depending on dose strength and body weight)
[c] Non-investigational medicinal product (NIMP)

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with national legislation and a copy of the label can be found in the Trial Materials Manual, see Section 9.

5.3.1 Concizumab arm

5.3.1.1 Concizumab prophylactic treatment (main and extension part)

Concizumab will be given s.c. once daily 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg). The dose escalation criteria are described, see Section 5.3.3. The first dose of concizumab will be given at the trial site under medical supervision.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 2 in order to ensure steady state levels at the time of the administration of eptacog alfa (rFVIIa) in a non-bleeding state at visit 3, see Section 5.3.4.

The patients will be trained in s.c. administration of concizumab with NovoPen®4 at the screening visit and at the first scheduled treatment visit.

5.3.2 Comparator arm (eptacog alfa (rFVIIa))

5.3.2.1 On-demand treatment (main part)

During the main part of the trial, patients will receive eptacog alfa (rFVIIa) for treatment of bleeding episodes, with a dose regimen at the discretion of the investigator.

5.3.2.2 Concizumab prophylactic treatment (extension part)

After completion of the main part, the patients will continue the trial in the extension part and will switch to prophylactic treatment with s.c. daily administration of concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) s.c. daily administration.

The same dose escalation criteria as described below (for the initial concizumab arm) will apply.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 9 in order to ensure steady state levels at the time of the administration of rFVIIa in a non-bleeding state at visit 9.1.

5.3.3 Dose escalation

The dose escalation criteria as described below will apply to all treatment arms.

Bleeding episodes will be assessed during the trial both at scheduled visit and also between visits. The first 2 weeks of the treatment with concizumab 0.15 mg/kg is considered as a run-in period. Hence, bleeding episodes occurring during first 2 weeks should not influence a dose escalation decision.

All spontaneous bleeding episodes (sBEs) are counted from 2 weeks after visit 2 (or visit 9 when switching from eptacog alfa (rFVIIa) to concizumab) (first treatment visit) until visit 16 (end of treatment visit), i.e. a total of 74 weeks. Dose escalation will be based on the number of spontaneous treated bleeding episodes in patients within preceding 12 weeks. However, before dose escalation can occur, to ensure the safety of the patients, the investigator must take into account the full clinical picture the patient is presenting with and all available laboratory results, including coagulation parameters.

Dose 0.15 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE). If yes, and if investigator deems it safe, the patient will be dose escalated from 0.15 to 0.20 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.20 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.20 mg/kg treatment period. If yes, and if investigator deems it safe, the patient will be dose escalated from 0.20 to 0.25 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.25 mg/kg:
Patients are not dose escalated further regardless of the number of sBEs. When an sBE occurs, the investigator will determine if ≥ 3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.25 mg/kg treatment period. If yes, then the patient must be discontinued due to lack of efficacy, see Section 6.4.

The possibility of dose escalation at unscheduled visits is necessary in order to avoid bleeding episodes at inadequate dose level: e.g. if the dose escalation eliciting bleeding episode occurs soon after a scheduled visit, the patient will avoid to wait8 weeks for the next scheduled visit (in the extension part).

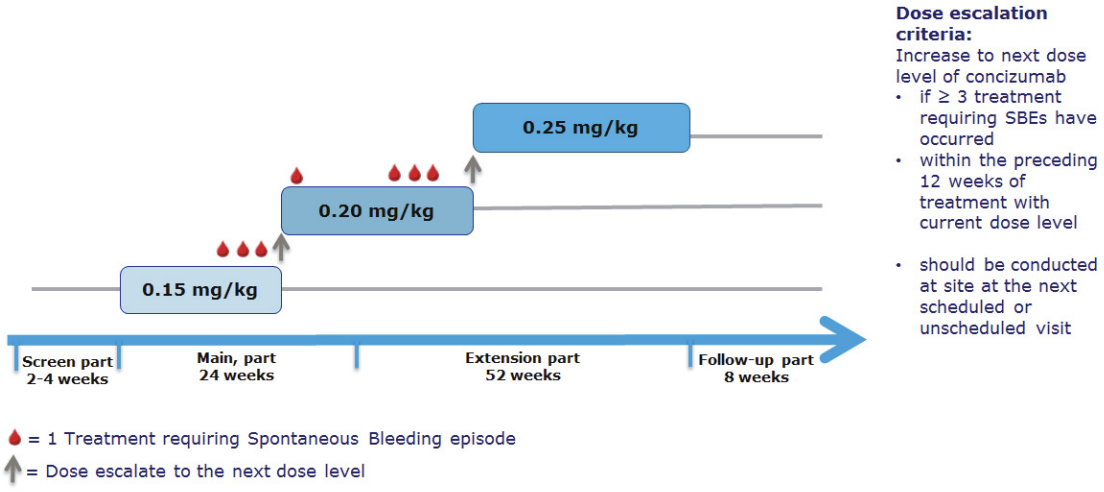


Figure 5–3 Dose escalation for one individual patient in the concizumab arm

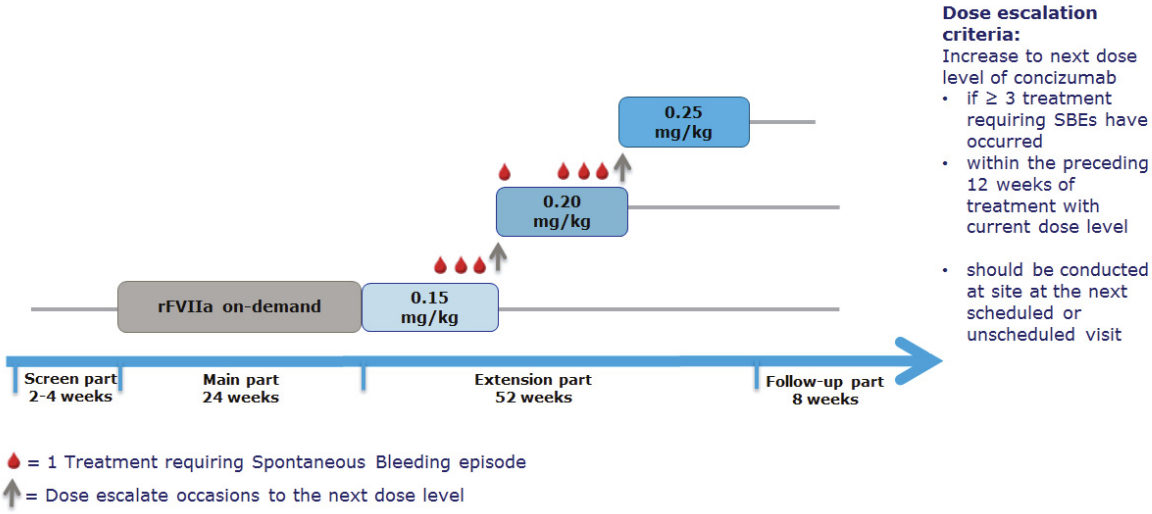


Figure 5–4 Dose escalation for one individual patient in the comparator arm

5.3.4 Co-administration of eptacog alfa (rFVIIa)

eptacog alfa (rFVIIa) will be used for treating breakthrough bleeding episodes in this trial; one week after initiation of dosing with concizumab, a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state at the trial site under medical supervision to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at site after 24h. Between 12h and 24h, the patient must either stay at the site or at a hotel or at home if he lives nearby to be able to continue visit 3 or 9.1 the day after. Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to concizumab arm will be staggered so that the period between eptacog alfa (rFVIIa) administrations from one patient to another is at least 48 hours. If no safety concerns are observed (for example signs and symptoms of thromboembolism, such as swelling, pain and redness of the leg, shortness of breath, and chest pain) by the investigator in the period between the administration of eptacog alfa (rFVIIa) and when the next daily concizumab dose is to be given, the investigator allows the individual patient to administer concizumab prophylactically at home and if needed, treat breakthrough bleeding episodes at home with eptacog alfa (rFVIIa). The patients will receive prophylactic doses of concizumab 0.15 mg/kg daily throughout the main part (24 weeks) and the extension part (52 weeks), unless dose escalation criteria are fulfilled, see Section 5.3.3.

In case safety concerns are raised by an investigator after eptacog alfa (rFVIIa) administration and these concerns meet the described criteria for putting enrolment of additional patients on hold, dosing in the individual patients will be halted and further recruitment in the trial will be halted, see

Section 12.7. In case safety concerns that do not meet the criteria for putting enrolment of additional patients on hold are observed by the investigator, dosing in that individual patient will be halted until further evaluation. In such cases, all available data will be assessed by the Data Monitoring Committee (DMC), see Section 12.8.2.

5.3.5 Treatment of bleeding episodes during the trial

Breakthrough bleeding episodes between visit 1 and visit 2 can be treated with any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) up to a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to first concizumab administration at visit 2. Novo Nordisk will provide eptacog alfa (rFVIIa) throughout the trial. The patient can treat himself and then he must call the site. The bleeding episode must be recorded in the eCRF.

Breakthrough bleeding episodes between visit 2-3 in the concizumab arm and visit 9-9.1 in the comparator arm must be treated with eptacog alfa (rFVIIa). Upon breakthrough bleeding episodes in this period the patient must first call the site. The investigator should instruct the patient about whether he should go to the site to receive treatment or if he can administer a single dose of eptacog alfa (rFVIIa) which is not higher than 90µg/kg without delay to treat the breakthrough bleeding episode. If the patient is instructed to administer the eptacog alfa (rFVIIa) dose at home, following the administration, the patient should immediately go to the site for further clinical evaluation. The bleeding episode must be recorded in the electronic Diary (eDiary).

Breakthrough bleeding episodes between visit 3 and visit 16 in the concizumab arm must be treated with eptacog alfa (rFVIIa). The patient can treat himself without delay but must inform the site that a bleeding episode has occurred. Doses of eptacog alfa (rFVIIa) those are lower than 90µg/kg may be used to treat breakthrough bleeding episodes at the discretion of the investigator. Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. If a single dose of eptacog alfa (rFVIIa) is not sufficient to stop a bleeding episode, the patient should inform the site and in agreement with the investigator may administer a second dose of eptacog alfa (rFVIIa) not higher than 90µg/kg 2-3h after the first dose has been administered. The same procedure should be repeated in case the second dose of eptacog alfa (rFVIIa) is not sufficient to stop the bleeding episode. If more than three 90µg/kg doses of eptacog alfa (rFVIIa) are needed to stop a bleeding episode, the patient should go to the site without delay. The definition and diagnostic criteria of DIC, acute myocardial infraction, stroke, deep vein thrombosis, pulmonary embolism and peripheral artery occlusion is provided in section 12.1.6. The bleeding episodes must be recorded in the eDiary.

Breakthrough bleeding episodes between visit 16 and visit 17 (follow-up part) may be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator. The patient can treat himself with eptacog alfa (rFVIIa) at home without delay. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The bleeding episodes must be recorded in the eDiary.

See Table 5–1 and Table 8–3.

5.3.6 Prohibited medication

- Treatment with anti-fibrinolytics (e.g. tranexamic acid, aminocaproic acid)
- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anticoagulants (DOACs)
- Home treatment (between visit 2 and visit 16) with activated prothrombin complex concentrates (FEIBA®)

5.4 Treatment after discontinuation of trial product

When discontinuing trial products (visit 16 or earlier), the patient should be switched to a suitable marketed product at the discretion of the investigator. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The patient will not be provided with concizumab or eptacog alfa (rFVIIa) after end of trial (EOT) (visit 17) by Novo Nordisk.

5.5 Rationale for treatment

Concizumab is a monoclonal antibody and as such offers the possibility of s.c. administration. S.c. administration of an effective prophylactic drug has potential to reduce the treatment burden compared to the currently approved prophylactic drugs which have to be administered i.v. Furthermore, the current treatment options for prophylaxis in inhibitor patients do not reduce the frequency of breakthrough bleeding episodes to the same extent as prophylaxis with replacement therapy in non-inhibitor patients. Concizumab may therefore show a better efficacy profile compared to current treatment options in haemophilia A and B patients with inhibitors.

The treatment period during at least 24 weeks (the main part of the trial) is considered necessary for providing robust data that allow demonstration of clinical proof of concept and to support decision making regarding a phase 3 confirmatory trial. Dosing for additional 52 weeks will provide valuable long term efficacy and safety data.

Breakthrough bleeding episodes occur in prophylactic regimens with both bypassing agents and replacement therapy. Therefore, it is expected that breakthrough bleeding episodes will occur during prophylaxis with concizumab even if clinical proof of concept is demonstrated. Consequently, eptacog alfa (rFVIIa) will be provided by Novo Nordisk in this trial for treatment of breakthrough bleeding episodes. In order to minimize the likelihood of any unforeseen adverse events associated with administration of eptacog alfa (rFVIIa) in these circumstances, administration of eptacog alfa (rFVIIa) in a controlled setting will be performed at visit 3 or 9.1.

Please refer to the Investigator's Brochure for further information.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 28

Number of patients planned to start on trial product: 26

Number of patients expected to complete the trial: 24

- Preferably 21 haemophilia A patients
- Preferably 3 haemophilia B patients

Discontinued patients will not be replaced.

6.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

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 the suitability for the trial
2. Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
3. Patients currently treated on-demand with a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening
4. Documented history of high-titer inhibitors towards FVIII or FIX, defined as ≥ 5 Bethesda Units
5. Patients currently in need of treatment with bypassing agents

6.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within the last 30 days or 5 half-lives (whichever is longer) from the last drug administration before screening
4. Any disorder which in the investigator's opinion, might jeopardise patient's safety or compliance with the protocol
5. Known inherited or acquired bleeding disorder other than haemophilia
6. Major surgery conducted within one month prior to the initiation of trial activities or major surgery planned to occur during the trial

7. Previous history of thromboembolic disease. Current clinical signs of thromboembolic disease or patients who in the judgement of the investigator are considered at high risk of thromboembolic events
8. Mental incapacity, unwillingness to cooperate or language barrier precluding adequate understanding and cooperation
9. Patients who, at screening, have a significant infection or known systemic inflammatory condition which requires systemic treatment according to the investigator's judgement
10. Hepatic dysfunction defined as elevated liver transaminases (ALT) >3 times the upper limit of normal laboratory reference ranges at screening
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m^2 for serum creatinine measured at screening for patients without evidence of renal damage
12. Platelet count ≤ $100x10^9$/L at screening
13. Fibrinogen level < the lower limit of normal
14. Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX
15. Antithrombin levels below the normal reference range at screening

6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation 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. Anaphylactic reaction
5. Thromboembolic event
6. Event of Disseminated Intravascular Coagulation
7. Lack of efficacy due to neutralizing antibodies
8. Lack of efficacy defined as ≥ 3 treated sBEs within the previous 12 weeks in patients being treated with the highest dose level (0.25 mg/kg) of concizumab.

See Section 8.1.4 for procedures to be performed for patients discontinuing trial product prematurely.

6.5 Withdrawal from trial

The patient may withdraw consent at will at any time.
See section 8.1.5 for procedures to be performed for patients withdrawing consent.

6.6 Patient replacement

Patients who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

The most important reason for choosing the trial population, haemophilia with inhibitors, is that there is a significant unmet medical need in this patient population for

1. A more effective treatment and
2. A treatment which reduces treatment burden.

In addition to this, since most of these patients are likely to have been treated and therefore familiar with eptacog alfa (rFVIIa) on-demand treatment, this trial population is considered the most suitable for assessing the safety of administering eptacog alfa (rFVIIa) to patients in whom plasma TFPI levels are inhibited. Finally, the trial population reflects the patient population that will be selected in a potential subsequent phase 3 trial in which the efficacy and safety of concizumab are to be confirmed.

7 Milestones

Planned duration of recruitment period (FPFV-LPFV): 28 weeks

Planned FPFV:	16-Aug-2017
Planned FPFT:	30-Aug-2017
Planned LPFV:	28-Feb-2018
Planned LPLV:	23-Oct-2019

The total duration of concizumab treatment in this trial is 76 weeks for an individual patient randomised to concizumab prophylaxis treatment at visit 2.

The total duration of concizumab treatment in the trial is 52 weeks for an individual patient randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2.

EOT is defined as last patient last visit (LPLV).

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further patients may be screened and the IWRS will be closed for further screening. All patients screened during the recruitment period and found eligible for randomisation can be randomised in a 2:1 allocation to either the concizumab or the comparator arm within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, how-we-disclose-trial-information, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE), [12] the Food and Drug Administration Amendment Act (FDAAA), [13] European Commission Requirements, [14] [15] 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.

Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this protocol LPFT (visit 2) + 24 weeks corresponding to visit 9. If the last patient is withdrawn early the PCD is the date when the last patient would have completed visit 9. The PCD determines the deadline for results disclosure at ClinicalTrials.gov according to FDAAA.[13]

8 Methods and assessments

Assessments to be performed at the scheduled and at the unscheduled visits in the trial are described in this section, Figure 8–1, Figure 8–2 and in Section 2.

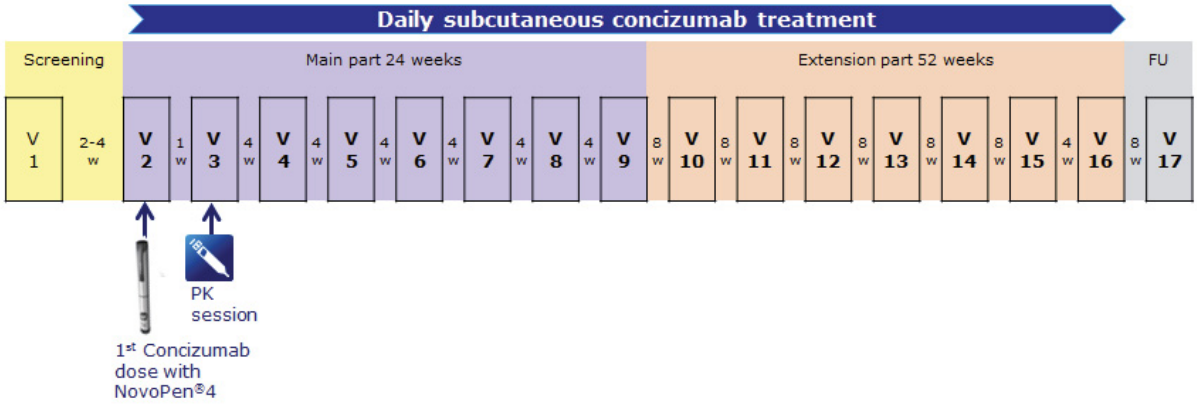


Figure 8–1 Visit schedule – concizumab arm.

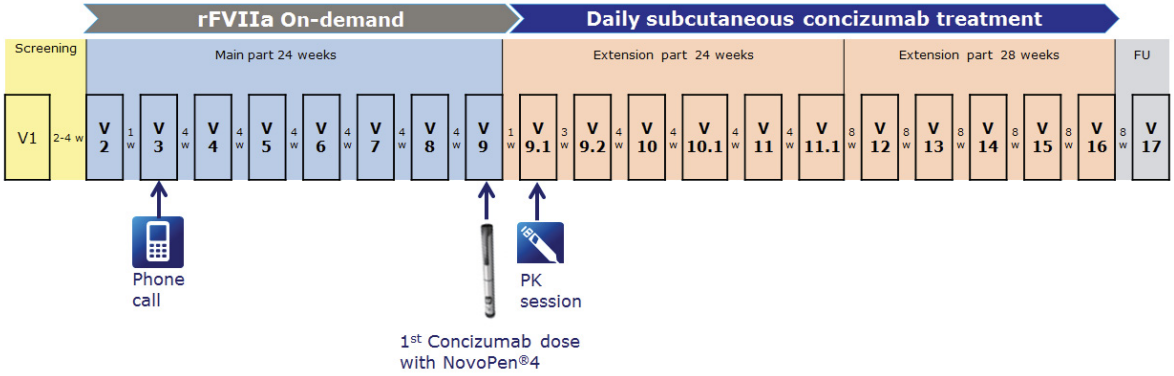


Figure 8–2 Visit schedule – eptacog alfa (rFVIIa) arm later switching to concizumab.

8.1 Visit procedures

For each patient the trial can consist of the following scheduled parts and visits depending upon which arm the patient is randomised to:

Screening Part:

- Visit 1 (screening visit)

Main Part:

- Visit 2 (Randomisation and 1st treatment visit with concizumab at site for patients randomised to the concizumab-arm)
- *Home treatment with concizumab daily*
- Visit 3 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site only for patients randomised to the concizumab-arm - phone visit for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 4 (Assessment visit, patients treat themselves at home)
- Visit 5 (Assessment visit, patients treat themselves at home)
- Visit 6 (Assessment visit, patients treat themselves at home)
- Visit 7 (Assessment visit, patients treat themselves at home)
- Visit 8 (Assessment visit, patients treat themselves at home)
- Visit 9 (Assessment visit, after the visit patients treat themselves at home – 1st treatment visit with concizumab at site for patients randomised to the eptacog alfa (rFVIIa) arm)

Extension Part:

- Visit 9.1 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 9.2 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 10 (Assessment visit, patients treat themselves at home)
- Visit 10.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 11 (Assessment visit, patients treat themselves at home)
- Visit 11.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on demand-arm)
- Visit 12 (Assessment visit, patients treat themselves at home)
- Visit 13 (Assessment visit, patients treat themselves at home)
- Visit 14 (Assessment visit, patients treat themselves at home)
- Visit 15 (Assessment visit, patients treat themselves at home)
- Visit 16 (Assessment visit, no treatment at home before the visit and End of Treatment)

Follow-up Part:

- Visit 17 (Assessment visit and End of Trial)

Unscheduled Part:

- Unscheduled visits can occur e.g. for dispensing of trial product, dose escalation or when an assessment of bleeding episodes is necessary at site or at the discretion of the investigator.

The duration of the visits (V1-V17) will depend on the assessments and the patient's individual training and/or discussion need on concizumab and eptacog alfa (rFVIIa) administration, NovoPen®4, usage of eDiary, completion of the PRO etc.

8.1.1 Informed consent, genotyping and long-term storage consent

Informed consent must be obtained before any trial related activity at visit 1, see Section 18.2.

The trial includes a separate informed consent for long-term storage of human biosamples, see Section 24.2.

Storage of human biosamples and/or genotyping is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for biological specimens and/or genotyping to be stored for future exploratory analysis.

8.1.2 Screening log, enrolment log, trial card and patient number

The investigator must keep a patients screening log, a patients identification code list and a patients enrolment log. Only patients who have signed the informed consent form should be included on the logs. The patients screening log and patients enrolment log may be combined in one log.

At screening, patients will be provided with a card stating that they are participating in a trial and given contact address(es) and telephone number(s) of relevant trial clinic staff. Patients should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each patient will be assigned a unique 6-digit patient number which will remain the same throughout the trial.

8.1.3 Screening failures and re-screening

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.

Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12. A screening failure session must be made in the IWRS. The case book must be signed in the eCRF.

Re-screening is NOT allowed if the patient has failed one of the inclusion or exclusion criteria; this includes re-sampling if the patient has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.1.4 Premature discontinuation of trial product

If a patient prematurely discontinues trial product, the investigator must undertake procedures similar to those for visit 9 (the last treatment in the main part) or visit 16 (the last treatment visit in the extension part) as soon as possible. The follow up visit (visit 17) must be performed 8 weeks (window minus 7 days) after last dose of trial drug.

The primary reason for premature 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.

Permanent premature discontinuation of treatment with trial product will lead to patient withdrawal from the trial.

8.1.5 Withdrawal from trial

If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for visit 9 (the last visit in the main part) or visit 16 (the last visit in the extension part) as soon as possible depending on where the patient is in the trial schedule.

The end-of-trial form must be completed, and 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 and the case book must be signed in the eCRF.

Although a patient is not obliged to give his reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.6 Review/ evaluation of clinical outcome

Novo Nordisk has constituted an internal concizumab safety committee and established an external DMC to perform ongoing safety surveillance of safety data relevant to concizumab, see Section 12.8.

Review of eDiary data and laboratory reports etc. must be documented either on the documents or in the patient's medical record.

If unclear entries or discrepancies in the eDiary or ePRO are identified and a clarification is needed, the patient must be asked for clarification and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

8.1.7 Visit 1 (Screening part)

Informed consent must be obtained before any trial related activity, see Section 18.2

All assessments to be performed at screening are listed in Section 2.

After informed consent is given, patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- Hemo-TEM,
- VERITAS-PRN®

Assessment results from physical examination and body measurements, as well as measurements of vital signs, urinalysis and ECG and details of any contemporary adverse events, must be entered into the eCRF.

A screening confirmation call must be performed in the IWRS, at the day of the visit.

The investigator must review all information obtained from the screening procedures. If a patient does not meet all inclusion criteria or meets one or more of the exclusion criteria for the trial the patient does not qualify to be enrolled.

For bleeding episodes that occur in the period from Screening visit (Visit1) to randomisation visit (Visit 2), information about the bleeding episode is to be entered in the eCRF at visit 2.

Patients will be provided with eptacog alfa (rFVIIa), trial injection kits and direction for use (DFU) to cover the potential eptacog alfa (rFVIIa) treatment after the screening part of the trial and investigator will ensure that the patients are capable of treating themselves with eptacog alfa (rFVIIa).

Dispensing of eptacog alfa (rFVIIa) should be performed in IWRS.

The patient must be instructed to call the site if any bleeding episodes, questions or issues arise after he has left the site.

8.1.8 Training of patients at visit 1, visit 2 and visit 9

During visit 1 and visit 2 and visit 9 (comparator arm) patients must be trained in self-administration of concizumab in the home setting using NovoPen®4. The dose of concizumab to be administered must be communicated to the patient at visit 2 (if they are randomised to concizumab)

or at visit 9 (if they are randomised to eptacog alfa (rFVIIa) and switching to concizumab at visit 9). Furthermore, patients must be instructed and trained in the importance of reporting all the home treatments with concizumab, details of the bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes in the eDiary. The patient should call the site if bleeding episodes occur between visit 1 and 2 for the site to register in the eCRF.

Patients should be trained on how to recognize signs of thromboembolic events, so that the patient contacts the site without delay.

The site and patient can arrange for additional training whenever needed during the remaining time of the trial.

8.1.9 Treatment period at home

Home treatment is defined as self-administration of trial product, performed independently by the patient, preferably in the morning. Home treatment starts after visit 2 (concizumab arm) or when the patient is comfortable self-administrating trial product subcutaneously (concizumab) and intravenously (eptacog alfa (rFVIIa)).

8.1.10 Staggered recruitment

Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to the concizumab arm will be staggered until the 4th patient randomised to the concizumab arm has completed visit 3 without any safety concerns raised by the investigator. Until this time point, enrolled patients will not be randomised until the previous patient randomised to concizumab has completed visit 3 without any safety concerns raised by the investigator. Novo Nordisk will as sponsor control and communicate the staggered recruitment process.

8.1.11 Treatment period – Main part

8.1.11.1 Visit 2 (Randomisation)

Visit 2 should be scheduled 14 to 28 days after visit 1. The date of visit 2 will be considered as trial day 1.

It is important to verify the in/exclusion criteria again and review central laboratory tests from screening.

The patients must be in a non-bleeding state and should not have received any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) for treatment of bleeding episodes within a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to the potential first concizumab administration (depending on the treatment arm). After visit 2 only treatment with eptacog alfa (rFVIIa) for bleeding episodes is allowed.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments listed in 2, must be performed before potential administration of concizumab (depending on the treatment arm). Vital signs must be assessed both before (within 1 hour) and after concizumab administration. Pre-dose blood sampling must take place no more than 1 hour before concizumab administration.

Assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

A randomisation and dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the Trial Materials Manual (TMM) on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

For patients randomised to the concizumab arm, the first treatment with the loading dose of concizumab will be given.

The time point at which the completion of the first dose takes place corresponds to 'Time on treatment' = 0 and must be recorded in the eCRF.

The patient must be observed at the trial site for at least 2 hours after the administration of the first dose of concizumab.

At the visit the patient will be provided with trial product concizumab and/or eptacog alfa (rFVIIa) and trial injection kits and an eDiary device to be able to conduct and report home treatment and bleeding episodes until next scheduled visit.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for eptacog alfa (rFVIIa), if applicable according to section 9.4.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site. If the patient on concizumab needs to treat a bleeding episode with eptacog alfa (rFVIIa) at home, then he must visit the site immediately after.

8.1.11.2 Visit 3 (Phone call for eptacog alfa (rFVIIa) on-demand arm and PK visit for concizumab arm)

eptacog alfa (rFVIIa) on-demand arm:

Visit 3 for eptacog alfa (rFVIIa) on-demand arm is a phone call scheduled 7 days after visit 2 (with a visit window of +1 day).

All relevant assessments listed in Section 2, must be discussed.

Assessment results from concomitant medication and details of adverse events must be entered into the eCRF.

concizumab arm:

Visit 3 is to be scheduled 7 days after visit 2 (with a visit window of +1 day) and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- PGI-C
- Hemo-TEM

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) dosing.

eptacog alfa (rFVIIa) should be administered to the trial patients at the site under the surveillance of medically trained trial site staff. Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.

Samples for thrombin generation, haematology, coagulation parameters and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

The investigator must ensure all assessments are performed as described in Section 2, Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF before next dose with concizumab is given the day after.

Recruitment of the first four patients will be staggered according to section 8.1.9.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.11.3 Visit 4, 5, 6, 7 and 8

Patients should treat themselves at home according to their individual dosing schedule regardless of when visits 4, 5, 6, 7 and 8 are scheduled.

Visits 4, 5, 6, 7 and 8 are to be scheduled on trial day 29 (4 weeks), day 57 (8 weeks), day 85 (12 weeks), day 113 (16 weeks) and day 141 (20 weeks) respectively with a visit window of ±7days.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM

All assessments are to be performed according to Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the e-Diary. Based on the assessment of any spontaneous

bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 8 patients should be reminded that treatment with concizumab (concizumab arm) must take place after the blood sampling at visit 9.

8.1.11.4 Visit 9

Visit 9 is to be scheduled on trial day 169 (24 weeks) with a visit window of ±7days.

Patients randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2 will now be switched to concizumab treatment. At this visit the first treatment (loading dose) with concizumab will take place.

Treatment with concizumab must take place after the blood sampling for both the patients on the concizumab arm as well as patients on the eptacog alfa (rFVIIa on-demand) arm.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM
- SF-36v2
- SDS

- TSQM
- SIAQ-ISRQ

All assessments are to be performed according to Section 2, and the assessment results from physical examination, concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through the available access to collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in Section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12 Treatment period – Extension part

8.1.12.1 Visit 9.1 (PK visit and ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.1 is to be scheduled on trial day 176 (25 weeks) with a visit window of +1 day and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) dosing.

eptacog alfa (rFVIIa) should be administered at the site under the surveillance of medically trained trial site staff. Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

Samples for thrombin generation, haematology, coagulation parameters and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9 h (± 10 min) and 12h (±20 min) and 24h (±20 min).

Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF before the next dose of concizumab is given the day after.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.2 Visit 9.2 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.2 is to be scheduled on trial day 197 (28 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9,

evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.3 Visit 10

Visits 10 is to be scheduled on trial day 225 (32 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1.

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.4 Visit 10.1 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 10.1 is to be scheduled on trial day 253 (36 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.5 Visit 11

Visit 11 is to be scheduled on trial day 281 (40 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.6 Visit 11.1 (ONLY patients previously on the rFVIIa on-demand arm)

Visit 11.1 is to be scheduled on trial day 309 (44 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.7 Visit 12, 13, 14 and 15

Visits 12, 13, 14 and 15 are to be scheduled on trial day 337 (48 weeks), 393(56 weeks), day 449 (64 weeks) and day 505 (72 weeks) respectively with a visit window of ±7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 15 patients should be reminded that treatment with concizumab must take place after the blood sampling at visit 16.

8.1.12.8 Visit 16

Visit 16 is to be scheduled on trial day 533 (76 weeks) with a visit window of ±7days. Further visit 16 should be scheduled to be conducted at the last day of treatment with concizumab.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary.

In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat eventual bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period.

If necessary, a dispensing call must be performed in the IWRS. At the visit the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa).

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes) arise after he has left the site.

8.1.13 Visit 17 (End of trial) - Follow-up part

Visit 17 is to be scheduled on trial day 589 (84 weeks) with a visit window of minus 7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, physical examination, body measurements (weight only), vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data. Patients should be asked if their female partner has become pregnant, see Section 12.5.1.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

End-of-Trial information must be entered in the End-of-Trial form in the eCRF.

Completion or treatment discontinuation (if the trial is not completed) session should be performed in IWRS, see Section 10.

8.1.14 Unscheduled Visit

Unscheduled visits can be performed at any time during the trial as listed in Section 2. The purpose of the unscheduled visit must be documented in the eCRF.

During unscheduled visits assessments and blood sampling must be performed according to Section 2. Assessment results must be recorded in the eCRF. Assessments and blood sampling can be omitted if the only reason for the unscheduled visit is dispensing of trial product.

If trial product administration or dispensing is required, dispensing of trial product must be performed via IWRS.

The following forms can be found in the unscheduled visit in the eCRF:

- Bleeding episodes
- Dosing with eptacog alfa (rFVIIa), concizumab including dose escalation, see Section 5.3.3.
- Surgery
- Local, special and central laboratory (re-)sampling/results
- Body measurements

8.2 Patient related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history other than haemophilia

A **concomitant illness** is any illness, other than haemophilia, 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 first exposure to trial product. All concomitant illnesses should be reported in the concomitant illness forms in the eCRF except information on haemophilia with inhibitors which is to be reported in the haemophilia medical history section of the eCRF.

Medical history is a medical event, other than haemophilia, which the patient has experienced in the past. Only relevant medical history should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the patient's medical history in source documents such as patient's medical record, see Section 6.2 and 6.3.

If a patient is not from the investigators own practice; the investigator must make a reasonable effort to obtain a copy of the patient's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the concizumab and eptacog alfa (rFVIIa), which is taken during the trial, including the screening and follow-up period.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Details of Haemophilia, Haemophilia treatment and bleed history

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

- Diagnosis of haemophilia (date)
  - Classification of haemophilia type (haemophilia A/B)
  - Severity of haemophilia (severe, moderate or mild)
  - Aetiology of haemophilia (congenital or acquired)
- Family history of
  - Haemophilia (Y/N)
  - Inhibitors (Y/N)
  - Prothrombotic disorders (Y/N)
  - Thromboembolism (Y/N)
- Inhibitor tests taken (Y/N)
  - Date (dd-mmm-yyyy)
  - Result (BU)
- Cut-off for positive inhibitor result
- Deficiency factor level

The following information on bleeding episodes one year prior to screening should be recorded in the eCRF:

- Type of treatment
  - 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
- Dosing frequency during prophylaxis
- Approximate dose to treat a bleeding episode
- Approximate number of doses to treat a bleeding episode
- Target joint listing (definition: a target joint is a joint in which 3 or more spontaneous bleeding episodes have occurred within a consecutive 6-month period)
  - Location
  - Position (left/right)
  - Number of bleeding episodes

8.3 Efficacy assessments

8.3.1 Bleeding episodes

All bleeding episodes treated with eptacog alfa (rFVIIa) and symptoms related to the underlying disease must be captured in the eDiary by the patient or in the eCRF by the investigator. The trial site should be informed of the details of all bleeding episodes, including those that are treated outside of the trial site.

All information captured during visits to the trial site will be collected in the eCRF.

When home treatment is initiated at visit 2 all bleeding episodes and injections with concizumab and eptacog alfa (rFVIIa) injection occurring outside the trial site should be entered in the eDiary by the patient, Section 13.3.

The completed eDiary is considered source data.

For reporting of bleeding episodes as AEs/SAEs, please refer to Section 12. In case of life-threatening bleeding episode, it should always be reported as an SAE, see Section 12.1.2.

The following must be recorded for any bleeding episode, including bleeding episodes that do not require treatment with eptacog alfa (rFVIIa):

- Start date and time
- Stop date and time (see Table 8–1)
- Anatomical location
  - Position (left/right)
- Cause (see Table 8–2)
  - spontaneous
  - traumatic
  - post-surgical

- Severity (see Table 8–3)
  - mild/moderate, severe
    - classification and recording of severe bleeding episodes is the responsibility of the investigator
- Treatment, if any
  - eptacog alfa (rFVIIa) administration or other product administration
    - dose, date, stop time
  - other medicinal treatments related to the bleeding episode (pain relieving medication, non-medical therapy etc.)
    - record as concomitant medication (section 8.2.3)
- Symptoms during bleeding episode(s)
  - Pain
  - 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 if fatal, life threatening or evaluated as related to trial product, see Section 12.1.1 and 12.1.2.

Table 8–1 Definition of stop of bleeding episode

Stop time is:	When the patient experiences/observes signs of cessation of the active bleeding episode 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 8–2 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

Category	Definition
	during surgery do not fall under this category

Table 8–3 Definition of bleeding episode severity and treatment recommendation

Category	Definition	Treatment recommendation
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeding episodes (joint, muscular bleeding episodes without compartment syndrome), mucosal- or subcutaneous bleeding episodes Mild/moderate bleeding episodes may occur in other anatomical locations	Mild/moderate bleeding episodes: • patient must call the site between visit 1-2 and visit 3-16 (see 2-3 and 9-9.1 below) • patient must call the site between visit 2-3 or visit 9-9.1 (eptacog alfa arm) and if treated at home, go to the site immediately after • patient can treat themselves at home between visit 16 and visit 17
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeding episodes; muscle bleeding episodes with compartment syndrome; bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeding episodes may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes	Severe bleeding episodes must be treated immediately
Instruction for patients	The patient must be instructed to contact the site immediately if in doubt regarding treatment of a bleeding episode and to discuss what other actions may need to be taken	

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.

Dosing for bleeding episodes with eptacog alfa (rFVIIa) should be documented in the eCRF (visit 1 to visit 2) and eDiary (visit 2 to visit 17). After visit 2 bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see section 13.3.

Investigator must instruct the patient not to perform preventive treatment with eptacog alfa (rFVIIa) after bleeding stop as defined in Table 8–1.

Investigator must instruct the patient to use eptacog alfa (rFVIIa) as rescue medication to treat bleeding episode between visit 2 and visit 16, see Section 5.3.5.

Furthermore investigator must instruct the patient to contact the site when a bleeding episode occurs. It is the responsibility of the investigator to instruct the patient about the timelines for timely completion of the eDiary.

Furthermore the investigator must review the bleeding and treatment data collected by the eDiary according to Section 13.3.

For in-between visit administrations of trial drug, patients will self-administer concizumab (and eptacog alfa (rFVIIa) as rescue medication) and will record treatment in the eDiary, which will be reviewed during periodic calls to/contact with the patient and at each visit by trial site staff and the sponsor staff.

8.4 Safety assessments

8.4.1 Physical examination

Performed as standard physical examination and include the following.

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

The investigator must evaluate the results of the examination and classify them 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 Medical History (Section 8.2.2)
  - If observed after screening: report an AE/SAE (Section 12)

Measurements will be reported in the eCRF.

8.4.2 Body measurements

- Height (cm), at screening
- Body weight (kg), (with one decimal)

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

Measurements will be reported in the eCRF.

8.4.3 Vital Signs

Before measurement of vital signs the patient should preferably rest comfortably for at least five minutes and all measurements should, if possible, be performed using the same method and in a sitting position throughout the trial.

Measurements at visits must be performed prior to any trial product administration unless otherwise specified.

- Body temperature (°C)
- Systolic and diastolic blood pressure, sitting (BP) (mmHg)
- Pulse, sitting (beats/min)
- Respiratory rate

Exception: At visits 2 and visit 3 (for patients randomised to concizumab) and at visit 9 and visit 9.1 (for patients initiating concizumab treatment at visit 9), the measurements are also performed after concizumab administration.

The investigator must evaluate the vital signs 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, section 8.2.2
- If observed after screening: report an AE/SAE, section 12

Measurements will be reported in the eCRF.

8.4.4 Electrocardiogram

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 Medical History, section 8.2.2
  - If observed after screening: report an AE/SAE, section 12

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.

8.4.5 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.5.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product involved
- Classification of medication error
- Whether the patient experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.5.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

Injection site reaction

Investigation of injection site reactions will be performed locally at all visits after visit 2 until visit 16 based on patient feedback and by following visual inspections of injection sites for concizumab administration:

Symptoms e.g.

- Pain
- Numbness
- Itching
- Burning

Signs e.g.

- Redness (mm x mm)
- Induration (mm x mm)
- Swelling
- Dimpling
- Macula
- Haematoma
- Bleeding
- Other (visual reactions)

Any injection site reaction symptom (evaluated at visit 2-16) should be recorded in the AE form and the injection site reaction form, see Section 12.1.5.

A separate AE should be recorded for each injection site reaction symptom. The affected area should also be evaluated for redness and induration in mm using a ruler. To ensure all local injection site assessments are performed at the injection site, the area around the site will be marked with a pen prior to injection.

In the event of a local reaction, additional visual assessments (as described above) 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.

Hypersensitivity reaction

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

All events of hypersensitivity reactions must be reported and the following information must be obtained if available on the hypersensitivity reaction form:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed, see Section 8.5.2.7
- Treatment given for the reaction
- Previous history of similar reactions
- Association with the trial product(s)
- Relevant risk factors associated with the event
- Storage condition of the trial product
- Total number of doses, from first day on trial product, up to the time of this event

8.5 Laboratory assessments

An approximate total blood volume of 725 mL will be taken from each patient on the concizumab arm and 625 mL from each patient on the eptacog alfa (rFVIIa) arm.

A laboratory manual will be provided for detailed description of obtaining and processing blood samples.

All laboratory blood samples collected for this trial except for haematology samples at all visits and coagulation parameters at visits 3 and 9.1 are to be shipped for analysis at central laboratories or further distribution to special laboratories. Haematology samples (all visits) and coagulation parameters (visit 3 and 9.1) are to be analysed locally. Ports cannot be used for blood sampling.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Laboratory reports listing results from centrally analysed samples will be made available for the investigator. Investigator must review and evaluate the results and report AEs for results which are clinically significant. Laboratory reports will where possible indicate normal ranges.

Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: FVIII/FIX activity, FVIII/FIX inhibitor

test, Thrombin generation, Free TFPI (TFPI not bound to concizumab), concizumab concentration in plasma, anti-concizumab antibodies, Total TFPI and FVII antigen concentration.

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 and report these according to Section 8.2.3 and Section 12.

Only laboratory samples specified in the protocol must 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 except for biomarkers and anti-drug antibodies (anti-concizumab IgE antibodies and anti-concizumab antibodies).

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and human biosamples, if applicable, will be stored as described in Section 24.2. The investigator may not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV.

8.5.1 Laboratory assessments for efficacy

8.5.1.1 Thrombin generation

The Thrombin Generation Assay (TGA) will be collected at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

The TGA is included as an exploratory PD assessment.

The generation of thrombin is a fundamental part of the haemostatic system, and is a key measurable parameter of the formation of a clot under bleeding or thrombotic conditions. The thrombin burst is crucial for the formation of a stable fibrin clot.

The Calibrated Automated Thrombogram (CAT) method (used by Thrombinoscope BV) will be used to measure thrombin generation (TG). This method uses a slow acting fluorogenic substrate that allows continuous measurement of thrombin generation in double centrifuged citrated plasma.

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.

The thrombin generation endpoints are defined but not limited to:

- The Endogenous Thrombin Potential (ETP) – the area under the curve
- Peak thrombin generation
- Velocity Index

8.5.1.2 Free TFPI

Free TFPI (TFPI not bound to concizumab) will be collected at all visits, pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm).

The free TFPI assay is an enzyme immunoassay measuring levels of free TFPI from [redacted] (named and referred to [redacted] TOTAL TFPI) and will be used for PD assessments.

8.5.2 Laboratory assessments for safety

8.5.2.1 Urinalysis

- pH
- Protein
- Glucose
- Bilirubin

This is a semi qualitative measurement which will be performed (locally) at the screening visit by the site by using the appropriate reagent strips for urinalysis. The results will be recorded in the eCRF.

The investigator must evaluate the results and record the outcome as:

- Normal or abnormal
- If abnormal the investigator must:
    - Record if the result is clinically significant? (Yes/No)
    - If observed before or at screening: record as concomitant illness (section 8.2.2)

8.5.2.2 Haematology

Haematology samples are to be sampled and analysed locally at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa), 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

- Haemoglobin
- Erythrocytes (cell count)
- Thrombocytes (platelet count)

- Leucocytes (cell count)
- Differential leucocytes cell count
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils

The investigator must evaluate the results and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Haematology results are to be entered into the eCRF.

8.5.2.3 Biochemistry

Biochemistry samples are to be sampled and analysed centrally at all visits.

- Creatinine
- Albumin
- Bilirubin; total, direct, indirect
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma glutamyltransferase (GGT)
- Alkaline phosphatase
- C-reactive protein (CRP)

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

8.5.2.4 FVIII/FIX activity

FVIII/FIX activity is to be sampled and analysed centrally at visit 1, visit 9 and visit 16.

- FVIII activity level (IU/mL) or
- FIX activity level (IU/mL)

8.5.2.5 Coagulation parameters

Coagulation parameters will be performed centrally at all visits with the exception of visit 3 and visit 9.1 where the PT, APTT, and Fibrinogen will be performed locally.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa) at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (±10 min) and 12h (±20 min) and 24h (± 20 min) locally.

- Fibrinogen – centrally and locally
- Prothrombin time (incl. INR) (PT) centrally and locally
- D-dimer – only centrally
- Prothrombin fragment 1+2 – only centrally
- Activated partial thromboplastin time (APTT) – centrally and locally
- Antithrombin (AT) activity – only centrally

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Coagulation parameters analysed locally are to be entered into the eCRF.

8.5.2.6 FVIII/FIX inhibitors

FVIII/FIX inhibitor level will be measured by the Nijmegen method at visit 1, visit 9 and visit 16.

- FVIII inhibitors (BU) or
- FIX inhibitors (BU)

8.5.2.7 Anti-concizumab antibodies

Samples for the determination of anti-drug antibodies collected during the treatment period must be drawn at all visits and prior to administering concizumab at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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. Confirmed positive samples will be characterised for binding to IgG backbone, CDR region or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a modified TFPI functionality assay (neutralising ADA assay). All antibody assays are validated according to international guidelines and recommendations.

The following analyses will be available:

- Anti-concizumab antibodies assay
- Specificity assay (Anti-concizumab antibodies cross reacting with IgG4 backbone, CDR region or S241P mutation)
- Anti-concizumab neutralising antibodies assay

The samples will be analysed in batches during the trial and results will be available to the data monitoring committee approximately every third month after the first patient has been dosed. Neutralising antibodies will be analysed and reported at the EOT. A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit. The ADA positive patients will be called for additional visits, e.g. every 4 to 6 weeks, for safety assessment and blood sampling for ADA and PD markers (free TFPI and Thrombin generation). The ADA positive patients will be followed no longer than one year after End-of-Trial.

Hypersensitivity

If suspicion of a hypersensitivity reaction occurs, patients should be instructed to contact the site staff as soon as possible for further guidance, see Section 12.1.5.

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 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 months post 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.

Results from the following additional tests will be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS database and included in the narratives, if measured.

Test to be performed in case of severe hypersensitivity

- Anti-concizumab IgE antibodies
- Anti-concizumab antibodies (additional to scheduled time points)

Additional testing may be performed if deemed relevant e.g.

- Anti-Host Cell Proteins (HCP) antibodies
- Anti-HCP IgE antibodies
- Basophil activation results
- Prick test/intra-dermal test
- Complement test results

Furthermore, it is recommended locally to test for

- Tryptase (total and/or mature tryptase)

8.5.2.8 Concizumab ELISA

Concizumab ELISA will be collected at all visits except at screening only for the concizumab arm. Samples will be collected pre-dose at visit 2 and 3 for concizumab arm and visit 9 and 9.1 for eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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 correlates 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.

8.5.2.9 FVII ELISA

FVII ELISA will be collected at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) pre-dose eptacog alfa (rFVIIa) and post-dose at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa (rFVIIa) administration.

FVII in plasma will be quantified using a validated enzyme-linked immunosorbent assay (ELISA). The FVII ELISA will detect the total sum of FVII in a sample, including endogenous FVII, eptacog alfa (rFVIIa) and FVII in complex with other molecules e.g. antithrombin. The ELISA has been validated for measuring FVII in human citrated plasma samples. Validation follows current guidelines for bioanalytical method validation. Bioanalytical data will be reported in a bioanalytical report.

8.5.2.10 Total TFPI

Total TFPI ELISA will be collected at all visits. Samples will be collected pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

The total TFPI level (free and concizumab bound) will be included as an exploratory biomarker assessment.

The assay is an ELISA, where TFPI is captured by a polyclonal anti-TFPI antibody, distanced from the binding site of concizumab; meaning that both free TFPI and concizumab bound TFPI will be captured. Detection will be obtained with a monoclonal antibody against TFPI, which does not bind to the concizumab epitope.

Data will be reported in ng/mL TFPI.

8.5.3 Human Biosamples

If patient permission is obtained plasma, serum and/or DNA for genotyping samples are to be taken for long term retention, see Section 2. The blood samples can be stored up to 15 years, for future potential exploratory purposes please refer to section 24.2.

Antibody samples storage and retention, see Section 24.2.1. The investigator is not able to review the results of antibody measurements in relation to AEs as these are analysed after LPLV. Plasma and serum is taken at visit 1 and 17. DNA for genotyping is only taken at visit 1.

8.6 Other assessments

8.6.1 Patient reported outcomes

A newly developed disease-specific electronic PRO (ePRO) the Hemophilia Treatment Experience Measure (Hemo-TEM) - is being validated in this trial. In order to assess the psychometric properties of Hemo-TEM, other questionnaires will be provided; see further appendix 1.

The following ePRO questionnaires will be used in the trial:

- Hemophilia Treatment Experience Measure (Hemo-TEM)
- Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®) [16]
- 36-Item Short Form Health Survey (SF-36v2) (4 week recall)[17]
- Patient's Global Impression of Change (PGI-C)
- Sheehan Disability Scale (SDS) [18]
- Treatment Satisfaction Questionnaire for Medication (TSQM, version II) [19] [20] [21]
- Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)[22]

The ePROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, VERITAS-PRN®)
- visit 2 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 3 (PGI-C, Hemo-TEM)
- visit 4 (PGI-C, Hemo-TEM)
- visit 5 (PGI-C, Hemo-TEM)
- visit 6 (PGI-C, Hemo-TEM)
- visit 7 (PGI-C, Hemo-TEM)
- visit 8 (PGI-C, Hemo-TEM)
- visit 9 (PGI-C, Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 10 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 16 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)

At visit 1: before any visit-related activities all patients should complete Hemo-TEM and VERITAS-PRN®.

At visit 2: before any visit-related activities all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 3-8: before any visit-related activities the patient should complete the PGI-C before the Hemo-Tem. These are the rules that apply:

- If the patient responds "1" to question 1 in the PGI-C, the patient should also complete the Hemo-TEM. In this case the patient should not fill in the PGI-C any more in the trial and the Hemo-TEM only again at visits 9, 10 and 16.
- If the patient responds "0" or "2" to question 1 in the PGI-C, the patient should not complete any other questionnaires at this visit, but should repeat the procedure at next visit.

Exception: Patients randomised to eptacog alfa (rFVIIa) on-demand should not complete the ePRO at visit 3 as this is a phone visit.

At visit 9 if the patient has responded "0" or "2" in the PGI-C at all previous visits, the patient should complete PGI-C. All patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 10 and 16 all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

The investigator must check the ePROs for potential AEs and SAEs. The completed ePROs should be transmitted at each visit to the PRO database by the Investigator.

8.6.2 Training

The patients must be trained in how to handle bleeding episodes and how to recognize the signs and symptoms of thrombosis. The training must be documented in the medical record.

8.6.2.1 Concizumab and NovoPen®4

Direction for use (DFUs) will be available as a hand out for patients at visit 2. Training in NovoPen®4 can start at screening (visit 1) and s.c administration of concizumab using the NovoPen®4 can start at the first dose at the trial site (visit 2). Patients must be instructed that injections are to be performed subcutaneously, not intravenously. Concizumab and NovoPen®4 will be dispensed to the patients at visit 2. Training must be performed at site until patients feel comfortable using the device or performing the treatment. The training must be documented in the medical records.

Detailed instructions can be found in the DFUs.

8.6.2.2 eptacog alfa (rFVIIa)

A direction for use (DFU) will be available as hand out for patients at visit 1. Training must be performed at site until patients feel comfortable performing the treatment. The training must be documented in the medical records.

The following should be emphasised for eptacog alfa (rFVIIa):

- eptacog alfa (rFVIIa) should be slowly injected intravenously over 2 to 5 minutes

Detailed instructions can be found in the DFU

8.6.2.3 eDiary

Training on the use of the eDiary can start at visit 1. The eDiary will be provided to the patients at visit 2.

Training must be repeated at the site until patients feel comfortable using the device. The training must be documented in the medical records.

During the home treatment period the patient must ensure that all home treatments of concizumab, details of bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes are captured in the eDiary as instructed and trained by investigator or delegated staff.

It will be the responsibility of the investigator or delegated staff to assess the eDiary data throughout the conduct of the trial and to ensure data entry compliance (timely entry, no duplicate data, no missing data etc.) and retraining if necessary.

For patients completing the trial or in case of withdrawal, the eDiary will be collected at the EOT.

8.6.3 Surgery

Minor surgery can be performed within this trial at the investigator's discretion according to local guidelines. Definition of minor surgery, see Section 5.1.1. Major surgery is not allowed, see exclusion criteria no 6.

For minor surgery the following should be recorded in the eCRF:

- Date, stop time and dose of preventive treatment with eptacog alfa (rFVIIa) before surgery, if this was deemed necessary by the investigator
- Indication for surgery
- Location of surgery
- Date of surgery
- Start and stop time of surgery

8.7 Patient 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.

8.8 Treatment compliance

Treatment compliance will be monitored and documented through timely review of eDiary data and drug accountability.

Concizumab will be administered at the trial site at visit 2 for the concizumab arm supervised by medically trained trial staff and administration at home can be initiated after visit 2 if the patient feels comfortable with the s.c. administration. Administration of eptacog alfa (rFVIIa) for bleeding episodes will be administered at the trial site by a medically trained trial staff or at home by the patient, see Section 8.3.1.

Drug accountability will be performed and will be used to assess patient compliance together with the patients' adherence to trial procedures.

Compliance check includes a cross check between records in EDC/eDiary (number of administrations and bleeding episodes) and the used/returned cartridges/vials.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the TMM.

The trial product, concizumab B, appears as clear to slightly opalescent and colourless to slightly yellow. The trial product must not be used if it contains visible particles or discoloration.

The reconstituted eptacog alfa (rFVIIa) solution appears clear and colourless. Do not use the reconstituted solution if it contains visible particles or if it is discoloured.

Trial products must not be dispensed to any person not included in the trial.

9.1 Trial products

The following trial products will be provided by Novo Nordisk, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
concizumab B (IMP)	100 mg/mL	Solution for injection	s.c. injection	3 mL cartridge
eptacog alfa (IMP [a] and NIMP [b])	5 mg/vial	Powder for solution for injection	i.v. injection	Vial
histidine 5 mL	N/A	Solvent for solution for injection	i.v. injection	prefilled syringe

[a] Investigational Medicinal Product (IMP) given as IMP for a single dose at visit 3 and 9.1.
[b] Non-Investigational Medicinal Product (NIMP) given as NIMP for bleeding episodes

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with the EMA directive on medical devices annex I [23] and similar national legislation. A description of how to use the device is given in the DFU.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13 [24], local regulations and trial requirements.

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 enrolment and randomisation.

The investigator must document that DFUs are given to the patient orally and in writing at the first dispensing visit (see Section 2).

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time [a]
concizumab B 100 mg/mL	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store at room temperature (below 30°C) Do not refrigerate Protect from light	Use within 4 weeks (28 days)
eptacog alfa 5mg	Store between 2°C-25°C Do not freeze Protect from light	For single use Do not freeze Protect from light To be used immediately after reconstitution	If not used immediately, store in refrigerator (2°C-8°C) for up to 3 hours
histidine 5 mL	Store between 2°C-25°C Do not freeze Protect from light	For single use	N/A

[a] In-use time for concizumab starts when first dose is administered from an individual cartridge and for eptacog alfa (rFVIIa) when the product is reconstituted

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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 must take appropriate action to ensure correct storage.

Investigator must instruct the patient to use and store trial product according to the label.

9.4 Drug accountability and destruction

Drug accountability of all trial products (concizumab and eptacog alfa (rFVIIa) received at site is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial product during the trial as instructed by the investigator, except for histidine which should be discarded at home and not accounted for.

All cartridges (concizumab) and vials (eptacog alfa (rFVIIa)) must be accounted for as used, partly used or unused.

The investigator will perform drug accountability using the IWRS Drug Accountability module.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial product including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Destruction of concizumab and eptacog alfa (rFVIIa) can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

For Japan only: Responsibility for storage and drug accountability of the trial drug product at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug product at the trial sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug product in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary supplies

Novo Nordisk will provide the auxiliaries for this trial:

- For concizumab administration: NovoPen®4, needles and DFUs
- For eptacog alfa (rFVIIa) reconstitution and administration: Trial Injection Kit and DFU

Only needles and trial injection kit provided by Novo Nordisk must be used for administration of trial product.

For further guidance please see the TMM.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

Randomisation will be handed by the IWRS.

All patients included in the screening period and eligible for the trial will enter the trial and be randomised at visit 2 in a 2:1 allocation to either concizumab prophylaxis arm or eptacog alfa (rFVIIa) on-demand arm.

11.2 Breaking of blinded codes

Not applicable for this trial.

12 Adverse events, and technical complaints

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality 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.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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
- Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. All bleeding episodes and other findings related to underlying disease will be captured in the eCRF/eDiary.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the patient's daily activities
  - **Moderate** – marked symptoms, moderate interference with the patient's daily activities
  - **Severe** – considerable interference with the patient's daily activities; unacceptable
- **Causality**

Relationship between an AE and the relevant trial product(s):

- **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

- **Final 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 fatal outcome must be reported as an SAE
  - **Unknown** - This term is only applicable if the patient is lost to follow-up

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death
- A life-threatening [a] experience
- In-patient hospitalisation [b] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity [c]
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening [a] or require hospitalisation [b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE [d]

[a.] The term "life threatening" in the definition of SAE 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 was more severe.

[b.] The term "hospitalisation" is used when a patient:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a patient's ability to conduct normal life functions (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE 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 ALT or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug

  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- 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

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.5.1

12.1.5 Adverse events 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.

In this trial the following AEs require the completion of specific event forms in the eCRF:

- Injection site reaction, see Section 8.4.5.2
- Hypersensitivity type reactions, incl. anaphylactic reactions, see Section 8.4.5.2

Injection site reactions:
Any injection site reaction symptom must be recorded on the AE form and the injection site reaction form.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction are present, blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. In the event of an immediate systemic hypersensitivity reaction to the trial product, it is recommended to also test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary ~1 week after the immediate severe hypersensitivity reaction due to individual to individual variation in tryptase baseline concentration. Tryptase concentrations (if measured) must be interpreted and considered in the context of a complete workup of each patient.

Special 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 type 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 cases where there is a suspicion of hypersensitivity reaction that requires systemic treatment, additional sampling for the purpose of measuring ADA will be performed.

Definition of anaphylaxis [25]
Anaphylaxis is highly likely when **any one of the following 3 criteria** is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
    a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

- **Two or more of the following** that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours): Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP.

If a patient fulfils any of the three criteria of anaphylaxis outlined above, the patient should receive epinephrine/adrenalin immediately. Dose regimen should be according to hospital operating procedure, and the patient should be transferred to an emergency department or intensive care unit, if clinically warranted.

Events not fulfilling the criteria for an anaphylactic reaction and other allergic reactions must be treated at the discretion of the treating physician. If according to the investigators judgement, hypersensitivity type reactions that require systemic treatment are suspected, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

12.1.6 Adverse Events of special interest

An adverse event of special interest (AESI) is an event, which in the evaluation of safety, has a special focus. In this trial, the following AEs fulfil the AESI criteria:

- Thromboembolic events including but not limited to,
    - disseminated intravascular coagulation (DIC) (A),
    - clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction (B),
    - pulmonary embolism (C),
    - stroke (D),
    - deep vein thrombosis (E),
    - other clinically significant thromboembolic events (F) and peripheral artery occlusion (see below G), see definitions below

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

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 × 10^9/L = 0, <100 × 10^9/L = 1, <50 × 10^9/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) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction" [26]
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.

C) 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 [27].

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

D) 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" [28].

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:

- 1. pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
- 2. 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 [(29)].

E) 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 DVT in the lower extremities[27]. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

F) 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 is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

G) 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, 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 [30].

12.1.7 Technical complaints

A technical complaint is any written, electronic or oral communication that alledges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until the end of the post-treatment follow-up period (visit 17). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the patient must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or patient, must be reported by the investigator and evaluated. All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

AESIs regardless of the seriousness must be reported using the AE form and safety information form.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

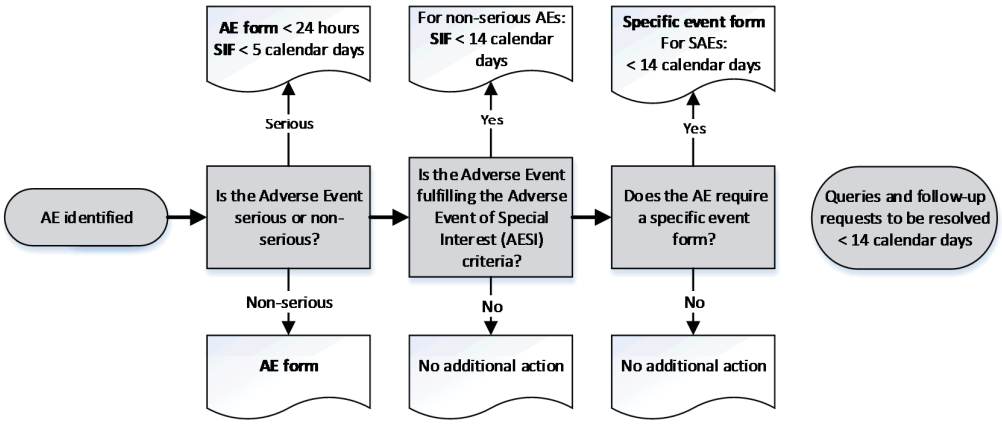
Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

- **Non-serious AEs fulfilling the AESI criteria:** The AE form and safety information form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are described in Section 12.1.5 *and 12.1.6*

AE: Adverse event **AESI:** Adverse event of special interest **SIF:** Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto.

When eptacog alfa (rFVIIa), NovoSeven® is used as IMP, expectedness should be performed according to the Company Core Data Sheet (CCDS).

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP [1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP [1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (eptacog alfa (rFVIIa)) or 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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AEs fulfilling the AESI criteria:** Non-serious AE fulfilling the AESI criteria must be followed as specified for non-serious AEs. Follow-up information on AESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the AESI criteria.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a patient after the patient has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Concizumab B 100 mg/mL, solution for injection in a 3 mL cartridge
- NovoPen®4
- Novo Nordisk needles
- Eptacog alfa (rFVIIa) 5 mg/vial, powder for solution for injection in a vial
- Histidine 5 mL, solvent for solution for injection in a prefilled syringe
- Novo Nordisk trial injection kit

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, AESI and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

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 Centre, 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.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Centre, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female partners of male patients

Male patients must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period (from visit 1 to dosing with concizumab at visit 2 or visit 9 depending on the arm). At the last scheduled visit (visit 17), male patients must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male patient and assess if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the patient's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax.

1. **Reporting of pregnancy information**
   Information from the male patient has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

   Initial reporting and follow-up information must be reported within **14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

- Paper AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE

SAEs:

- Paper AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Dose limiting toxicities of concizumab have not been investigated in clinical trials.

There have been no reports about overdosing of concizumab and therefore no experience with overdose and overdose reactions exists. In case of a concizumab overdose, symptomatic medical treatment according to the clinical condition should be applied. No antidote exists in case of concizumab overdose.

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors.

Treatment should be as appropriate and in accordance with hospital practice and guidelines.

12.7 Rules for putting enrolment on hold

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee. A substantial amendment with relevant data must be submitted to the regulatory authorities to support restart of the trial.

- Significant thromboembolic event*
- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product
- Two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements
- Trends in AEs, clinical observations or laboratory parameters which raise concerns about the safety of continued treatment.

*Superficial thrombophlebitis or venous thrombosis associated with indwelling catheters is not considered a significant thromboembolic event unless evaluated as such by the investigator

If two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements, or if trends in AEs, clinical observations or laboratory parameters raise concerns about the safety of continued treatment, the safety committee (see Section 12.8.1) will decide if further dosing of any patients in the clinical trial programme should be continued, paused or discontinued.

12.8 Committees related to safety

12.8.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal concizumab safety committee to perform ongoing safety surveillance of safety data relevant to concizumab. The safety committee is a cross functional group within Novo Nordisk.

12.8.2 Data monitoring committee

The 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 in order to protect the safety of the patients and to evaluate the benefit-risk balance. The DMC will have access to the data, and will provide recommendations on trial continuation, modification or termination.

In case there is any safety concern, data will be compiled and the DMC will review these data. Their recommendation will go to the Novo Nordisk Safety committee for final decision of what next step is in this trial.

The DMC members will only have direct contact with the Novo Nordisk Global Safety department through the safety surveillance representatives, and will have no direct interaction with those in trial management. The DMC recommendations should be addressed directly to the Novo Nordisk Global Safety department and the internal Novo Nordisk safety committee for concizumab. It is the responsibility of the Novo Nordisk internal safety committee for concizumab to take action(s) for patient safety based on the DMC recommendations.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms
- AE forms
- Safety information forms

The paper version of the technical complaint form, AE form, and safety information form must only be used to ensure timely reporting when/if the electronic CRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

13.3 Electronic diary

Novo Nordisk will provide the patient with an eDiary for electronic recording of details of their home treatment, bleeding episodes and treatment of bleeding episodes (i.e. use of eptacog alfa (rFVIIa)).
The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

Patients will be instructed in the use of the eDiary by the investigator or delegated person before entering of any data. The eDiary will be dispensed to the patient at visit 2. After visit 2 and onwards, data will be entered by the patient in the eDiary device during home treatment.

The eDiary will be returned by the patient at the EOT visit.

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

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.

Investigator review of eDiary data

It is the responsibility of the Investigator or delegated staff to review the eDiary data reported by the patient. As a minimum it must be verified that the eDiary data is complete, consistent and according to the requirements defined in this protocol. This also includes that the number of doses reported in the eDiary is reviewed against the number of vials/cartridge accounted for as used by the patient. Upon review the Investigator must document that the review has taken place and any actions required e.g. retraining of the patient or decision to amend or correct the data reported by the patient.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. Monitoring visits should be scheduled as frequently as needed to support the first 6 patients recruited in the trial. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site. This only applies to sites with scheduled, ongoing and/or discontinued patients.

The monitor must be given direct access to all source 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 or text message).

All data must be verifiable in source documentation other than the eCRF. eDiary data is entered by the patient and will also be treated as source data.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

For historical data such as medical history, details of haemophilia and haemophilia treatment history, a reasonable effort must be made by the investigator, considering local requirements, to obtain this information from external sources, if not known by the patient. It is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document. This means that for laboratory results (e.g. biochemistry and haematology) a signed printout of the electronic results must be available.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The monitor will ensure that the eCRFs are completed and paper CRFs (if any) collected, that ePROs and eDiaries are completed and reviewed by the investigator at the relevant scheduled visits and needed action has been taken and documented, if any.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Inclusion and exclusion criteria
- Screen failure reason if possible
- Date patient left the trial
- Data relating to AEs if applicable
- Demography, see section 8.2.1
- Date of visit

Monitors will review the patient's medical records and other source data (e.g. the eDiaries and ePROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of patient data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide all laboratory reports to the investigator for filing at the trial site. The laboratory report must be signed and dated by the investigator or delegated person and stored at the trial site as source data.

The patient and any biological material obtained from the patient will be identified by patient number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

Novo Nordisk will use the Global Haemophilia Network Investigator Portal to distribute and share trial-related documents and information with the participating sites. After trial completion, Novo Nordisk will supply each trial site with long-life CDs or other relevant archiving containing the electronic Investigator Trial Master File (eITMF) for each trial site. These CDs or other relevant archiving will contain site-specific trial documentation as well as trial specific news and other relevant trial information, including audit trail on documents and site staff users. The GHN Portal software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1, 31]

Novo Nordisk will provide electronic tablets for reporting of all PROs questionnaires described in section 8.6.1 and in Appendix 1. In case the electronic tablet is revoked the questionnaires will be available in paper.

The eDiary and ePRO software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1], [31] After trial completion, each trial site will be supplied with long-life CDs. These CDs will contain site-specific patient records including the patient's eDiaries and audit trail including any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 15 years or as required by local data retention laws for trial data.

17 Statistical considerations

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Please refer to Figure 17–1 for further information.

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

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. Further, the endpoints will not include re-bleed. A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping, the treatment is defined as a new bleeding episode.

Clinical proof of concept

The statistical analysis of the collected data aims to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia patients with inhibitors. The objective will be assessed when the last of the 24 patients has completed 24 weeks of dosing (or has withdrawn before that).

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

The referred comparisons will be made using a negative binomial model with log of exposure time in main part as offset and regimen as factor (concizumab vs. on-demand). For each criterion, evidence of effect will be concluded if the 95% confidence interval of the treatment ratio is below 1.

Clinical arguments for the hierarchical test approach

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

17.1 Sample size calculation

The estimand will be defined as the "if all patients had adhered" estimand.

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

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

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

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm. It is expected that the treatment duration of the main part allowing for escalation time for some patients is on average 6 months in the below calculations.

When evaluating the power of the negative binomial analysis referred above, annual bleeding rates of 24 and 6 are assumed for the on-demand patients and the end dose concizumab regimen, respectively. Assuming further over-dispersion of 7, the power for concluding superiority of the concizumab regimen becomes approximately 80%. The power under varying values of true ABR and over-dispersion for the primary CPoC criterion are shown below in Table 17–1.

Table 17–1 Power in superiority comparison between concizumab prophylaxis and on-demand treatment under different assumptions of ABR for concizumab and over-dispersion (assuming on-demand ABR=24).

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

For the secondary CPoC criterion that includes data prior to potential dose escalation, it is expected that the treatment duration of the main part is on average 8 months with an average ABR of 7.6 for the concizumab regimen. This yields a marginal power of approximately 70% for the secondary CPoC criterion.

In prior Novo Nordisk trials conducted in haemophilia patients, the typical 1-year over-dispersion for non-inhibitor patients on prophylaxis with FVIII or FIX has been in the range 4-8, implying 24 weeks over-dispersion of 3-5 (e.g. in NN7008-3543, NN7088-3859 and NN7999-3747). In the NN7128-1907 trial in inhibitor patients, larger 1-year over-dispersion values of approximately 21 and 18, respectively, were observed during an initial 3-month on-demand period and a subsequent 3-month prophylaxis period. It is expected that the variation in the current trial will be smaller, partly due to the longer duration of the trial and partly due to an expected more homogenous patient population. Another published trial including inhibitor patients, comparing prophylaxis using FEIBA® with on-demand treatment, showed 6-month over-dispersion of 4-5 [32]. On that background, an over-dispersion of 7 over the 24 weeks in main part of the current trial is deemed realistic.

17.2 Definition of analysis sets

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

17.3 Primary endpoint

The primary endpoint is the number of bleeding episodes during at least 24 weeks from treatment onset.

The endpoint will be analysed when the main part of trial has been completed.

17.3.1 Estimand and primary statistical analysis

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

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

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

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time in main part as offset and regimen as factor, providing an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is "missing at random", i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

17.3.2 Sensitivity analysis

To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis will be performed where patients having discontinued before finalization of the main part are assumed to have a worse outcome compared to what was observed during the main part of the trial. This will be done by adding a value Δ to the observed bleeding episodes in the main part of the trial before analysing the data. The offset is maintained as being the exposure during the main part since it is not possible to identify the amount of missing observation time. The degree of worsening, $\Delta_{i,}$ will gradually be increased to evaluate at which point concizumab prophylaxis no longer is superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis will be considered robust if the tipping point is above what is considered clinically plausible.

17.3.3 Additional analysis

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

administration, peak thrombin generation (nM), Endogenous thrombin potential (nM^{x}min) and velocity index (nM/min).

17.4 Supportive secondary endpoints

17.4.1 Supportive secondary efficacy endpoints

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

The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset will be addressed in terms of the same estimand as for the primary endpoint. The estimand will be estimated using the same negative binomial regression model as for the primary endpoint.

Furthermore, an additional evaluation will be made, where actual concizumab dose is included as factors in the model.

The remaining supportive secondary efficacy endpoints will be summarised descriptively by treatment regimen. In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed using a negative binomial model with log of trial duration as offset, providing estimates of the ABR with confidence interval for that particular regimen.

17.4.2 Supportive secondary safety endpoints

- Number of TEAEs during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence rate of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset
- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset

- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

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

TEAE is defined as an event that has onset from the first exposure to treatment until the last visit in the trial. Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All adverse events will further be listed.

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

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

17.4.3 Supportive secondary pharmacokinetic endpoints

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

The pharmacokinetic endpoints will be summarised and listed.

17.4.4 Supportive secondary pharmacodynamic endpoints

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

The PD endpoints will be summarized and listed.

17.4.5 Exploratory endpoints

17.4.5.1 Exploratory safety endpoints

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

Adverse events related to technical complaints will be listed and summarised

17.4.5.2 Exploratory patient reported-outcome endpoints

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

VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

The PRO endpoints will be summarised using descriptive statistics and the remaining questionnaires (Hemo-TEM, PGI-C, SIAQ-ISRQ) will be summarised and listed using descriptive statistics.

17.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. Main part is defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual CTRs might in such case be issued. A CTR describing results

from the main and the extension part will be written when the last patient has either completed or withdrawn from the trial. All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 17–1.

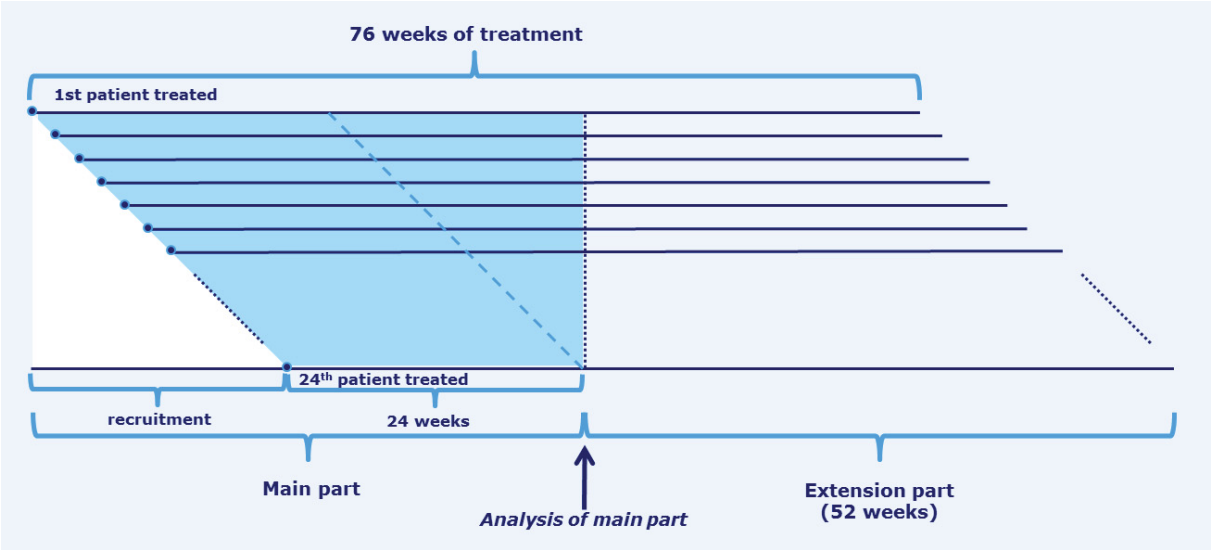


Figure 17–1 Definition of main and extension part

18 Ethics

18.1 Benefit-risk assessment of the trial

Benefits

Results from a multiple dose phase 1 trial where concizumab was dosed for approximately 6 weeks showed a trend towards efficacy in a limited number of patients who reached concizumab plasma concentrations above 100 ng/mL, see Section 3.1.2. Based on these results, it is expected that the majority of the patients randomised to the concizumab treatment with 0.15 mg/kg daily dose will be protected from bleeding episodes. Patients who experience excessive bleeding episodes on the lowest dose will have a possibility to be escalated to a higher dose where bleeding preventive efficacy of concizumab treatment is expected to improve. For haemophilia patients with inhibitors and who are treated on-demand, expected improved efficacy is considered to be a major benefit in participating in this trial. Also, concizumab is administered s.c. and might reduce the burden of frequent i.v. injections associated with current treatment options in haemophilia patients with inhibitors.

Information gained from this trial will contribute to gaining regulatory approval for a product that is anticipated to offer clinical advantages over currently available products.

Risks

No risks have been recognised as identified risks by review of safety data from the activities in the clinical development so far. However, the nonclinical toxicity studies have identified thromboembolic events as a potential risk when treating non-human primates with concizumab at high exposures.

As observed for other pro-coagulant compounds, there is a potential safety risk of thrombosis and vascular ischemia with reaching very high concizumab plasma concentrations. In non-clinical toxicity studies with concizumab, thrombi were observed at high doses. However, a no observed adverse effect level (NOAEL) for concizumab has been identified in non-haemophilic animals at plasma concentrations several folds higher than the currently anticipated effective plasma concentration (mean area under curve [AUC] and C_{max}) based on PK modelling.

In a drug–drug interaction study in monkeys, three doses of up to 1 mg/kg of NovoSeven® were administered at 2-h intervals, alone or in the presence of a steady state concentration of concizumab. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation. No notable clinical observations were made.

In clinical trials, except for one case of superficial thrombophlebitis in a healthy volunteer who received a single dose of 1mg/kg, no other thromboembolic events were observed. A phase 1

multiple dose trial was finalised in haemophilia A patients (0.8 mg/kg s.c. every 4 days for 6 weeks). In this clinical trial, marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range in patients with high plasma concentrations of concizumab. These changes were not judged as clinically significant by the investigators and were not followed by thromboembolic AEs or an increase in the number of bleeding episodes in the explorer™3 trial.

A potential risk identified in non-clinical studies is vascular vessel wall changes due to immune complex deposition causing localized vascular vessel wall changes such as hypertrophy and inflammatory cell infiltration. Concizumab is a foreign protein to animals and it is generally recognized that animal studies are limited in their ability to predict human immune responses to a therapeutic protein product. The concentrations of concizumab in plasma in animals in the non-clinical studies have reached levels far above the anticipated effective concentration. Humans are expected to have a very low immunogenic response towards a humanised mAb. The antibodies towards concizumab have not been observed so far in clinical trials. Furthermore, even if antibodies towards concizumab occur, the risk for the rate of immune complex formation exceeding the clearance capacity is considered low. Please refer to the Investigator's Brochure for further information.

If antibodies against concizumab develop, they might also inhibit the function of the administered drug. The consequence of this could be that the patient may not be able to benefit from the drug in the future. Antibody development against concizumab is not expected to reduce the effect of other treatment options.

Theoretical risks include bleeding due to consumption of coagulation factors and adverse reactions due to potentiation of inflammatory reactions or tissue damage due to impairment of tissue repair mechanisms[33 34]. TFPI is an important inhibitor of TF which, in addition to its role in haemostasis, is implicated in tissue repair processes and in a variety of physiological and pathophysiological states where repair mechanisms are activated. These include sepsis, DIC, inflammation, atherosclerosis, cancer and crush injuries[35 36, 37].

There may be a risk of allergic reactions, including severe (anaphylactic) reactions, in connection with concizumab administration. Severe allergic reactions may potentially be life-threatening and thus, the trial products will be administered to the trial patients at the site under the surveillance of medically trained trial site staff in the beginning of the trial.

Overall the anticipated benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki [2].

Before any trial-related activity, the investigator must give the patient verbal and written information about the trial and the procedures involved in a form that the patient can read and understand.

The patients must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the patient before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

Only applicable for Japan: As a minor is unable to provide legally binding consent, informed consent must be sought from the parent(s)/LAR(s) on the child's behalf prior to enrolling a child in the trial, according to local requirements.

18.3 Data handling

If the patient withdraws from the trial or is lost to follow up, then the patient's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to patients during 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided and protocol waivers are not acceptable under any circumstances.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances are likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated (potential serious breach) and if it should be reported to the Regulatory Authorities as a serious breach of GCP and/or the protocol.

In addition, 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.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The below process will be in place to prevent missing data in this trial.

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 is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. 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).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

An Investigator Portal (Global Haemophilia Network [GHN]) will be used as primary media for exchange and handling of investigator trial master file documents between Novo Nordisk and the site and for electronic storage of these documents during trial conduct.

Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- SmPC or similar labelling of eptacog alfa (rFVIIa)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- Description of research facility obtained (applicable for sites outside the US)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

For local laboratory parameters the following will be collected:

- Laboratory normal ranges
- Laboratory certification, QA scheme or similar documentation
- Laboratory assay methods (only non-standard assays) and/or analytical methods

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP [1] applicable regulatory requirements and the Declaration of Helsinki [2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 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.

At least investigator must be trained in the current protocol version at a Novo Nordisk Investigator meeting or by the most recent version of the web training. It is recommended that all site staff completes the web protocol training.

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 will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [38].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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 subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure how-we-disclose-trial-information.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. 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.

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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[38] (sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Patients' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

Only applicable for Spain: 25 years retention according to the Spanish Royal Decree 1090/2015.

The files from the trial site/institution must be retained for 15 years after EOT as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

This trial will involve collection of human biosamples at visit 1 (screening visit) and at visit 17 (EOT) and these samples are to be stored maximum 15 years from EOT. In addition, samples which have been drawn as back-up samples during the conduct of the trial and have not been analysed will be captured and stored under the same conditions.

Storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and

participate, while refusing permission for biological specimens to be stored for future exploratory analysis.

- Human biosamples will be stored at the central laboratory
- 1.0 mL citrated plasma, 1.2 mL serum and/or 2.0 mL whole blood (DNA for genotyping) will be obtained
- The intended use of the stored human biosamples e.g.: 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 human biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- Human biosamples may be transferred to third parties e.g. research consortia
- The human biosamples will be transferred and stored after the EOT at a designated central laboratory
- Confidentiality and personal data protection will be ensured during storage after the EOT
- The human biosamples may be transferred to other countries (not applicable if local regulations prohibit export of human biosamples)
- The human biosamples will be destroyed at the latest 15 years from EOT
- The patient may request the stored human biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used
- Novo Nordisk and laboratory will have access to the stored human biosamples
- Potential consequences for the patient and their relatives: In the event that the collected human biosamples (plasma, serum and/or DNA for genotyping) 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 human biosamples obtained from their own body, see Section 5.1.

24.2.1 Antibody samples

Antibody samples will be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

The retained antibody samples may be used 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 assays, and will not be reported in this trial. The samples will be stored at a central bio-repository after EOT and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from EOT after which they will be destroyed.

The patients' identity will remain confidential and the antibody samples will be identified only by patient number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Patients can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC (not applicable for Japan).

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the patients.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

26 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.

Novo Nordisk accepts liability in accordance with:

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. II Nr. 105/2015

Only applicable for 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 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 or the fault 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".

Only applicable for Poland: Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal pf Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigators are covered by the Insurance Policy issued according to applicable Polish law.

27 References

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Protocol

NN7415-4310

explorer™4

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

Trial phase: 2

Includes: Protocol Version 1 (15 March 2017); Protocol Amendment no 1 (05 May 2017) for all participating countries; Protocol Amendment no 2 (15 November 2017) for all participating countries.

Protocol originator

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Biopharm Trial Ops 1

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List of abbreviations

ABI	ankle-brachial index
ABR	annualised bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under curve
BP	blood pressure
BU	Bethesda Unit
CCDS	company core data sheet
CLAE	clinical laboratory adverse event
C_{max}	maximum plasma concentration
CNS	central nervous system
concizumab B	the name concizumab is being used as an abbreviation for concizumab B. B is the formulation

CPoC	clinical proof of concept
CRF	case report form
CRO	contract research organisation
CRP	c-reactive protein
CT	computerized tomography
cTn	cardiac troponin
CTR	clinical trial report
DFU	direction for use
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
DRC	data request correction
DUN	dispensing unit number
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eITMF	electronic investigator trial master file
ELISA	enzyme-linked immunosorbent assay

EMA	european medicines agency
EOT	end of trial
ePRO	electronic patient reported outcome
eptacog alfa	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to rFVIIa,'NovoSeven®, and 'NiaStaseRT®'
ETP	endogenous thrombin potential
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendment Act
FIX	coagulation factor IX
FPFV	first patient first visit
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FVIII:C	plasma activity of factor VIII
FX	coagulation factor X
FX_a	activated coagulation factor X
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHN	global haemophilia network

HCP	host cell protein
Hemo-TEM	Hemophilia Treatment Experience Measure
IB	investigator's brochure
IC	informed consent
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	independent ethics committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
INN	International Non-Proprietary Names for Pharmaceutical Substances
IRB	institutional review board
ISRQ-SIAQ	Injection Site Reaction Questionnaire – Self-Injection Assessment Questionnaire
ISTH	International Society on Thrombosis and Haemostasis
IT	information technology
i.v.	intravenous(-ly)
IWRS	interactive web response system

LBBB	left bundle branch block
LPFV	last patient first visit
LPLV	last patient last visit
mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NIMP	non investigational medicinal product
PCD	primary completion date
PD	pharmacodynamics
PEF	peak expiratory flow
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome

PT	prothrombin time
Q	Inter compartmental clearance
QA	quality assurance
Q4D	every 4th day
eptacog alfa (rFVIIa)	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to 'NovoSeven®'
sABR	spontaneous annualised bleeding rate
SAE	serious adverse event
SAS	safety analysis set
sBE	spontaneous bleeding episodes
s.c.	subcutaneous(-ly)
SDS	Sheehan Disability Scale
SF-36v2	36-Item Short Form Health Survey
SI	international system of units
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TAT	thrombin-antithrombin complex
TEAE	treatment emergent adverse events
TIA	transient ischemic attack

TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TMM	trial materials manual
TSQM	Treatment Satisfaction Questionnaire for Medication
TVP	trial validation plan
UTN	Universal Trial Number
VERITAS-PRN®	Validated Hemophilia Regimen Treatment Adherence Scale

1 Summary

The main objective for the phase 2 trial NN7415-4310, explorer™4, is to assess the efficacy of concizumab administered s.c. once daily to prevent bleeding episodes in haemophilia A and B patients with inhibitors. Furthermore, this trial aims to assess the longer-term efficacy and safety of concizumab in haemophilia A and B patients with inhibitors and to establish the safety of treating breakthrough bleeding episodes with recombinant factor VIIa (rFVIIa) in these patients.

Objective(s) and endpoint(s)

Primary objective

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors.

Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

Primary endpoint

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

Key secondary endpoints

- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset
- Number of treatment emergent adverse events (TEAEs) during at least 24 weeks from treatment onset

Time frames for evaluation of Objectives/Endpoints

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of dosing treatment with trial product (or has withdrawn). In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial design

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. We expect 16 patients to complete treatment in concizumab arm (concizumab prophylaxis) and 8 patients in comparator arm (rFVIIa on demand). The dose regimen is selected based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

For all patients treated with concizumab (concizumab arm and comparator arm extention part) a loading dose of 0,5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0,15 mg/kg. All patients in treatment with concizumab will in a non-bleeding state receive a single dose of 90 µg/kg eptacog alfa (rFVIIa) one week after dosing with concizumab. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at the site after 24h.

The total trial duration for the individual patient will be approximately 86-88 weeks, consisting of a 2-4 week screening period, a subsequent 76-week treatment period and an 8-week follow-up period. eptacog alfa (rFVIIa) for treatment of bleeding episodes during the trial will be provided by Novo Nordisk. The patient will not be provided with trial product or eptacog alfa (rFVIIa) after end of trial.

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn. The analysis of the main part of the trial aims to substantiate the clinical proof of concept (CPoC) that concizumab has the potential to prevent bleeding episodes in patients with haemophilia and inhibitors. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial population

Number of patients planned to be screened: 28
Number of patients planned to be started on trial product: 26
Number of patients expected to complete the trial: 24

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 the suitability for the trial
- Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
- Patients currently in need of treatment with bypassing agents

Key exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Known inherited or acquired bleeding disorder other than haemophilia
- Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX

Key Efficacy assessment

- Number of bleeding episodes during at least 24 weeks of treatment onset

Key Safety assessment

- Number of treatment emergent adverse events during at least 24 weeks of treatment onset

Trial products

The following products will be used in the trial:

- **Investigational Medicinal Products:**
  - concizumab B, 100mg/mL to be administered s.c. with NovoPen®4 and needles
  - eptacog alfa (rFVIIa), 5mg /vial and histidine (solvent). Reconstituted eptacog alfa (rFVIIa) is for intravenous administration and used in the trial at visit 3 and 9.1 for all patients with the purpose of investigating the safety of administering eptacog alfa (rFVIIa) to haemophilia patients
- **Non Investigational Medicinal Product**:
  - eptacog alfa (rFVIIa) 5 mg /vial and histidine (solvent). Reconstituted eptacog alfa is for intravenous administration and used in this trial for treatment of bleeding episodes

2 Flow chart

2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a, b]								Treatment extension [b]													Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176 7 days after V9	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
PATIENT RELATED INFO/ASSESSMENTS																						
Informed consent/ Genotyping and Long-term storage consent	●																					
In/exclusion criteria	●	●[g]																				
Demography	●																					
Concomitant illness/Medical history	●																					
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Details of Haemophilia/Haemophilia treatment and bleed history	●																					
Withdrawal criteria/ Criteria for premature discontinuation of trial product		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Randomisation (IWRS)		●																				
EFFICACY																						
Bleeding episodes [h, i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Thrombin generation (central lab)	●	●[l]	●[j, k, l]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Free TFPI (central lab)	●	●[l]	●[k, l]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
SAFETY																						
Physical examination	●	●	●[k]						●	●						●				●	●	●
Body measurements	●	●[m]	●[k, m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]		●[m]	●[m]
Vital signs	●	●[n]	●[k, n]	●	●	●	●	●	●[n]	●[n]	●	●	●	●	●	●	●	●	●	●	●	●	●
ECG	●																						
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

explorer™4 trial periods	Screening	Treatment main [a, b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176 7 days after V9	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Injection site reaction		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Urinalysis (local lab)	●																					
Haematology (local lab)	●	●[l]	●[j, k, l]	●	●	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Biochemistry (central lab)	●	●[l]	●[k, l]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVIII/ FIX activity (central lab)	●								●[l]											●[l]		
Coagulation parameters (central lab)	●	●[l]		●	●	●	●	●	●[l]		●	●	●	●	●	●	●	●	●	●[l]	●	●
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			●[j, k, l]							●[j]												
FVIII/FIX inhibitors (central lab)	●								●[l]											●[l]		
Anti-concizumab antibodies (ADA) (special lab) [o]	●	●[l]	●[k, l, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
Concizumab ELISA (special lab)		●[l]	●[j, k, l, p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[l, p]	●[j]	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVII ELISA (special lab)			●[j, k, l]							●[j]												
Total TFPI (special lab)	●	●[l]	●[k, l]	●	●	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●	●[l]	●	●
TRIAL MATERIAL																						
IWRS call	●	●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●	●[w]	●[k]			●			●	●		●		●		●	●	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]						●[d, s]	●										●[s]	●	
Administration of trial product (eptacog alfa)			●[k, t]							●[t]												
Drug accountability (concizumab)			●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New dose of trial product [e, u]				●	●	●	●	●	●		●	●	●	●	●	●	●	●	●		●	
PRO questionnaires	●	●	●[k]	●	●	●	●	●	●			●								●		
REMINDERS																						
Human biological specimen for storage (central lab)	●																					●

explorer™4 trial periods	Screening	Treatment main [a, b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176 7 days after V9	197	225	253	281	309	337	393	449	505	533	When applicable	589
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Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
Handout ID card	●																					
Training [v]	●	●							●	●											●	
Compliance: eDiary			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of treatment																				●		
End of trial																						●

The cells marked in 'red' are only for the patients randomised to eptacog alfa (rFVIIa) arm.

2.2 Explanatory descriptions

Footer	Description
a	There is staggered recruitment for the 4 first patients in the trial on the concizumab arm.
b	Concizumab administration is performed at home except for visit 2 and visit 3 for patients randomised to concizumab and visit 9 and 9.1 for patients randomised to eptacog alfa. Sampling for Free TFPI, Anti-concizumab antibodies, Concizumab ELISA and Total TFPI are done prior to concizumab administration.
c	The duration of the visits will last according to patient's individual training need on concizumab administration, NovoPen® 4, eDiary training etc. Visit 3 and visit 9.1 have a PK session of 24 hours and a safety follow up visit the following day.
d	Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment.Visit 9.1 should be performed 7 days (+ 1 day) after visit 9.
e	For patients being dose escalated on concizumab a phone call is recommended 1 week after first dose of concizumab.
f	Daily dosing preferably at the same time in the morning.
g	Evaluation of the laboratory results obtained from samples taken at screening.
h	Bleeding episodes occurring between visit 1 and visit 2 or at site should be registered in the eCRF. All bleeding episodes except for severe occurring after visit 2 at home should be registered in the eDiary. Severe bleeding episodes must be registered in the eCRF.
i	Eptacog alfa will be given to treat breakthrough bleeding episodes.
j	Sampling time schedule for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.
k	ONLY for patients randomised to concizumab arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
l	At visit 2, visit 3, visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.
m	Only body weight should be measured.
n	Vital signs should be evaluated before and after trial drug administration at visit 2 and visit 3 for concizumab arm and at visit 9 and visit 9.1 for patients in eptacog alfa arm switching to concizumab treatment.
o	In case clinical signs of e.g. hypersensitivity reactions or immune related events are seen, additional samples for ADAs may be taken. All antibody samples from the affected patient will be analysed on an ongoing basis. If antibodies are detected, additional blood samples will be taken and stored for characterisation of the antibodies.
p	Blood sampling for anti-concizumab antibodies and concizumab ELISA testing should only be collected for patients on concizumab.
q	If needed dispensing of eptacog alfa, histidine, trial injection kits and Direction For Use (DFU).
r	First treatment dose of concizumab is a loading dose and will be administered at visit 2 for the concizumab arm and visit 9 for the eptacog arm.
s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g.,

	eptacog alfa, FEIBA®) for treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2.
t	Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
u	Patient treated with concizumab should be dose escalated at next scheduled visit if he experiences ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab. If the investigator judges that next scheduled visit is too late an unscheduled visit should be performed for dose escalation.
v	Home treatment training must take place at visit 2 at the latest and whenever needed afterwards. Patients randomised to eptacog alfa will be re-trained in NovoPen®4 and s.c. administration at visit 9 and 9.1. If necessary training can be performed as needed at other visits. The eDiary will be provided to the patients at visit 2 if the patient feels capable in s.c. administration and using the eDiary. Further the patients will be trained in recognition of signs/symptoms of thrombosis.
w	Only for patients randomised to on-demand arm.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [1], applicable regulatory requirements, in accordance with the Declaration of Helsinki [2] and ISO 14155 [3].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

The INN name of the active pharmaceutical ingredient is concizumab (synonyms used during early development are NNC0172-2021, anti-TFPI, NN7415 or mab2021). Throughout this document "concizumab" is used as the name of the trial drug.

3.1 Background information

3.1.1 Haemophilia

Haemophilia is an inherited bleeding disorder characterised by an increased bleeding tendency, typically in weight bearing joints. Haemophilia A is caused by a partial or complete deficiency of blood coagulation factor VIII (FVIII). In haemophilia B, it is factor IX (FIX) that is deficient. Inheritance is chromosome X-linked; therefore the disease mainly affects males. The incidence of haemophilia A and B on average is estimated to be about 1 in 5000 live male births [4]. According to the World Federation of Haemophilia global survey of 2014[5], about 178,500 persons are diagnosed with haemophilia worldwide. Of these, about 80% have haemophilia A.

Haemophilia is classified as "severe", "moderate" or "mild" according to the plasma activity level of the affected coagulation factor [6]. 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 [7]. The haemostatic plug, if formed, in these patients 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 occurs spontaneously and is the most frequent symptoms 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 majority of children with severe haemophilia experience their first bleeding episode into a joint prior to age 4 year. Many children also bleed from other body sites before this age is reached [8]. For this reason, primary prophylaxis with regular FVIII or FIX injections in the non-bleeding state is the recommended treatment from early childhood.

In patients who have developed inhibitors towards FVIII or FIX, replacement therapy is rendered ineffective. Though prevalence studies and registry data indicate that the prevalence of inhibitors in the haemophiliac population overall has been reported to be between 5% and 7% [9], the prevalence

amongst patients with severe haemophilia (FVIII:C < 1%) is higher and has been reported to be up to 30% [9, 10]. These patients may be treated with bypassing agents, activated FVII (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) given as i.v. injections.

Current treatment options in haemophilia, replacement therapy or bypassing therapy, are hampered by the fact that these products must be given as i.v. injections. Furthermore, bypassing agents are characterized by relatively short half-lives, therefore prophylactic treatment is burdensome. It is also generally acknowledged that the efficacy profile of bypassing agents is inferior to replacement therapy. Consequently, delayed or sub-optimal treatment occurs in a significant number of patients with inhibitors. A new therapeutic agent that can be administered subcutaneously will represent a major improvement in the treatment of these patients in a prophylaxis setting.

3.1.2 Concizumab

The trial product, concizumab, is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype with a molecular weight of 149 kilo Dalton's. Like other antibodies, concizumab is composed of two light chains and two heavy chains linked together by disulfide bridges. To prevent formation of half-antibodies, the serine at position 241 in the heavy chain has been replaced with a proline (S241P (Kabat annotation)) [10]. The mechanism of action of concizumab is based on the concept of inhibiting the activity of a natural coagulation inhibitor, tissue factor pathway inhibitor (TFPI). TFPI is a potent inhibitor of the initiation phase of the coagulation process, i.e. the activation of (FX) to FXa by the tissue factor (TF)/factor VIIa (FVIIa) complex. TFPI first binds to and inhibits activated FXa and subsequently binds to and inhibits the TF/FVIIa complex, forming a TF/FVIIa/FXa/TFPI complex. Thus, concizumab prevents both inhibition of FXa and inhibition of FVIIa/TF by TFPI. In this manner, sufficient amounts of FXa to ensure effective haemostasis in the absence of a functional activated factor IX/activated factor VIII (FIXa/ FVIIIa) complex may be generated. This is a new concept that remains to be documented safe and efficacious in patients with haemophilia. More information about the physiological role of TFPI and the mode of action of concizumab is provided in the Investigator's Brochure.

Key differentiators of this new mode of action (MoA) and the key benefit of concizumab in patients with severe haemophilia A and B with inhibitors is reduced treatment burden due to subcutaneous administration potentially leading to better adherence, more patients on prophylactic treatment and ultimately better outcome.

Four clinical trials with concizumab have been completed thus far: the first human-dose trial (NN7415-3813, explorer™1) [11], a single dose trial in Japanese healthy subjects (NN7415-3981), two multiple dose trials (NN7415-3986, explorer™2) and (NN7415-4159, explorer™3). When the first cohort with 4 (four) healthy subjects in explorer™2 was completed, prior to the initiation of the 2nd cohort, the trial was halted, due to findings related to thrombosis in an ongoing 26-week toxicity study in primates. In this trial animal had concizumab plasma concentrations several hundred fold

above clinically relevant concentrations. Follow up investigations confirmed that the animal's condition was related to thrombosis in the lungs caused by exaggerated pharmacology at these high plasma concentrations. Before the initiation of the fourth phase 1 trial (NN7415-4159), explorer™3, a new 52 week non-clinical toxicology study was conducted in primates to investigate the findings in the previous study. The conclusion from this new non-clinical study was that the results from non-clinical studies support further clinical development of concizumab. Explorer™3 was a multiple dose clinical trial which aimed to investigate the safety, pharmacokinetics and pharmacodynamics of concizumab at five different dose levels in adult severe haemophilia A patients without inhibitors. In this trial multiple doses of concizumab were administered s.c. over a period of six weeks.

The explorer™3 trial was finalised following the completion of cohort 3 (0.8 mg/kg s.c. every 4 days for 6 weeks). Blinded preliminary safety and PK/PD data from the cohort was reviewed by the concizumab safety committee. Marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range. In addition, a substantial inter subject variation in pro-coagulant response to the drug was observed. Based on this, the Novo Nordisk safety committee (see Section 12.8.1) decided not to proceed to cohort 4 (1.1 mg/kg s.c. every 4 days for 6 weeks). No clinical consequences or serious adverse events were seen in the completed cohorts in explorer™3.

The PK results from explorer™3 showed exposure-response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL. Individual predicted PK profiles merged with recorded spontaneous and traumatic bleeding episodes are shown in Figure 3–1.

Figure 3–1 Individual predicted PK profiles based on data merged with recorded spontaneous (circles) and traumatic (triangles) bleeding episodes during the dosing period and follow-up period. All data originates from explorer™3 (N=24 patients). PK of concizumab is subdivided into three exposure levels of ≤ 20 ng/mL, 20-100 ng/mL, and > 100 ng/mL together with the number of contributing patients. LLOQ: lower limit of quantification.

[a] 'Time in trial' refers to the time that the patients spent on each concizumab exposure level, and the ≤ 20 ng/mL level therefore also includes the screening period (not shown on this figure).

A large difference between the peak and trough plasma concentrations of concizumab were observed as well, especially in the highest dose group (0.80 mg/kg) of explorer™3. In patients who received 0.25, 0.5 and 0.8 mg/kg doses a significant overlap in plasma concentrations of concizumab was seen due to high between-patient variability in concizumab.

Single doses of concizumab up to 9 mg/kg have been administered to haemophilia patients in the first human dose trial with concizumab, explorer™1. These doses resulted in plasma concentrations of concizumab that were significantly higher than the ones that are modelled to be reached in the highest escalated daily dose (0.25 mg/kg) of explorer™4.

In a drug–drug interaction study in monkeys (NN215431), three doses of up to 1 mg/kg of NovoSeven® were administered at 2h intervals, alone or in the presence of a steady state concentration of concizumab. No notable clinical observations were made, no treatment-related

adverse findings were seen, i.e. no thrombi or other signs of excessive coagulation. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation.

For an assessment of benefits and risks of the trial, see Section 18.1.

For further information, please refer to the Investigator's Brochure.

3.2 Rationale for the trial

Four phase 1 clinical studies with concizumab have been finalised. Key safety and preliminary efficacy results from these phase 1 studies support further development of concizumab in haemophilia patients. Therefore, the main objective in the phase 2 of concizumab development is to assess efficacy and safety and provide data that will guide for the confirmatory phase 3 concizumab trials.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors

4.1.2 Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

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

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset

- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset
- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

Supportive secondary pharmacokinetic endpoints

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

Supportive secondary pharmacodynamic endpoints

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

4.2.3 Exploratory endpoints

4.2.3.1 Exploratory safety endpoints

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

4.2.3.2 Exploratory patient reported outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset

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

All endpoints referring to a time frame of either 24 weeks, or of at least 24 weeks, will be evaluated in the main part of the trial.

All endpoints referring to a time frame of 76 weeks will be evaluated in the extension part of the trial.

5 Trial design

5.1 Type of trial

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. The selected dose regimen is based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

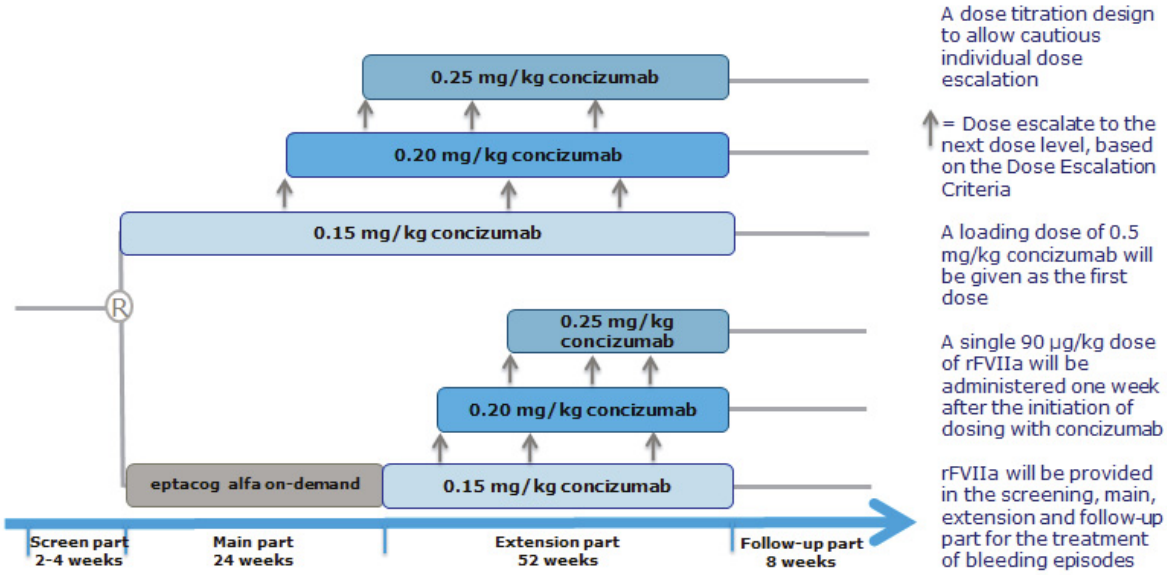

Figure 5–1 Schematic diagram of the trial design

The total trial duration for the individual patient will be approximately 86-88 weeks, including a 2-4 week screening period, a 76 week treatment period, and a follow-up period of 8 weeks, see Figure 5–1

The trial is split into a main part which lasts 24 weeks for all patients in the trial and an extension part which lasts up to 52 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn.

In the concizumab arm bleeding episodes occurring during the trial will be treated with eptacog alfa (rFVIIa). In all patients treated with concizumab a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state one week after dosing with concizumab has been initiated. The investigator will evaluate if there are any safety concerns 24 hours post eptacog alfa (rFVIIa) administration. Furthermore, the scheduled administration of eptacog alfa (rFVIIa) for the first 4 patients entering the trial with concizumab will be staggered.

In the comparator arm, in the main part, patients will receive eptacog alfa (rFVIIa) on-demand treatment. After completion of the main part, the patients will continue the trial in the extension part being treated with prophylactic concizumab 0.15 mg/kg (with potential dose escalation) s.c. daily administration.

Human biosamples (plasma, serum, and/or DNA for genotyping) will be collected in this trial for future exploratory analysis to pursue a deeper insight into the biology of TFPI, coagulation, and effect of concizumab on joint health. That may include coagulation parameters and markers of joint status and damage. Acceptance of storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for human biosamples to be stored for future exploratory analysis, see Section 8.1.1.

An independent data monitoring committee (DMC) will be established for this trial. The DMC will review all safety data from the ongoing trial with concizumab exposure, see Section 12.8.2.

5.1.1 Surgery

Minor surgery is allowed in this trial. Major surgery conducted earlier than one month (30 days) prior to trial start is allowed, see exclusion criteria no 6.

Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. Examples of minor surgery include implanting of central venous access devices (ports, CVC, pumps and other CVADs) in subcutaneous tissue, skin biopsies or simple dental procedures.

5.2 Rationale for trial design

Explorer™4 is a phase 2, clinical proof of concept (CPoC), and safety trial. The trial aims to substantiate CPoC that concizumab has the potential to prevent bleeding episodes in haemophilia patients with inhibitors. A dose escalation design will allow cautious dose escalation in order to identify an efficacious and safe concizumab dose for the individual patient. A comparator arm is included to assess if concizumab is superior to on-demand treatment. Furthermore, the trial will give a possibility to assess safety of co-administration of eptacog alfa (rFVIIa) to the patients exposed to the concizumab treatment.

The duration of 24 weeks for the main part of the trial is deemed necessary in order to obtain information on the annualised bleeding rate on concizumab prophylaxis. The duration of the extension part of the trial will be 52 weeks and provide further information on efficacy, i.e. annualised bleeding rate, and also provide additional safety data upon 76 weeks treatment with concizumab.

A total of 26 patients previously on-demand (OD) treatment will be randomised into one of the two arms, with 16 patients in the concizumab arm and 8 patients in the comparator arm see Figure 5–1. Concizumab will be administered s.c. daily for patients randomised to the concizumab arm in the main and the extension part of the trial. For patients in the comparator arm in the extension part treatment will be changed from on-demand with rFVIIa to prophylaxis with concizumab.

The concizumab dose regimens will be starting with 0.15 mg/kg with the possibility to escalate to 0.20 mg/kg and 0.25 mg/kg based on bleeding frequency, see Section 5.3.3.

Daily dosing with concizumab 0.15 mg/kg aims to ensure steady-state levels of concizumab plasma concentrations above 100 ng/mL for the majority of the patients starting on this dose. The PK results from explorer™3 showed exposure response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL, see Figure 3–1 . The minority of patients which are predicted to have steady-state plasma concentrations below this threshold are expected to experience bleeding episodes and therefore will have the opportunity to be dose escalated to the dose of 0.2 mg/kg. A further dose escalation to 0.25 mg/kg per day is permitted, again based on the bleeding rate, see Section 5.3.3.

Figure 5–2 Individual predicted concizumab concentration profiles for all concizumab-treated patients in explorer™2 (n=4 patients) and explorer™3 (n=18 patients). The horizontal lines indicate 100 ng/mL, and the shaded areas represent the full range (min-max) of the individual predicted profiles.[1]

Due to the high between patient variability in concizumab concentration observed in explorer™3, a significant overlap in plasma concentrations of concizumab in patients who received 0.25, 0.5 and 0.8 mg/kg doses was seen, see Figure 5–2. Therefore, choosing three doses that would lead to reasonably distinct mean plasma concentrations of concizumab, and thus different efficacy at each

[1] Plasma concentrations in the same range as those in explorer™3 are expected to be reached in this trial with daily dose administration. The starting dose for all patients will be 0.15 mg/kg daily. The plasma steady-state exposure for a typical subject at this dose level is predicted to fourfold lower compared to a typical subject on 0.8 mg/kg Q4D (cohort 3 of explorer3) in terms of both Cmax and AUC 0-24h. For 0.20 mg/kg daily and 0.25 mg/kg, the plasma steady-state exposure levels for a typical subject are predicted to be less than 40% and 70% respectively, compared to the typical subject exposure in the 3rd cohort of explorer™3 (AUC and Cmax). The maximum predicted plasma exposure levels (Cmax and AUC 0-24h) for the 0.15 mg/kg daily dose level is predicted to be more than 8 fold lower than for 0.80 mg/kg Q4D. For 0.20 mg/kg daily both Cmax and AUC 0-24h are predicted to be more than 3 times lower than for 0.80 mg/kg Q4D. For 0.25 mg/kg daily, the maximum Cmax and AUC 0-24h are predicted to be 35% lower than for 0.80 mg/kg Q4D.

dose level was not deemed possible. For this reason, a traditional parallel arm design was not chosen for the phase 2 trials. In contrast, the titration trial design allows patients to start on a low dose, which is expected to ensure prophylaxis but not marked changes in coagulation parameters, for the majority of patients. Escalation to the next dose level will only occur in the case of lack of efficacy (≥ 3 spontaneous bleeding episodes within the preceding 12 weeks). In addition, the PK of concizumab is heavily influenced by target mediated drug disposition, which means that small differences in concizumab dose ultimately leads to large differences in plasma concentrations. Therefore, daily dosing is proposed for the phase 2 trial, explorer™4. Daily dosing will allow for the increase in trough levels and thus better efficacy may be expected with a lower dose.

A loading dose of 0.5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0.15 mg/kg in order to ensure steady-state levels at the time of eptacog alfa (rFVIIa) administration. eptacog alfa (rFVIIa) will be administered one week after initiation of dosing with concizumab in a non-bleeding state to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment.

Embryonic exposure in pregnant female partners of men treated with concizumab is highly unlikely and there is no need for protocol requirements for use of contraception in phase 2 and 3 trials.

5.3 Treatment of patients

The following products will be administered in the trial.

Table 5–1 List of products provided by Novo Nordisk

Compound Name	Strength	Dosage form	Route of administration	Treatment period
concizumab B [a]	100 mg/mL	solution for s.c. injection in a 3 mL cartridge [b]	Subcutaneous administration using NovoPen®4	For prophylactic treatment in 76 weeks (for concizumab arm in the main part and extension part). For prophylactic treatment in 52 weeks (for comparator arm in the extension part).
eptacog alfa (rFVIIa) [a, c]	5 mg/vial	Powder for solution for i.v. injection	Intravenous administration	For treatment of breakthrough bleeding episodes at the discretion of the investigator (screening, main, extension and follow up part). [c] Administration of doses higher than
histidine solvent (5 mL)		Prefilled syringes for solution for i.v. injection		

				90µg/kg to patients exposed to concizumab is not allowed. For on-demand treatment at the discretion of the investigator in 24 weeks for comparator arm in the main part. In the concizumab arm and comparator arm after switching to concizumab in the extension part of the study a single 90µg/kg dose for initial safety assessments in a non-bleeding state. [a] Will be provided for as long as patients participate in the trial (screening, main, extension and follow up part)

[a] Investigational medicinal product (IMP)
[b] Not to be confused with the daily injected volume (~150 µL, depending on dose strength and body weight)
[c] Non-investigational medicinal product (NIMP)

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with national legislation and a copy of the label can be found in the Trial Materials Manual, see Section 9.

5.3.1 Concizumab arm

5.3.1.1 Concizumab prophylactic treatment (main and extension part)

Concizumab will be given s.c. once daily 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg). The dose escalation criteria are described, see Section 5.3.3. The first dose of concizumab will be given at the trial site under medical supervision.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 2 in order to ensure steady state levels at the time of the administration of eptacog alfa (rFVIIa) in a non-bleeding state at visit 3, see Section 5.3.4.

The patients will be trained in s.c. administration of concizumab with NovoPen®4 at the screening visit and at the first scheduled treatment visit.

5.3.2 Comparator arm (eptacog alfa (rFVIIa))

5.3.2.1 On-demand treatment (main part)

During the main part of the trial, patients will receive eptacog alfa (rFVIIa) for treatment of bleeding episodes, with a dose regimen at the discretion of the investigator.

5.3.2.2 Concizumab prophylactic treatment (extension part)

After completion of the main part, the patients will continue the trial in the extension part and will switch to prophylactic treatment with s.c. daily administration of concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) s.c. daily administration.

The same dose escalation criteria as described below (for the initial concizumab arm) will apply.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 9 in order to ensure steady state levels at the time of the administration of rFVIIa in a non-bleeding state at visit 9.1.

5.3.3 Dose escalation

The dose escalation criteria as described below will apply to all treatment arms.

Bleeding episodes will be assessed during the trial both at scheduled visit and also between visits. The first 2 weeks of the treatment with concizumab 0.15 mg/kg is considered as a run-in period. Hence, bleeding episodes occurring during first 2 weeks should not influence a dose escalation decision.

All spontaneous bleeding episodes (sBEs) are counted from 2 weeks after visit 2 (or visit 9 when switching from eptacog alfa (rFVIIa) to concizumab) (first treatment visit) until visit 16 (end of treatment visit), i.e. a total of 74 weeks. Dose escalation will be based on the number of spontaneous treated bleeding episodes in patients within preceding 12 weeks. However, before dose escalation can occur, to ensure the safety of the patients, the investigator must take into account the full clinical picture the patient is presenting with and all available laboratory results, including coagulation parameters.

Dose 0.15 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE). If yes, and if investigator deems it safe, the patient will be dose escalated from 0.15 to 0.20 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.20 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.20 mg/kg treatment period. If yes, and if investigator deems it safe, the patient will be dose escalated from 0.20 to 0.25 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.25 mg/kg:
Patients are not dose escalated further regardless of the number of sBEs. When an sBE occurs, the investigator will determine if ≥ 3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.25 mg/kg treatment period. If yes, then the patient must be discontinued due to lack of efficacy, see Section 6.4.

The possibility of dose escalation at unscheduled visits is necessary in order to avoid bleeding episodes at inadequate dose level: e.g. if the dose escalation eliciting bleeding episode occurs soon after a scheduled visit, the patient will avoid to wait 8 weeks for the next scheduled visit (in the extension part).

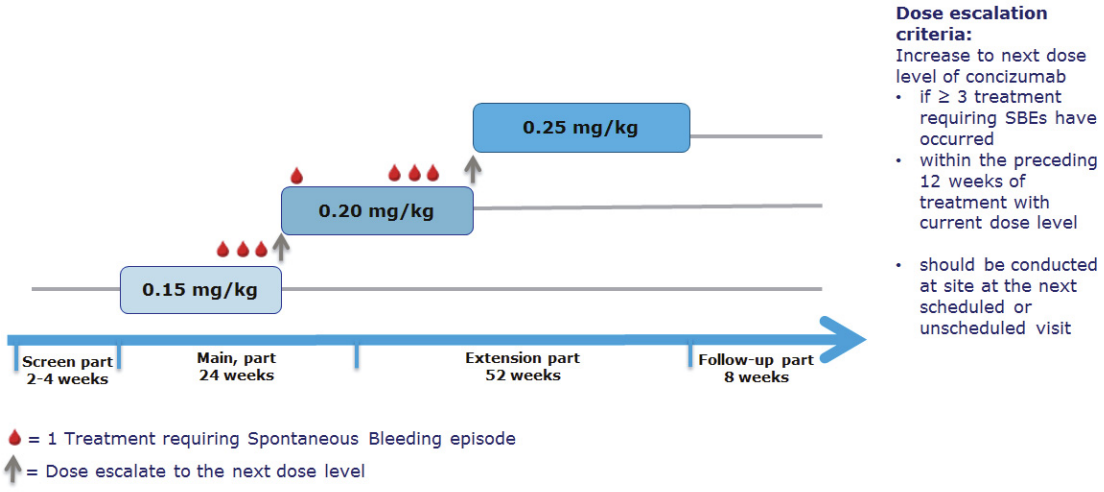

Figure 5–3 Dose escalation for one individual patient in the concizumab arm

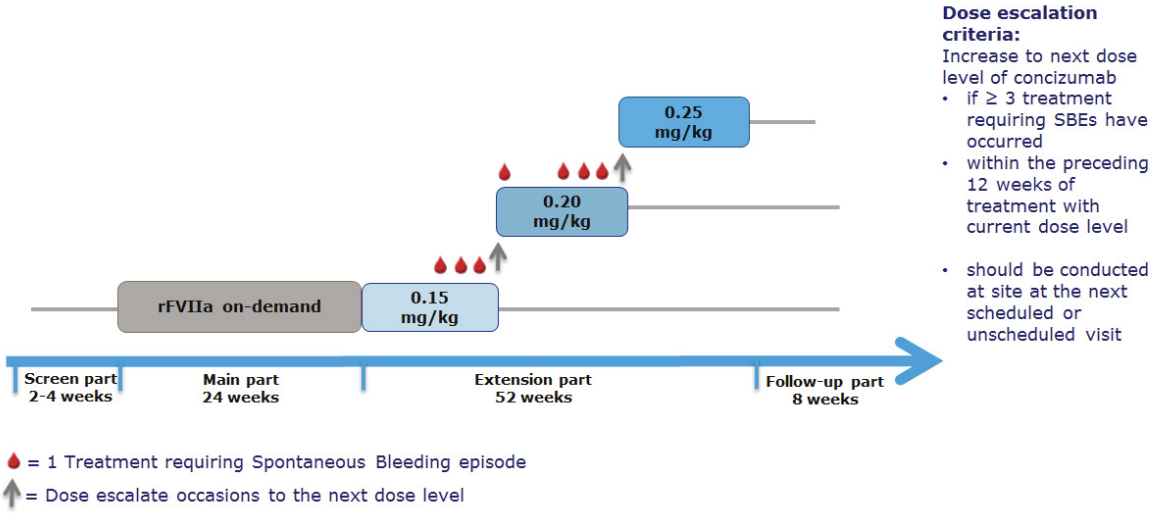

Figure 5–4 Dose escalation for one individual patient in the comparator arm

5.3.4 Co-administration of eptacog alfa (rFVIIa)

eptacog alfa (rFVIIa) will be used for treating breakthrough bleeding episodes in this trial; one week after initiation of dosing with concizumab, a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state at the trial site under medical supervision to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at site after 24h. Between 12h and 24h, the patient must either stay at the site or at a hotel or at home if he lives nearby to be able to continue visit 3 or 9.1 the day after. Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to concizumab arm will be staggered so that the period between eptacog alfa (rFVIIa) administrations from one patient to another is at least 48 hours. If no safety concerns are observed (for example signs and symptoms of thromboembolism, such as swelling, pain and redness of the leg, shortness of breath, and chest pain) by the investigator in the period between the administration of eptacog alfa (rFVIIa) and when the next daily concizumab dose is to be given, the investigator allows the individual patient to administer concizumab prophylactically at home and if needed, treat breakthrough bleeding episodes at home with eptacog alfa (rFVIIa). The patients will receive prophylactic doses of concizumab 0.15 mg/kg daily throughout the main part (24 weeks) and the extension part (52 weeks), unless dose escalation criteria are fulfilled, see Section 5.3.3.

In case safety concerns are raised by an investigator after eptacog alfa (rFVIIa) administration and these concerns meet the described criteria for putting enrolment of additional patients on hold, dosing in the individual patients will be halted and further recruitment in the trial will be halted, see

Section 12.7. In case safety concerns that do not meet the criteria for putting enrolment of additional patients on hold are observed by the investigator, dosing in that individual patient will be halted until further evaluation. In such cases, all available data will be assessed by the Data Monitoring Committee (DMC), see Section 12.8.2.

5.3.5 Treatment of bleeding episodes during the trial

Breakthrough bleeding episodes between visit 1 and visit 2 can be treated with any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) up to a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to first concizumab administration at visit 2. Novo Nordisk will provide eptacog alfa (rFVIIa) throughout the trial. The patient can treat himself and then he must call the site. The bleeding episode must be recorded in the eCRF.

Breakthrough bleeding episodes between visit 2-3 in the concizumab arm and visit 9-9.1 in the comparator arm must be treated with eptacog alfa (rFVIIa). Upon breakthrough bleeding episodes in this period the patient must first call the site. The investigator should instruct the patient about whether he should go to the site to receive treatment or if he can administer a single dose of eptacog alfa (rFVIIa) which is not higher than 90µg/kg without delay to treat the breakthrough bleeding episode. If the patient is instructed to administer the eptacog alfa (rFVIIa) dose at home, following the administration, the patient should immediately go to the site for further clinical evaluation. The bleeding episode must be recorded in the electronic Diary (eDiary).

Breakthrough bleeding episodes between visit 3 and visit 16 in the concizumab arm must be treated with eptacog alfa (rFVIIa). The patient can treat himself without delay but must inform the site that a bleeding episode has occurred. Doses of eptacog alfa (rFVIIa) those are lower than 90µg/kg may be used to treat breakthrough bleeding episodes at the discretion of the investigator. Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. If a single dose of eptacog alfa (rFVIIa) is not sufficient to stop a bleeding episode, the patient should inform the site and in agreement with the investigator may administer a second dose of eptacog alfa (rFVIIa) not higher than 90µg/kg 2-3h after the first dose has been administered. The same procedure should be repeated in case the second dose of eptacog alfa (rFVIIa) is not sufficient to stop the bleeding episode. If more than three 90µg/kg doses of eptacog alfa (rFVIIa) are needed to stop a bleeding episode, the patient should go to the site without delay. The definition and diagnostic criteria of DIC, acute myocardial infraction, stroke, deep vein thrombosis, pulmonary embolism and peripheral artery occlusion is provided in section 12.1.6. The bleeding episodes must be recorded in the eDiary.

Breakthrough bleeding episodes between visit 16 and visit 17 (follow-up part) may be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator. The patient can treat himself with eptacog alfa (rFVIIa) at home without delay. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The bleeding episodes must be recorded in the eDiary.

See Table 5–1 and Table 8–3.

5.3.6 Prohibited medication

- Treatment with anti-fibrinolytics (e.g. tranexamic acid, aminocaproic acid)*
- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anticoagulants (DOACs)
- Home treatment (between visit 2 and visit 16) with activated prothrombin complex concentrates (FEIBA®)

* Local/topical use is allowed. Use of single systemic doses in severe bleeding episodes, after careful benefit risk evaluation, is allowed.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products (visit 16 or earlier), the patient should be switched to a suitable marketed product at the discretion of the investigator. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The patient will not be provided with concizumab or eptacog alfa (rFVIIa) after end of trial (EOT) (visit 17) by Novo Nordisk.

5.5 Rationale for treatment

Concizumab is a monoclonal antibody and as such offers the possibility of s.c. administration. S.c. administration of an effective prophylactic drug has potential to reduce the treatment burden compared to the currently approved prophylactic drugs which have to be administered i.v. Furthermore, the current treatment options for prophylaxis in inhibitor patients do not reduce the frequency of breakthrough bleeding episodes to the same extent as prophylaxis with replacement therapy in non-inhibitor patients. Concizumab may therefore show a better efficacy profile compared to current treatment options in haemophilia A and B patients with inhibitors.

The treatment period during at least 24 weeks (the main part of the trial) is considered necessary for providing robust data that allow demonstration of clinical proof of concept and to support decision making regarding a phase 3 confirmatory trial. Dosing for additional 52 weeks will provide valuable long term efficacy and safety data.

Breakthrough bleeding episodes occur in prophylactic regimens with both bypassing agents and replacement therapy. Therefore, it is expected that breakthrough bleeding episodes will occur during prophylaxis with concizumab even if clinical proof of concept is demonstrated. Consequently, eptacog alfa (rFVIIa) will be provided by Novo Nordisk in this trial for treatment of breakthrough bleeding episodes. In order to minimize the likelihood of any unforeseen adverse events associated with administration of eptacog alfa (rFVIIa) in these circumstances, administration of eptacog alfa (rFVIIa) in a controlled setting will be performed at visit 3 or 9.1. Please refer to the Investigator's Brochure for further information.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 28

Number of patients planned to start on trial product: 26

Number of patients expected to complete the trial: 24

- Preferably 21 haemophilia A patients
- Preferably 3 haemophilia B patients

Discontinued patients will not be replaced.

6.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

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 the suitability for the trial
2. Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
3. Patients currently treated on-demand with a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening
4. Documented history of high-titer inhibitors towards FVIII or FIX, defined as ≥ 5 Bethesda Units
5. Patients currently in need of treatment with bypassing agents

6.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within the last 30 days or 5 half-lives (whichever is longer) from the last drug administration before screening
4. Any disorder which in the investigator's opinion, might jeopardise patient's safety or compliance with the protocol
5. Known inherited or acquired bleeding disorder other than haemophilia
6. Major surgery conducted within one month prior to the initiation of trial activities or major surgery planned to occur during the trial

7. Previous history of thromboembolic disease. Current clinical signs of thromboembolic disease or patients who in the judgement of the investigator are considered at high risk of thromboembolic events
8. Mental incapacity, unwillingness to cooperate or language barrier precluding adequate understanding and cooperation
9. Patients who, at screening, have a significant infection or known systemic inflammatory condition which requires systemic treatment according to the investigator's judgement
10. Hepatic dysfunction defined as elevated liver transaminases (ALT) >3 times the upper limit of normal laboratory reference ranges at screening
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m^2 for serum creatinine measured at screening for patients without evidence of renal damage
12. Platelet count ≤ $100x10^9$/L at screening
13. Fibrinogen level < the lower limit of normal
14. Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX
15. Antithrombin levels below the normal reference range at screening

6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation 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. Anaphylactic reaction
5. Thromboembolic event
6. Event of Disseminated Intravascular Coagulation
7. Lack of efficacy due to neutralizing antibodies
8. Lack of efficacy defined as ≥ 3 treated sBEs within the previous 12 weeks in patients being treated with the highest dose level (0.25 mg/kg) of concizumab.

See Section 8.1.4 for procedures to be performed for patients discontinuing trial product prematurely.

6.5 Withdrawal from trial

The patient may withdraw consent at will at any time.
See section 8.1.5 for procedures to be performed for patients withdrawing consent.

6.6 Patient replacement

Patients who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

The most important reason for choosing the trial population, haemophilia with inhibitors, is that there is a significant unmet medical need in this patient population for

1. A more effective treatment and
2. A treatment which reduces treatment burden.

In addition to this, since most of these patients are likely to have been treated and therefore familiar with eptacog alfa (rFVIIa) on-demand treatment, this trial population is considered the most suitable for assessing the safety of administering eptacog alfa (rFVIIa) to patients in whom plasma TFPI levels are inhibited. Finally, the trial population reflects the patient population that will be selected in a potential subsequent phase 3 trial in which the efficacy and safety of concizumab are to be confirmed.

7 Milestones

Planned duration of recruitment period (FPFV-LPFV): 28 weeks

Planned FPFV:	16-Aug-2017
Planned FPFT:	30-Aug-2017
Planned LPFV:	28-Feb-2018
Planned LPLV:	23-Oct-2019

The total duration of concizumab treatment in this trial is 76 weeks for an individual patient randomised to concizumab prophylaxis treatment at visit 2.

The total duration of concizumab treatment in the trial is 52 weeks for an individual patient randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2.

EOT is defined as last patient last visit (LPLV).

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further patients may be screened and the IWRS will be closed for further screening. All patients screened during the recruitment period and found eligible for randomisation can be randomised in a 2:1 allocation to either the concizumab or the comparator arm within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, how-we-disclose-trial-information, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE), [12] the Food and Drug Administration Amendment Act (FDAAA), [13] European Commission Requirements, [14 15] 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.

Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this protocol LPFT (visit 2) + 24 weeks corresponding to visit 9. If the last patient is withdrawn early the PCD is the date when the last patient would have completed visit 9. The PCD determines the deadline for results disclosure at ClinicalTrials.gov according to FDAAA.[13]

8 Methods and assessments

Assessments to be performed at the scheduled and at the unscheduled visits in the trial are described in this section, Figure 8–1, Figure 8–2 and in Section 2.

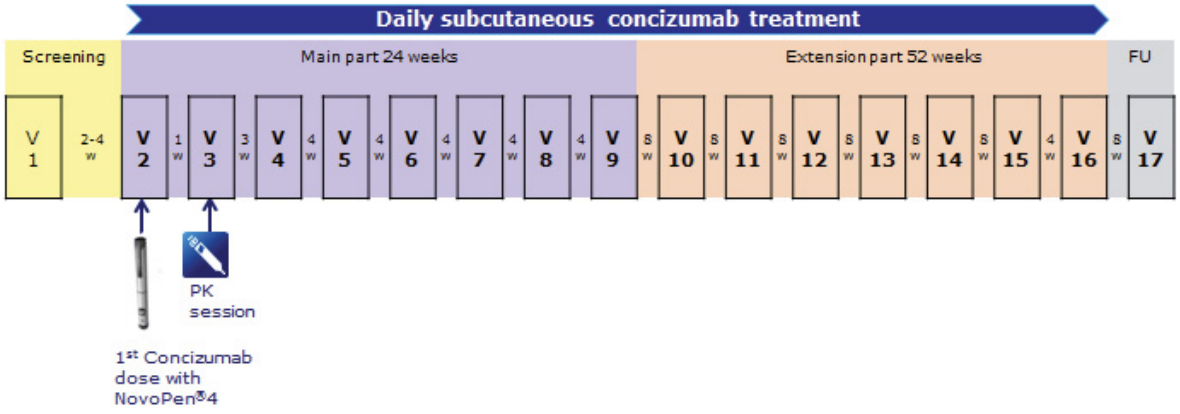

Figure 8–1 Visit schedule – concizumab arm.

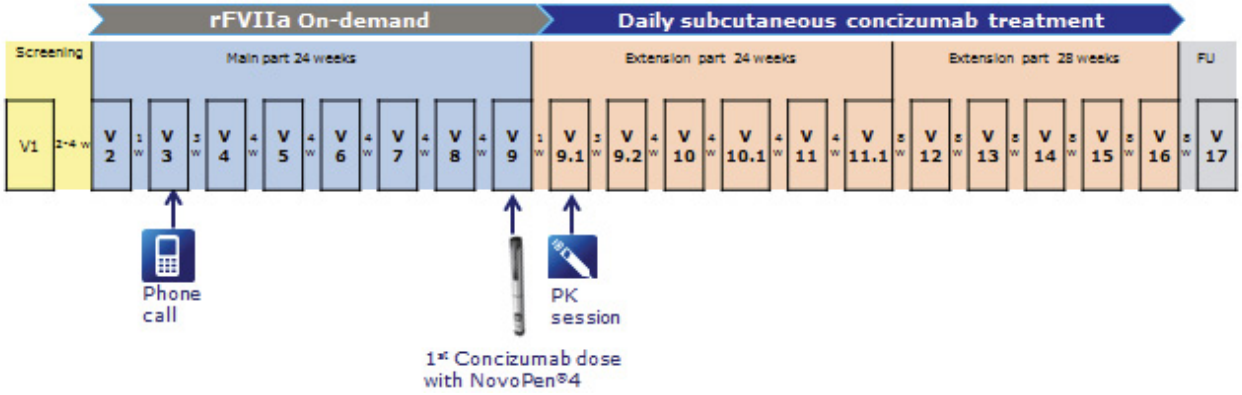

Figure 8–2 Visit schedule – eptacog alfa (rFVIIa) arm later switching to concizumab.

8.1 Visit procedures

For each patient the trial can consist of the following scheduled parts and visits depending upon which arm the patient is randomised to:

Screening Part:

- Visit 1 (screening visit)

Main Part:

- Visit 2 (Randomisation and 1st treatment visit with concizumab at site for patients randomised to the concizumab-arm)
- *Home treatment with concizumab daily*
- Visit 3 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site only for patients randomised to the concizumab-arm - phone visit for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 4 (Assessment visit, patients treat themselves at home)
- Visit 5 (Assessment visit, patients treat themselves at home)
- Visit 6 (Assessment visit, patients treat themselves at home)
- Visit 7 (Assessment visit, patients treat themselves at home)
- Visit 8 (Assessment visit, patients treat themselves at home)
- Visit 9 (Assessment visit, after the visit patients treat themselves at home – 1st treatment visit with concizumab at site for patients randomised to the eptacog alfa (rFVIIa) arm)

Extension Part:

- Visit 9.1 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 9.2 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 10 (Assessment visit, patients treat themselves at home)
- Visit 10.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 11 (Assessment visit, patients treat themselves at home)
- Visit 11.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on demand-arm)
- Visit 12 (Assessment visit, patients treat themselves at home)
- Visit 13 (Assessment visit, patients treat themselves at home)
- Visit 14 (Assessment visit, patients treat themselves at home)
- Visit 15 (Assessment visit, patients treat themselves at home)
- Visit 16 (Assessment visit, no treatment at home before the visit and End of Treatment)

Follow-up Part:

- Visit 17 (Assessment visit and End of Trial)

Unscheduled Part:

- Unscheduled visits can occur e.g. for dispensing of trial product, dose escalation or when an assessment of bleeding episodes is necessary at site or at the discretion of the investigator.

The duration of the visits (V1-V17) will depend on the assessments and the patient's individual training and/or discussion need on concizumab and eptacog alfa (rFVIIa) administration, NovoPen®4, usage of eDiary, completion of the PRO etc.

8.1.1 Informed consent, genotyping and long-term storage consent

Informed consent must be obtained before any trial related activity at visit 1, see Section 18.2.

The trial includes a separate informed consent for long-term storage of human biosamples, see Section 24.2.

Storage of human biosamples and/or genotyping is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for biological specimens and/or genotyping to be stored for future exploratory analysis.

8.1.2 Screening log, enrolment log, trial card and patient number

The investigator must keep a patients screening log, a patients identification code list and a patients enrolment log. Only patients who have signed the informed consent form should be included on the logs. The patients screening log and patients enrolment log may be combined in one log.

At screening, patients will be provided with a card stating that they are participating in a trial and given contact address(es) and telephone number(s) of relevant trial clinic staff. Patients should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each patient will be assigned a unique 6-digit patient number which will remain the same throughout the trial.

8.1.3 Screening failures and re-screening

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.

Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12. A screening failure session must be made in the IWRS. The case book must be signed in the eCRF.

Re-screening is NOT allowed if the patient has failed one of the inclusion or exclusion criteria; this includes re-sampling if the patient has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.1.4 Premature discontinuation of trial product

If a patient prematurely discontinues trial product, the investigator must undertake procedures similar to those for visit 9 (the last treatment in the main part) or visit 16 (the last treatment visit in the extension part) as soon as possible. The follow up visit (visit 17) must be performed 8 weeks (window minus 7 days) after last dose of trial drug.

The primary reason for premature 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.

Permanent premature discontinuation of treatment with trial product will lead to patient withdrawal from the trial.

8.1.5 Withdrawal from trial

If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for visit 9 (the last visit in the main part) or visit 16 (the last visit in the extension part) as soon as possible depending on where the patient is in the trial schedule.

The end-of-trial form must be completed, and 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 and the case book must be signed in the eCRF.

Although a patient is not obliged to give his reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.6 Review/ evaluation of clinical outcome

Novo Nordisk has constituted an internal concizumab safety committee and established an external DMC to perform ongoing safety surveillance of safety data relevant to concizumab, see Section 12.8.

Review of eDiary data and laboratory reports etc. must be documented either on the documents or in the patient's medical record.

If unclear entries or discrepancies in the eDiary or ePRO are identified and a clarification is needed, the patient must be asked for clarification and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

8.1.7 Visit 1 (Screening part)

Informed consent must be obtained before any trial related activity, see Section 18.2

All assessments to be performed at screening are listed in Section 2.

After informed consent is given, patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- Hemo-TEM,
- VERITAS-PRN®

Assessment results from physical examination and body measurements, as well as measurements of vital signs, urinalysis and ECG and details of any contemporary adverse events, must be entered into the eCRF.

A screening confirmation call must be performed in the IWRS, at the day of the visit.

The investigator must review all information obtained from the screening procedures. If a patient does not meet all inclusion criteria or meets one or more of the exclusion criteria for the trial the patient does not qualify to be enrolled.

For bleeding episodes that occur in the period from Screening visit (Visit1) to randomisation visit (Visit 2), information about the bleeding episode is to be entered in the eCRF at visit 2.

Patients will be provided with eptacog alfa (rFVIIa), trial injection kits and direction for use (DFU) to cover the potential eptacog alfa (rFVIIa) treatment after the screening part of the trial and investigator will ensure that the patients are capable of treating themselves with eptacog alfa (rFVIIa).

Dispensing of eptacog alfa (rFVIIa) should be performed in IWRS.

The patient must be instructed to call the site if any bleeding episodes, questions or issues arise after he has left the site.

8.1.8 Training of patients at visit 1, visit 2 and visit 9

During visit 1 and visit 2 and visit 9 (comparator arm) patients must be trained in self-administration of concizumab in the home setting using NovoPen®4. The dose of concizumab to be administered must be communicated to the patient at visit 2 (if they are randomised to concizumab)

or at visit 9 (if they are randomised to eptacog alfa (rFVIIa) and switching to concizumab at visit 9). Furthermore, patients must be instructed and trained in the importance of reporting all the home treatments with concizumab, details of the bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes in the eDiary. The patient should call the site if bleeding episodes occur between visit 1 and 2 for the site to register in the eCRF.

Patients should be trained on how to recognize signs of thromboembolic events, so that the patient contacts the site without delay.

The site and patient can arrange for additional training whenever needed during the remaining time of the trial.

8.1.9 Treatment period at home

Home treatment is defined as self-administration of trial product, performed independently by the patient, preferably in the morning. Home treatment starts after visit 2 (concizumab arm) or when the patient is comfortable self-administrating trial product subcutaneously (concizumab) and intravenously (eptacog alfa (rFVIIa)).

8.1.10 Staggered recruitment

Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to the concizumab arm will be staggered until the 4th patient randomised to the concizumab arm has completed visit 3 without any safety concerns raised by the investigator. Until this time point, enrolled patients will not be randomised until the previous patient randomised to concizumab has completed visit 3 without any safety concerns raised by the investigator. Novo Nordisk will as sponsor control and communicate the staggered recruitment process.

8.1.11 Treatment period – Main part

8.1.11.1 Visit 2 (Randomisation)

Visit 2 should be scheduled 14 to 28 days after visit 1. The date of visit 2 will be considered as trial day 1.

It is important to verify the in/exclusion criteria again and review central laboratory tests from screening.

The patients must be in a non-bleeding state and should not have received any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) for treatment of bleeding episodes within a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to the potential first concizumab administration (depending on the treatment arm). After visit 2 only treatment with eptacog alfa (rFVIIa) for bleeding episodes is allowed.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments listed in 2, must be performed before potential administration of concizumab (depending on the treatment arm). Vital signs must be assessed both before (within 1 hour) and after concizumab administration. Pre-dose blood sampling must take place no more than 1 hour before concizumab administration.

Assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

A randomisation and dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the Trial Materials Manual (TMM) on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

For patients randomised to the concizumab arm, the first treatment with the loading dose of concizumab will be given.

The time point at which the completion of the first dose takes place corresponds to 'Time on treatment' = 0 and must be recorded in the eCRF.

The patient must be observed at the trial site for at least 2 hours after the administration of the first dose of concizumab.

At the visit the patient will be provided with trial product concizumab and/or eptacog alfa (rFVIIa) and trial injection kits and an eDiary device to be able to conduct and report home treatment and bleeding episodes until next scheduled visit.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for eptacog alfa (rFVIIa), if applicable according to section 9.4. Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site. If the patient on concizumab needs to treat a bleeding episode with eptacog alfa (rFVIIa) at home, then he must visit the site immediately after.

8.1.11.2 Visit 3 (Phone call for eptacog alfa (rFVIIa) on-demand arm and PK visit for concizumab arm)

eptacog alfa (rFVIIa) on-demand arm:

Visit 3 for eptacog alfa (rFVIIa) on-demand arm is a phone call scheduled 7 days after visit 2 (with a visit window of +1 day).

All relevant assessments listed in Section 2, must be discussed.

Assessment results from concomitant medication and details of adverse events must be entered into the eCRF.

concizumab arm:

Visit 3 is to be scheduled 7 days after visit 2 (with a visit window of +1 day) and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- PGI-C
- Hemo-TEM

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) administration.

The concizumab dose should be administered first followed by eptacog alfa dose. eptacog alfa (rFVIIa) should be administered to the trial patients at the site under the surveillance of medically trained trial site staff. The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min.

Samples for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa):

10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

The investigator must ensure that all assessments are performed as described in Section 2, The Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF prior to administration of the next dose of concizumab.

Recruitment of the first four patients will be staggered according to section 8.1.9.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.11.3 Visit 4, 5, 6, 7 and 8

Patients should treat themselves at home according to their individual dosing schedule regardless of when visits 4, 5, 6, 7 and 8 are scheduled.

Visits 4, 5, 6, 7 and 8 are to be scheduled on trial day 29 (4 weeks), day 57 (8 weeks), day 85 (12 weeks), day 113 (16 weeks) and day 141 (20 weeks) respectively with a visit window of ±7days.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM

All assessments are to be performed according to Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 8 patients should be reminded that treatment with concizumab (concizumab arm) must take place after the blood sampling at visit 9.

8.1.11.4 Visit 9

Visit 9 is to be scheduled on trial day 169 (24 weeks) with a visit window of ±7days.

Patients randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2 will now be switched to concizumab treatment. At this visit the first treatment (loading dose) with concizumab will take place.

Treatment with concizumab must take place after the blood sampling for both the patients on the concizumab arm as well as patients on the eptacog alfa (rFVIIa on-demand) arm.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are to be performed according to Section 2, and the assessment results from physical examination, concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through the available access to collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in Section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12 Treatment period – Extension part

8.1.12.1 Visit 9.1 (PK visit and ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.1 is to be scheduled on trial day 176 (25 weeks) with a visit window of +1 day and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) administration.

The concizumab dose should be taken first followed by eptacog alfa dose. eptacog alfa (rFVIIa) should be administered at the site under the surveillance of medically trained trial site staff. The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min. A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

Samples for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9 h (± 10 min) and 12h (±20 min) and 24h (±20 min).

The Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF prior to administration of the next dose of concizumab.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.2 Visit 9.2 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.2 is to be scheduled on trial day 197 (28 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.3 Visit 10

Visits 10 is to be scheduled on trial day 225 (32 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1.

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.4 Visit 10.1 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 10.1 is to be scheduled on trial day 253 (36 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9,

evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.5 Visit 11

Visit 11 is to be scheduled on trial day 281 (40 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.6 Visit 11.1 (ONLY patients previously on the rFVIIa on-demand arm)

Visit 11.1 is to be scheduled on trial day 309 (44 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.7 Visit 12, 13, 14 and 15

Visits 12, 13, 14 and 15 are to be scheduled on trial day 337 (48 weeks), 393(56 weeks), day 449 (64 weeks) and day 505 (72 weeks) respectively with a visit window of ±7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 15 patients should be reminded that treatment with concizumab must take place after the blood sampling at visit 16.

8.1.12.8 Visit 16

Visit 16 is to be scheduled on trial day 533 (76 weeks) with a visit window of ±7days. Further visit 16 should be scheduled to be conducted at the last day of treatment with concizumab.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF. Treatment with concizumab must take place after the blood sampling at this visit.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary.

In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat eventual bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period.

If necessary, a dispensing call must be performed in the IWRS. At the visit the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes) arise after he has left the site.

8.1.13 Visit 17 (End of trial) - Follow-up part

Visit 17 is to be scheduled on trial day 589 (84 weeks) with a visit window of minus 7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, physical examination, body measurements (weight only), vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data. Patients should be asked if their female partner has become pregnant, see Section 12.5.1.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), unused histidine syringes, eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

End-of-Trial information must be entered in the End-of-Trial form in the eCRF.

Completion or treatment discontinuation (if the trial is not completed) session should be performed in IWRS, see Section 10.

8.1.14 Unscheduled Visit

Unscheduled visits can be performed at any time during the trial as listed in Section 2. The purpose of the unscheduled visit must be documented in the eCRF.

During unscheduled visits assessments and blood sampling must be performed according to Section 2. Assessment results must be recorded in the eCRF. Assessments and blood sampling can be omitted if the only reason for the unscheduled visit is dispensing of trial product.

If trial product administration or dispensing is required, dispensing of trial product must be performed via IWRS.

The following forms can be found in the unscheduled visit in the eCRF:

- Bleeding episodes
- Dosing with eptacog alfa (rFVIIa), concizumab including dose escalation, see Section 5.3.3.
- Surgery
- Local, special and central laboratory (re-)sampling/results
- Body measurements

8.2 Patient related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history other than haemophilia

A **concomitant illness** is any illness, other than haemophilia, 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 first exposure to trial product. All concomitant illnesses should be reported in the

concomitant illness forms in the eCRF except information on haemophilia with inhibitors which is to be reported in the haemophilia medical history section of the eCRF.

Medical history is a medical event, other than haemophilia, which the patient has experienced in the past. Only relevant medical history should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the patient's medical history in source documents such as patient's medical record, see Section 6.2 and 6.3.

If a patient is not from the investigators own practice; the investigator must make a reasonable effort to obtain a copy of the patient's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the concizumab and eptacog alfa (rFVIIa), which is taken during the trial, including the screening and follow-up period.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Details of Haemophilia, Haemophilia treatment and bleed history

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

- Diagnosis of haemophilia (date)
    - Classification of haemophilia type (haemophilia A/B)
    - Severity of haemophilia (severe, moderate or mild)
    - Aetiology of haemophilia (congenital or acquired)
- Family history of
    - Haemophilia (Y/N)

- Inhibitors (Y/N)
- Prothrombotic disorders (Y/N)
- Thromboembolism (Y/N)

- Inhibitor tests taken (Y/N)
  - Date (dd-mmm-yyyy)
  - Result (BU)
- Cut-off for positive inhibitor result
- Deficiency factor level

The following information on bleeding episodes one year prior to screening should be recorded in the eCRF:

- Type of treatment
  - 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
- Dosing frequency during prophylaxis
- Approximate dose to treat a bleeding episode
- Approximate number of doses to treat a bleeding episode
- Target joint listing (definition: a target joint is a joint in which 3 or more spontaneous bleeding episodes have occurred within a consecutive 6-month period)
  - Location
  - Position (left/right)
  - Number of bleeding episodes

8.3 Efficacy assessments

8.3.1 Bleeding episodes

All bleeding episodes treated with eptacog alfa (rFVIIa) and symptoms related to the underlying disease must be captured in the eDiary by the patient or in the eCRF by the investigator. The trial site should be informed of the details of all bleeding episodes, including those that are treated outside of the trial site.

All information captured during visits to the trial site will be collected in the eCRF.

When home treatment is initiated at visit 2 all bleeding episodes and injections with concizumab and eptacog alfa (rFVIIa) injection occurring outside the trial site should be entered in the eDiary by the patient, Section 13.3.

The completed eDiary is considered source data.

For reporting of bleeding episodes as AEs/SAEs, please refer to Section 12. In case of life-threatening bleeding episode, it should always be reported as an SAE, see Section 12.1.2.

The following must be recorded for any bleeding episode, including bleeding episodes that do not require treatment with eptacog alfa (rFVIIa):

- Start date and time
- Stop date and time (see Table 8–1)
- Anatomical location
    - Position (left/right)
- Cause (see Table 8–2)
    - spontaneous
    - traumatic
    - post-surgical
- Severity (see Table 8–3)
    - mild/moderate, severe
        - classification and recording of severe bleeding episodes is the responsibility of the investigator
- Treatment, if any
    - eptacog alfa (rFVIIa) administration or other product administration
        - dose, date, stop time
    - other medicinal treatments related to the bleeding episode (pain relieving medication, non-medical therapy etc.)
        - record as concomitant medication (section 8.2.3)
- Symptoms during bleeding episode(s)
    - Pain
    - 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 if fatal, life threatening or evaluated as related to trial product, see Section 12.1.1 and 12.1.2.

Table 8–1 Definition of stop of bleeding episode

Stop time is:	When the patient experiences/observes signs of cessation of the active bleeding episode 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 8–2 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 8–3 Definition of bleeding episode severity and treatment recommendation

Category	**Definition**	**Treatment recommendation**
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeding episodes (joint, muscular bleeding episodes without compartment syndrome), mucosal- or subcutaneous bleeding episodes Mild/moderate bleeding episodes may occur in other anatomical locations	Mild/moderate bleeding episodes: • patient must call the site between visit 1-2 and visit 3-16 (see 2-3 and 9-9.1 below) • patient must call the site between visit 2-3 or visit 9-9.1 (eptacog alfa arm) and if treated at home, go to the site immediately after • patient can treat themselves at home between visit 16 and visit 17

Category	Definition	Treatment recommendation
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeding episodes; muscle bleeding episodes with compartment syndrome; bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeding episodes may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes	Severe bleeding episodes must be treated immediately
Instruction for patients	The patient must be instructed to contact the site immediately if in doubt regarding treatment of a bleeding episode and to discuss what other actions may need to be taken	

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.

Dosing for bleeding episodes with eptacog alfa (rFVIIa) should be documented in the eCRF (visit 1 to visit 2) and eDiary (visit 2 to visit 17). After visit 2 bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see section 13.3.

Investigator must instruct the patient not to perform preventive treatment with eptacog alfa (rFVIIa) after bleeding stop as defined in Table 8–1.

Investigator must instruct the patient to use eptacog alfa (rFVIIa) as rescue medication to treat bleeding episode between visit 2 and visit 16, see Section 5.3.5.

Furthermore investigator must instruct the patient to contact the site when a bleeding episode occurs. It is the responsibility of the investigator to instruct the patient about the timelines for timely completion of the eDiary.

Furthermore the investigator must review the bleeding and treatment data collected by the eDiary according to Section 13.3.

For in-between visit administrations of trial drug, patients will self-administer concizumab (and eptacog alfa (rFVIIa) as rescue medication) and will record treatment in the eDiary, which will be reviewed during periodic calls to/contact with the patient and at each visit by trial site staff and the sponsor staff.

8.4 Safety assessments

8.4.1 Physical examination

Performed as standard physical examination and include the following.

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

The investigator must evaluate the results of the examination and classify them 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 Medical History (Section 8.2.2)
    - If observed after screening: report an AE/SAE (Section 12)

Measurements will be reported in the eCRF.

8.4.2 Body measurements

- Height (cm), at screening
- Body weight (kg), (with one decimal)

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

Measurements will be reported in the eCRF.

8.4.3 Vital Signs

Before measurement of vital signs the patient should preferably rest comfortably for at least five minutes and all measurements should, if possible, be performed using the same method and in a sitting position throughout the trial.

Measurements at visits must be performed prior to any trial product administration unless otherwise specified.

- Body temperature (°C)
- Systolic and diastolic blood pressure, sitting (BP) (mmHg)
- Pulse, sitting (beats/min)
- Respiratory rate

Exception: At visits 2 and visit 3 (for patients randomised to concizumab) and at visit 9 and visit 9.1 (for patients initiating concizumab treatment at visit 9), the measurements are also performed after concizumab administration.

The investigator must evaluate the vital signs 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, section 8.2.2
    - If observed after screening: report an AE/SAE, section 12

Measurements will be reported in the eCRF.

8.4.4 Electrocardiogram

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 Medical History, section 8.2.2
    - If observed after screening: report an AE/SAE, section 12

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.

8.4.5 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.5.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product involved
- Classification of medication error
- Whether the patient experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.5.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

Injection site reaction

Investigation of injection site reactions will be performed locally at all visits after visit 2 until visit 16 based on patient feedback and by following visual inspections of injection sites for concizumab administration:

Symptoms e.g.

- Pain
- Numbness
- Itching
- Burning

Signs e.g.

- Redness (mm x mm)
- Induration (mm x mm)

- Swelling
- Dimpling
- Macula
- Haematoma
- Bleeding
- Other (visual reactions)

Any injection site reaction symptom (evaluated at visit 2-16) should be recorded in the AE form and the injection site reaction form, see Section 12.1.5.

A separate AE should be recorded for each injection site reaction symptom. The affected area should also be evaluated for redness and induration in mm using a ruler. To ensure all local injection site assessments are performed at the injection site, the area around the site will be marked with a pen prior to injection.

In the event of a local reaction, additional visual assessments (as described above) 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.

Hypersensitivity reaction

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

All events of hypersensitivity reactions must be reported and the following information must be obtained if available on the hypersensitivity reaction form:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed, see Section 8.5.2.7
- Treatment given for the reaction
- Previous history of similar reactions
- Association with the trial product(s)
- Relevant risk factors associated with the event
- Storage condition of the trial product
- Total number of doses, from first day on trial product, up to the time of this event

8.5 Laboratory assessments

An approximate total blood volume of 625 mL will be taken from each patient on the concizumab arm and 725 mL from each patient on the eptacog alfa (rFVIIa) arm.

A laboratory manual will be provided for detailed description of obtaining and processing blood samples.

All laboratory blood samples collected for this trial except for haematology samples at all visits and coagulation parameters at visits 3 and 9.1 are to be shipped for analysis at central laboratories or further distribution to special laboratories. Haematology samples (all visits) and coagulation parameters (visit 3 and 9.1) are to be analysed locally. Ports cannot be used for blood sampling.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Laboratory reports listing results from centrally analysed samples will be made available for the investigator. Investigator must review and evaluate the results and report AEs for results which are clinically significant. Laboratory reports will where possible indicate normal ranges.

Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: FVIII/FIX activity, FVIII/FIX inhibitor

test, Thrombin generation, Free TFPI (TFPI not bound to concizumab), concizumab concentration in plasma, anti-concizumab antibodies, Total TFPI and FVII antigen concentration.

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 and report these according to Section 8.2.3 and Section 12.

Only laboratory samples specified in the protocol must 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 except for biomarkers and anti-drug antibodies (anti-concizumab IgE antibodies and anti-concizumab antibodies).

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and human biosamples, if applicable, will be stored as described in Section 24.2. The investigator may not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV.

8.5.1 Laboratory assessments for efficacy

8.5.1.1 Thrombin generation

The Thrombin Generation Assay (TGA) will be collected at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

The TGA is included as an exploratory PD assessment.

The generation of thrombin is a fundamental part of the haemostatic system, and is a key measurable parameter of the formation of a clot under bleeding or thrombotic conditions. The thrombin burst is crucial for the formation of a stable fibrin clot.

The Calibrated Automated Thrombogram (CAT) method (used by Thrombinoscope BV) will be used to measure thrombin generation (TG). This method uses a slow acting fluorogenic substrate that allows continuous measurement of thrombin generation in double centrifuged citrated plasma.

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.

The thrombin generation endpoints are defined but not limited to:

- The Endogenous Thrombin Potential (ETP) – the area under the curve
- Peak thrombin generation
- Velocity Index

8.5.1.2 Free TFPI

Free TFPI (TFPI not bound to concizumab) will be collected at all visits, pre-dose at visit 2 and 3 (concizumab arm), visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16.

The free TFPI assay is an enzyme immunoassay measuring levels of free TFPI from [redacted] (named and referred to [redacted] TOTAL TFPI) and will be used for PD assessments.

8.5.2 Laboratory assessments for safety

8.5.2.1 Urinalysis

- pH
- Protein
- Glucose
- Bilirubin

This is a semi qualitative measurement which will be performed (locally) at the screening visit by the site by using the appropriate reagent strips for urinalysis. The results will be recorded in the eCRF.

The investigator must evaluate the results and record the outcome as:

- Normal or abnormal
- If abnormal the investigator must:
    - Record if the result is clinically significant? (Yes/No)
    - If observed before or at screening: record as concomitant illness (section 8.2.2)

8.5.2.2 Haematology

Haematology samples are to be sampled and analysed locally at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa), 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

- Haemoglobin
- Erythrocytes (cell count)
- Thrombocytes (platelet count)

- Leucocytes (cell count)
- Differential leucocytes cell count
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils

The investigator must evaluate the results and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Haematology results are to be entered into the eCRF.

8.5.2.3 Biochemistry

Biochemistry samples are to be sampled and analysed centrally at all visits.

- Creatinine
- Albumin
- Bilirubin; total, direct, indirect
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma glutamyltransferase (GGT)
- Alkaline phosphatase
- C-reactive protein (CRP)

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

8.5.2.4 FVIII/FIX activity

FVIII/FIX activity is to be sampled and analysed centrally at visit 1, visit 9 and visit 16.

- FVIII activity level (IU/mL) or
- FIX activity level (IU/mL)

8.5.2.5 Coagulation parameters

Coagulation parameters will be performed centrally at all visits with the exception of visit 3 and visit 9.1 where the PT, APTT, and Fibrinogen will be performed locally.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa) at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (±10 min) and 12h (±20 min) and 24h (± 20 min) locally.

- Fibrinogen – centrally and locally
- Prothrombin time (incl. INR) (PT) centrally and locally
- D-dimer – only centrally
- Prothrombin fragment 1+2 – only centrally
- Activated partial thromboplastin time (APTT) – centrally and locally
- Antithrombin (AT) activity – only centrally

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Coagulation parameters analysed locally are to be entered into the eCRF.

8.5.2.6 FVIII/FIX inhibitors

FVIII/FIX inhibitor level will be measured by the Nijmegen method at visit 1, visit 9 and visit 16.

- FVIII inhibitors (BU) or
- FIX inhibitors (BU)

8.5.2.7 Anti-concizumab antibodies

Samples for the determination of anti-drug antibodies collected during the treatment period must be drawn at all visits and prior to administering concizumab at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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, CDR region or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a modified TFPI functionality assay (neutralising ADA assay). All antibody assays are validated according to international guidelines and recommendations.

The following analyses will be available:

- Anti-concizumab antibodies assay
- Specificity assay (Anti-concizumab antibodies cross reacting with IgG4 backbone, CDR region or S241P mutation)
- Anti-concizumab neutralising antibodies assay

The samples will be analysed in batches during the trial and results will be available to the data monitoring committee approximately every third month after the first patient has been dosed. Neutralising antibodies will be analysed and reported at the EOT. A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

Investigators will be notified in case their patient is shown to have developed neutralising antibodies against concizumab.

In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit. The ADA positive patients will be called for additional visits, e.g. every 4 to 6 weeks, for safety assessment and blood sampling for ADA and PD markers (free TFPI and Thrombin generation). The ADA positive patients will be followed no longer than one year after End-of-Trial.

Hypersensitivity

If suspicion of a hypersensitivity reaction occurs, patients should be instructed to contact the site staff as soon as possible for further guidance, see Section 12.1.5.

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 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 months post 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.

Results from the following additional tests will be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS database and included in the narratives, if measured.

Test to be performed in case of severe hypersensitivity

- Anti-concizumab IgE antibodies
- Anti-concizumab antibodies (additional to scheduled time points)

Additional testing may be performed if deemed relevant e.g.

- Anti-Host Cell Proteins (HCP) antibodies
- Anti-HCP IgE antibodies
- Basophil activation results
- Prick test/intra-dermal test
- Complement test results

Furthermore, it is recommended locally to test for

- Tryptase (total and/or mature tryptase)

8.5.2.8 Concizumab ELISA

Concizumab ELISA will be collected at all visits where patients are in treatment with concizumab. Samples will be collected pre-dose at visit 2 for concizumab arm and visit 9 for eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

At visit 3 for concizumab arm and visit 9.1 for eptacog alfa arm samples for concizumab ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

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 correlates 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.

8.5.2.9 FVII ELISA

FVII ELISA will be collected at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) pre-dose eptacog alfa (rFVIIa) and post-dose at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa (rFVIIa) administration.

FVII in plasma will be quantified using a validated enzyme-linked immunosorbent assay (ELISA). The FVII ELISA will detect the total sum of FVII in a sample, including endogenous FVII, eptacog alfa (rFVIIa) and FVII in complex with other molecules e.g. antithrombin. The ELISA has been validated for measuring FVII in human citrated plasma samples. Validation follows current guidelines for bioanalytical method validation. Bioanalytical data will be reported in a bioanalytical report.

8.5.2.10 Total TFPI

Total TFPI ELISA will be collected at all visits. Samples will be collected pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

The total TFPI level (free and concizumab bound) will be included as an exploratory biomarker assessment.

The assay is an ELISA, where TFPI is captured by a polyclonal anti-TFPI antibody, distanced from the binding site of concizumab; meaning that both free TFPI and concizumab bound TFPI will be captured. Detection will be obtained with a monoclonal antibody against TFPI, which does not bind to the concizumab epitope.

Data will be reported in ng/mL TFPI.

8.5.3 Human Biosamples

If patient permission is obtained plasma, serum and/or DNA for genotyping samples are to be taken for long term retention, see Section 2. The blood samples can be stored up to 15 years, for future potential exploratory purposes please refer to section 24.2.

Antibody samples storage and retention, see Section 24.2.1. The investigator is not able to review the results of antibody measurements in relation to AEs as these are analysed after LPLV. Plasma and serum is taken at visit 1 and 17. DNA for genotyping is only taken at visit 1.

8.6 Other assessments

8.6.1 Patient reported outcomes

A newly developed disease-specific electronic PRO (ePRO) the Hemophilia Treatment Experience Measure (Hemo-TEM) - is being validated in this trial. In order to assess the psychometric properties of Hemo-TEM, other questionnaires will be provided; see further appendix 1.

The following ePRO questionnaires will be used in the trial:

- Hemophilia Treatment Experience Measure (Hemo-TEM)
- Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®) [16]
- 36-Item Short Form Health Survey (SF-36v2) (4 week recall)[17]
- Patient's Global Impression of Change (PGI-C)
- Sheehan Disability Scale (SDS) [18]
- Treatment Satisfaction Questionnaire for Medication (TSQM, version II) [19] [20] [21]
- Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)[22]

The ePROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, VERITAS-PRN®)
- visit 2 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 3 (PGI-C, Hemo-TEM)
- visit 4 (PGI-C, Hemo-TEM)
- visit 5 (PGI-C, Hemo-TEM)
- visit 6 (PGI-C, Hemo-TEM)
- visit 7 (PGI-C, Hemo-TEM)
- visit 8 (PGI-C, Hemo-TEM)
- visit 9 (PGI-C, Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 10 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 16 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)

At visit 1: before any visit-related activities all patients should complete Hemo-TEM and VERITAS-PRN®.

At visit 2: before any visit-related activities all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 3-8: before any visit-related activities the patient should complete the PGI-C before the Hemo-Tem. These are the rules that apply:

- If the patient responds "1" to question 1 in the PGI-C, the patient should also complete the Hemo-TEM. In this case the patient should not fill in the PGI-C any more in the trial and the Hemo-TEM only again at visits 9, 10 and 16.
- If the patient responds "0" or "2" to question 1 in the PGI-C, the patient should not complete any other questionnaires at this visit, but should repeat the procedure at next visit.

Exception: Patients randomised to eptacog alfa (rFVIIa) on-demand should not complete the ePRO at visit 3 as this is a phone visit.

At visit 9 if the patient has responded "0" or "2" in the PGI-C at all previous visits, the patient should complete PGI-C. All patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 10 and 16 all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

The investigator must check the ePROs for potential AEs and SAEs. The completed ePROs should be transmitted at each visit to the PRO database by the Investigator.

8.6.2 Training

The patients must be trained in how to handle bleeding episodes and how to recognize the signs and symptoms of thrombosis. The training must be documented in the medical record.

8.6.2.1 Concizumab and NovoPen®4

Direction for use (DFUs) will be available as a hand out for patients at visit 2. Training in NovoPen®4 can start at screening (visit 1) and s.c administration of concizumab using the NovoPen®4 can start at the first dose at the trial site (visit 2). Patients must be instructed that injections are to be performed subcutaneously, not intravenously. Concizumab and NovoPen®4 will be dispensed to the patients at visit 2. Training must be performed at site until patients feel comfortable using the device or performing the treatment. The training must be documented in the medical records.

Detailed instructions can be found in the DFUs.

8.6.2.2 eptacog alfa (rFVIIa)

A direction for use (DFU) will be available as hand out for patients at visit 1. Training must be performed at site until patients feel comfortable performing the treatment. The training must be documented in the medical records.

The following should be emphasised for eptacog alfa (rFVIIa):

- eptacog alfa (rFVIIa) should be slowly injected intravenously over 2 to 5 minutes

Detailed instructions can be found in the DFU

8.6.2.3 eDiary

Training on the use of the eDiary can start at visit 1. The eDiary will be provided to the patients at visit 2.

Training must be repeated at the site until patients feel comfortable using the device. The training must be documented in the medical records.

During the home treatment period the patient must ensure that all home treatments of concizumab, details of bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes are captured in the eDiary as instructed and trained by investigator or delegated staff.

It will be the responsibility of the investigator or delegated staff to assess the eDiary data throughout the conduct of the trial and to ensure data entry compliance (timely entry, no duplicate data, no missing data etc.) and retraining if necessary.

For patients completing the trial or in case of withdrawal, the eDiary will be collected at the EOT.

8.6.3 Surgery

Minor surgery can be performed within this trial at the investigator's discretion according to local guidelines. Definition of minor surgery, see Section 5.1.1. Major surgery is not allowed, see exclusion criteria no 6.

For minor surgery the following should be recorded in the eCRF:

- Date, stop time and dose of preventive treatment with eptacog alfa (rFVIIa) before surgery, if this was deemed necessary by the investigator
- Indication for surgery
- Location of surgery
- Date of surgery
- Start and stop time of surgery

8.7 Patient 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.

8.8 Treatment compliance

Treatment compliance will be monitored and documented through timely review of eDiary data and drug accountability.

Concizumab will be administered at the trial site at visit 2 for the concizumab arm supervised by medically trained trial staff and administration at home can be initiated after visit 2 if the patient feels comfortable with the s.c. administration. Administration of eptacog alfa (rFVIIa) for bleeding episodes will be administered at the trial site by a medically trained trial staff or at home by the patient, see Section 8.3.1.

Drug accountability will be performed and will be used to assess patient compliance together with the patients' adherence to trial procedures.

Compliance check includes a cross check between records in EDC/eDiary (number of administrations and bleeding episodes) and the used/returned cartridges/vials.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the TMM.

The trial product, concizumab B, appears as clear to slightly opalescent and colourless to slightly yellow. The trial product must not be used if it contains visible particles or discoloration.

The reconstituted eptacog alfa (rFVIIa) solution appears clear and colourless. Do not use the reconstituted solution if it contains visible particles or if it is discoloured.

Trial products must not be dispensed to any person not included in the trial.

9.1 Trial products

The following trial products will be provided by Novo Nordisk, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
concizumab B (IMP)	100 mg/mL	Solution for injection	s.c. injection	3 mL cartridge
eptacog alfa (IMP [a] and NIMP [b])	5 mg/vial	Powder for solution for injection	i.v. injection	Vial
histidine 5 mL	N/A	Solvent for solution for injection	i.v. injection	prefilled syringe

[a] Investigational Medicinal Product (IMP) given as IMP for a single dose at visit 3 and 9.1.
[b] Non-Investigational Medicinal Product (NIMP) given as NIMP for bleeding episodes

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with the EMA directive on medical devices annex I [23] and similar national legislation. A description of how to use the device is given in the DFU.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13 [24], local regulations and trial requirements.

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 enrolment and randomisation.

The investigator must document that DFUs are given to the patient orally and in writing at the first dispensing visit (see Section 2).

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time [a]
concizumab B 100 mg/mL	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store at room temperature (below 30°C) Do not refrigerate Protect from light	Use within 4 weeks (28 days)
eptacog alfa 5mg	Store between 2°C-25°C Do not freeze Protect from light	For single use Do not freeze Protect from light To be used immediately after reconstitution	If not used immediately, store in refrigerator (2°C-8°C) for up to 3 hours
histidine 5 mL	Store between 2°C-25°C Do not freeze Protect from light	For single use	N/A

[a] In-use time for concizumab starts when first dose is administered from an individual cartridge and for eptacog alfa (rFVIIa) when the product is reconstituted

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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 must take appropriate action to ensure correct storage.

Investigator must instruct the patient to use and store trial product according to the label.

9.4 Drug accountability and destruction

Drug accountability of all trial products (concizumab and eptacog alfa (rFVIIa) received at site is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial product during the trial as instructed by the investigator, except for used histidine syringes which should be discarded at home and not accounted for. Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

All cartridges (concizumab) and vials (eptacog alfa (rFVIIa)) must be accounted for as used, partly used or unused.

The investigator will perform drug accountability using the IWRS Drug Accountability module.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial product including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Destruction of concizumab and eptacog alfa (rFVIIa) can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

For Japan only: Responsibility for storage and drug accountability of the trial drug product at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug product at the trial sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug product in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary supplies

Novo Nordisk will provide the auxiliaries for this trial:

- For concizumab administration: NovoPen®4, needles and DFUs
- For eptacog alfa (rFVIIa) reconstitution and administration: Trial Injection Kit and DFU

Only needles and trial injection kit provided by Novo Nordisk must be used for administration of trial product.

For further guidance please see the TMM.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

Randomisation will be handed by the IWRS.

All patients included in the screening period and eligible for the trial will enter the trial and be randomised at visit 2 in a 2:1 allocation to either concizumab prophylaxis arm or eptacog alfa (rFVIIa) on-demand arm.

11.2 Breaking of blinded codes

Not applicable for this trial.

12 Adverse events, and technical complaints

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality 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.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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
- Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia, injection site haematoma) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. All bleeding episodes and other findings related to underlying disease will be captured in the eCRF/eDiary.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the patient's daily activities
  - **Moderate** – marked symptoms, moderate interference with the patient's daily activities
  - **Severe** – considerable interference with the patient's daily activities; unacceptable
- **Causality**

Relationship between an AE and the relevant trial product(s):

- **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

- **Final 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 fatal outcome must be reported as an SAE
  - **Unknown** - This term is only applicable if the patient is lost to follow-up

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death
- A life-threatening [a] experience
- In-patient hospitalisation [b] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity [c]
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening [a] or require hospitalisation [b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE [d]

[a.] The term "life threatening" in the definition of SAE 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 was more severe.

[b.] The term "hospitalisation" is used when a patient:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a patient's ability to conduct normal life functions (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE 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 ALT or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug

  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- 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

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.5.1

12.1.5 Adverse events 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.

In this trial the following AEs require the completion of specific event forms in the eCRF:

- Injection site reaction, see Section 8.4.5.2
- Hypersensitivity type reactions, incl. anaphylactic reactions, see Section 8.4.5.2

Injection site reactions:
Any injection site reaction symptom must be recorded on the AE form and the injection site reaction form.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction are present, blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. In the event of an immediate systemic hypersensitivity reaction to the trial product, it is recommended to also test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary ~1 week after the immediate severe hypersensitivity reaction due to individual to individual variation in tryptase baseline concentration. Tryptase concentrations (if measured) must be interpreted and considered in the context of a complete workup of each patient.

Special 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 type 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 cases where there is a suspicion of hypersensitivity reaction that requires systemic treatment, additional sampling for the purpose of measuring ADA will be performed.

Definition of anaphylaxis [25]
Anaphylaxis is highly likely when **any one of the following 3 criteria** is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
    a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

- **Two or more of the following** that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours): Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP.

If a patient fulfils any of the three criteria of anaphylaxis outlined above, the patient should receive epinephrine/adrenalin immediately. Dose regimen should be according to hospital operating procedure, and the patient should be transferred to an emergency department or intensive care unit, if clinically warranted.

Events not fulfilling the criteria for an anaphylactic reaction and other allergic reactions must be treated at the discretion of the treating physician. If according to the investigators judgement, hypersensitivity type reactions that require systemic treatment are suspected, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

12.1.6 Adverse Events of special interest

An adverse event of special interest (AESI) is an event, which in the evaluation of safety, has a special focus. In this trial, the following AEs fulfil the AESI criteria:

- Thromboembolic events including but not limited to,
    - disseminated intravascular coagulation (DIC) (A),
    - clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction (B),
    - pulmonary embolism (C),
    - stroke (D),
    - deep vein thrombosis (E),
    - other clinically significant thromboembolic events (F) and peripheral artery occlusion (see below G), see definitions below

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

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 × 10^9/L = 0, <100 × 10^9/L = 1, <50 × 10^9/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) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction" [26]
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.

C) 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 [27].

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

D) 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" [28].

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:

- 1. pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
- 2. 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 [(29)].

E) 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 DVT in the lower extremities[27]. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

F) 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 is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

G) 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, 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 [30].

12.1.7 Technical complaints

A technical complaint is any written, electronic or oral communication that alledges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until the end of the post-treatment follow-up period (visit 17). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the patient must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or patient, must be reported by the investigator and evaluated. All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

AESIs regardless of the seriousness must be reported using the AE form and safety information form.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

- **Non-serious AEs fulfilling the AESI criteria:** The AE form and safety information form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

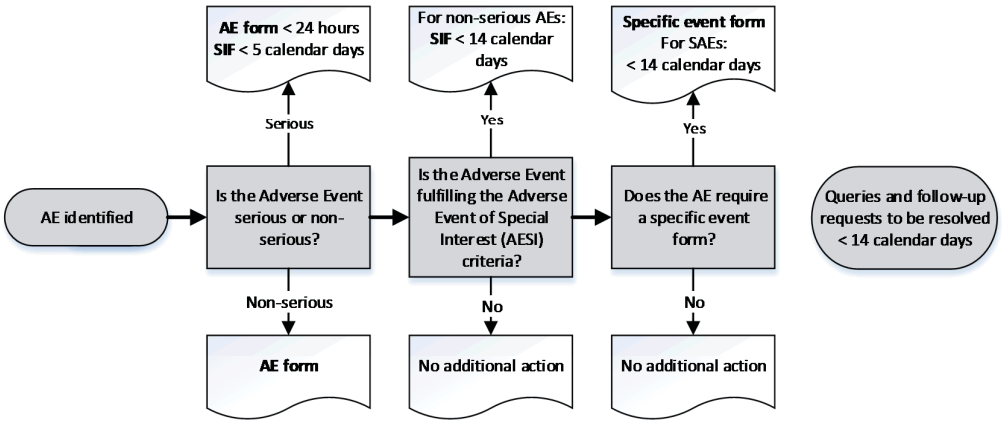

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto.

When eptacog alfa (rFVIIa), NovoSeven® is used as IMP, expectedness should be performed according to the Company Core Data Sheet (CCDS).

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP [1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP [1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (eptacog alfa (rFVIIa)) or 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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AEs fulfilling the AESI criteria:** Non-serious AE fulfilling the AESI criteria must be followed as specified for non-serious AEs. Follow-up information on AESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the AESI criteria.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a patient after the patient has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Concizumab B 100 mg/mL, solution for injection in a 3 mL cartridge
- NovoPen®4
- Novo Nordisk needles
- Eptacog alfa (rFVIIa) 5 mg/vial, powder for solution for injection in a vial
- Histidine 5 mL, solvent for solution for injection in a prefilled syringe
- Novo Nordisk trial injection kit

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, AESI and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

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 Centre, 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.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Centre, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female partners of male patients

Male patients must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period (from visit 1 to dosing with concizumab at visit 2 or visit 9 depending on the arm). At the last scheduled visit (visit 17), male patients must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male patient and assess if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the patient's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax.

1. **Reporting of pregnancy information**
   Information from the male patient has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

   Initial reporting and follow-up information must be reported within **14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

- Paper AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE

SAEs:

- Paper AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Dose limiting toxicities of concizumab have not been investigated in clinical trials.

There have been no reports about overdosing of concizumab and therefore no experience with overdose and overdose reactions exists. In case of a concizumab overdose, symptomatic medical treatment according to the clinical condition should be applied. No antidote exists in case of concizumab overdose.

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors.

Treatment should be as appropriate and in accordance with hospital practice and guidelines.

12.7 Rules for putting enrolment on hold

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee. A substantial amendment with relevant data must be submitted to the regulatory authorities to support restart of the trial.

- Significant thromboembolic event*
- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product
- Two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements
- Trends in AEs, clinical observations or laboratory parameters which raise concerns about the safety of continued treatment.

*Superficial thrombophlebitis or venous thrombosis associated with indwelling catheters is not considered a significant thromboembolic event unless evaluated as such by the investigator

12.8 Committees related to safety

12.8.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal concizumab safety committee to perform ongoing safety surveillance of safety data relevant to concizumab. The safety committee is a cross functional group within Novo Nordisk.

12.8.2 Data monitoring committee

The 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 in order to protect the safety

of the patients and to evaluate the benefit-risk balance. The DMC will have access to the data, and will provide recommendations on trial continuation, modification or termination.

In case there is any safety concern, data will be compiled and the DMC will review these data. Their recommendation will go to the Novo Nordisk Safety committee for final decision of what next step is in this trial.

The DMC members will only have direct contact with the Novo Nordisk Global Safety department through the safety surveillance representatives, and will have no direct interaction with those in trial management. The DMC recommendations should be addressed directly to the Novo Nordisk Global Safety department and the internal Novo Nordisk safety committee for concizumab. It is the responsibility of the Novo Nordisk internal safety committee for concizumab to take action(s) for patient safety based on the DMC recommendations.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms
- AE forms
- Safety information forms

The paper version of the technical complaint form, AE form, and safety information form must only be used to ensure timely reporting when/if the electronic CRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable)

indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

13.3 Electronic diary

Novo Nordisk will provide the patient with an eDiary for electronic recording of details of their home treatment, bleeding episodes and treatment of bleeding episodes (i.e. use of eptacog alfa (rFVIIa)).
The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

Patients will be instructed in the use of the eDiary by the investigator or delegated person before entering of any data. The eDiary will be dispensed to the patient at visit 2. After visit 2 and onwards, data will be entered by the patient in the eDiary device during home treatment.

The eDiary will be returned by the patient at the EOT visit.

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

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.

Investigator review of eDiary data

It is the responsibility of the Investigator or delegated staff to review the eDiary data reported by the patient. As a minimum it must be verified that the eDiary data is complete, consistent and according to the requirements defined in this protocol. This also includes that the number of doses reported in the eDiary is reviewed against the number of vials/cartridge accounted for as used by the patient. Upon review the Investigator must document that the review has taken place and any actions required e.g. retraining of the patient or decision to amend or correct the data reported by the patient.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. Monitoring visits should be scheduled as frequently as needed to support the first 6 patients recruited in the trial. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site. This only applies to sites with scheduled, ongoing and/or discontinued patients.

The monitor must be given direct access to all source 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 or text message).

All data must be verifiable in source documentation other than the eCRF. eDiary data is entered by the patient and will also be treated as source data.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

For historical data such as medical history, details of haemophilia and haemophilia treatment history, a reasonable effort must be made by the investigator, considering local requirements, to obtain this information from external sources, if not known by the patient. It is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document. This means that for laboratory results (e.g. biochemistry and haematology) a signed printout of the electronic results must be available.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The monitor will ensure that the eCRFs are completed and paper CRFs (if any) collected, that ePROs and eDiaries are completed and reviewed by the investigator at the relevant scheduled visits and needed action has been taken and documented, if any.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Inclusion and exclusion criteria
- Screen failure reason if possible
- Date patient left the trial
- Data relating to AEs if applicable
- Demography, see section 8.2.1
- Date of visit

Monitors will review the patient's medical records and other source data (e.g. the eDiaries and ePROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of patient data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide all laboratory reports to the investigator for filing at the trial site. The laboratory report must be signed and dated by the investigator or delegated person and stored at the trial site as source data.

The patient and any biological material obtained from the patient will be identified by patient number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

Novo Nordisk will use the Global Haemophilia Network Investigator Portal to distribute and share trial-related documents and information with the participating sites. After trial completion, Novo Nordisk will supply each trial site with long-life CDs or other relevant archiving containing the electronic Investigator Trial Master File (eITMF) for each trial site. These CDs or other relevant archiving will contain site-specific trial documentation as well as trial specific news and other relevant trial information, including audit trail on documents and site staff users. The GHN Portal software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1, 31]

Novo Nordisk will provide electronic tablets for reporting of all PROs questionnaires described in section 8.6.1 and in Appendix 1. In case the electronic tablet is revoked the questionnaires will be available in paper.

The eDiary and ePRO software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1], [31] After trial completion, each trial site will be supplied with long-life CDs. These CDs will contain site-specific patient records including the patient's eDiaries and audit trail including any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 15 years or as required by local data retention laws for trial data.

17 Statistical considerations

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Please refer to Figure 17–1 for further information.

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

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. Further, the endpoints will not include re-bleed. A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping, the treatment is defined as a new bleeding episode.

Clinical proof of concept

The statistical analysis of the collected data aims to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia patients with inhibitors. The objective will be assessed when the last of the 24 patients has completed 24 weeks of dosing (or has withdrawn before that).

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

The referred comparisons will be made using a negative binomial model with log of exposure time in main part as offset and regimen as factor (concizumab vs. on-demand). For each criterion, evidence of effect will be concluded if the 95% confidence interval of the treatment ratio is below 1.

Clinical arguments for the hierarchical test approach

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

17.1 Sample size calculation

The estimand will be defined as the "if all patients had adhered" estimand.

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

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

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

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm. It is expected that the treatment duration of the main part allowing for escalation time for some patients is on average 6 months in the below calculations.

When evaluating the power of the negative binomial analysis referred above, annual bleeding rates of 24 and 6 are assumed for the on-demand patients and the end dose concizumab regimen, respectively. Assuming further over-dispersion of 7, the power for concluding superiority of the concizumab regimen becomes approximately 80%. The power under varying values of true ABR and over-dispersion for the primary CPoC criterion are shown below in Table 17–1.

Table 17–1 Power in superiority comparison between concizumab prophylaxis and on-demand treatment under different assumptions of ABR for concizumab and over-dispersion (assuming on-demand ABR=24).

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

For the secondary CPoC criterion that includes data prior to potential dose escalation, it is expected that the treatment duration of the main part is on average 8 months with an average ABR of 7.6 for the concizumab regimen. This yields a marginal power of approximately 70% for the secondary CPoC criterion.

In prior Novo Nordisk trials conducted in haemophilia patients, the typical 1-year over-dispersion for non-inhibitor patients on prophylaxis with FVIII or FIX has been in the range 4-8, implying 24 weeks over-dispersion of 3-5 (e.g. in NN7008-3543, NN7088-3859 and NN7999-3747). In the NN7128-1907 trial in inhibitor patients, larger 1-year over-dispersion values of approximately 21 and 18, respectively, were observed during an initial 3-month on-demand period and a subsequent 3-month prophylaxis period. It is expected that the variation in the current trial will be smaller, partly due to the longer duration of the trial and partly due to an expected more homogenous patient population. Another published trial including inhibitor patients, comparing prophylaxis using FEIBA® with on-demand treatment, showed 6-month over-dispersion of 4-5 [32]. On that background, an over-dispersion of 7 over the 24 weeks in main part of the current trial is deemed realistic.

17.2 Definition of analysis sets

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

17.3 Primary endpoint

The primary endpoint is the number of bleeding episodes during at least 24 weeks from treatment onset.

The endpoint will be analysed when the main part of trial has been completed.

17.3.1 Estimand and primary statistical analysis

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

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

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

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time in main part as offset and regimen as factor, providing an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is "missing at random", i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

17.3.2 Sensitivity analysis

To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis will be performed where patients having discontinued before finalization of the main part are assumed to have a worse outcome compared to what was observed during the main part of the trial. This will be done by adding a value Δ to the observed bleeding episodes in the main part of the trial before analysing the data. The offset is maintained as being the exposure during the main part since it is not possible to identify the amount of missing observation time. The degree of worsening, $\Delta_{i,}$ will gradually be increased to evaluate at which point concizumab prophylaxis no longer is superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis will be considered robust if the tipping point is above what is considered clinically plausible.

17.3.3 Additional analysis

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

administration, peak thrombin generation (nM), Endogenous thrombin potential (nM^{x}min) and velocity index (nM/min).

17.4 Supportive secondary endpoints

17.4.1 Supportive secondary efficacy endpoints

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

The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset will be addressed in terms of the same estimand as for the primary endpoint. The estimand will be estimated using the same negative binomial regression model as for the primary endpoint.

Furthermore, an additional evaluation will be made, where actual concizumab dose is included as factors in the model.

The remaining supportive secondary efficacy endpoints will be summarised descriptively by treatment regimen. In addition, number of bleeding episodes during 76 weeks of treatment with prophylactic concizumab will be analysed using a negative binomial model with log of trial duration as offset, providing estimates of the ABR with confidence interval for that particular regimen.

17.4.2 Supportive secondary safety endpoints

- Number of TEAEs during at least 24 weeks from treatment onset
- Number of TEAEs during 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence rate of anti-concizumab antibodies during 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset
- Change from baseline of D-dimer during 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset

- Change from baseline of APTT during 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT 76 weeks from treatment onset

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

TEAE is defined as an event that has onset from the first exposure to treatment until the last visit in the trial. Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All adverse events will further be listed.

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

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

17.4.3 Supportive secondary pharmacokinetic endpoints

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

The pharmacokinetic endpoints will be summarised and listed.

17.4.4 Supportive secondary pharmacodynamic endpoints

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

The PD endpoints will be summarized and listed.

17.4.5 Exploratory endpoints

17.4.5.1 Exploratory safety endpoints

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

Adverse events related to technical complaints will be listed and summarised

17.4.5.2 Exploratory patient reported-outcome endpoints

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

VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

The PRO endpoints will be summarised using descriptive statistics and the remaining questionnaires (Hemo-TEM, PGI-C, SIAQ-ISRQ) will be summarised and listed using descriptive statistics.

17.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. Main part is defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual CTRs might in such case be issued. A CTR describing results from the main and the extension part will be written when the last patient has either completed or withdrawn from the trial. All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 17–1.

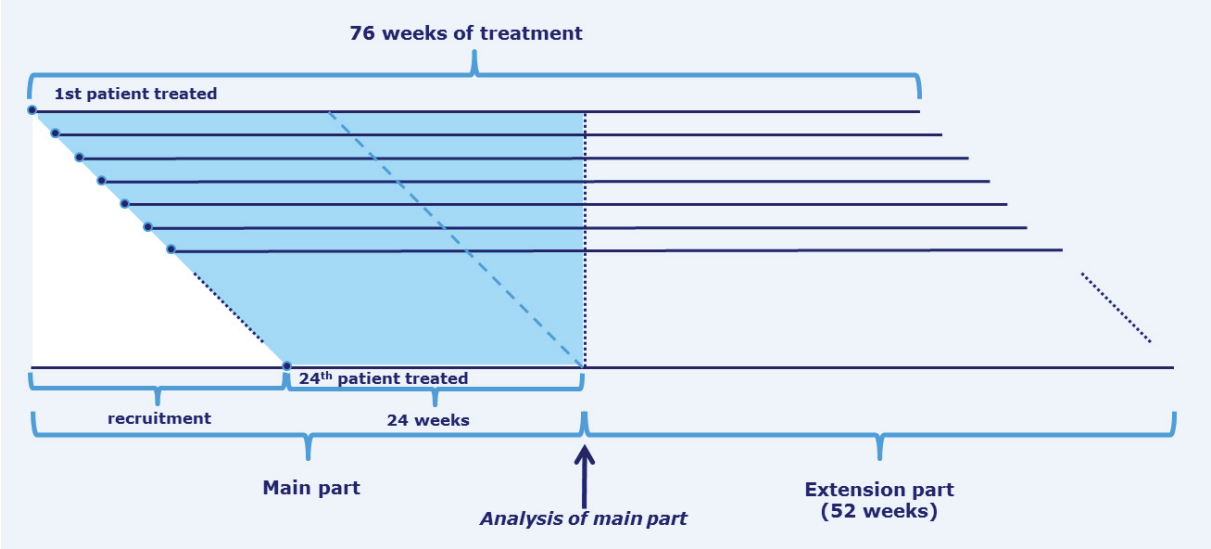

Figure 17–1 Definition of main and extension part

18 Ethics

18.1 Benefit-risk assessment of the trial

Benefits
Results from a multiple dose phase 1 trial where concizumab was dosed for approximately 6 weeks showed a trend towards efficacy in a limited number of patients who reached concizumab plasma concentrations above 100 ng/mL, see Section 3.1.2. Based on these results, it is expected that the majority of the patients randomised to the concizumab treatment with 0.15 mg/kg daily dose will be protected from bleeding episodes. Patients who experience excessive bleeding episodes on the lowest dose will have a possibility to be escalated to a higher dose where bleeding preventive efficacy of concizumab treatment is expected to improve. For haemophilia patients with inhibitors and who are treated on-demand, expected improved efficacy is considered to be a major benefit in participating in this trial. Also, concizumab is administered s.c. and might reduce the burden of frequent i.v. injections associated with current treatment options in haemophilia patients with inhibitors.

Information gained from this trial will contribute to gaining regulatory approval for a product that is anticipated to offer clinical advantages over currently available products.

Risks
No risks have been recognised as identified risks by review of safety data from the activities in the clinical development so far. However, the nonclinical toxicity studies have identified thromboembolic events as a potential risk when treating non-human primates with concizumab at high exposures.

As observed for other pro-coagulant compounds, there is a potential safety risk of thrombosis and vascular ischemia with reaching very high concizumab plasma concentrations. In non-clinical toxicity studies with concizumab, thrombi were observed at high doses. However, a no observed adverse effect level (NOAEL) for concizumab has been identified in non-haemophilic animals at plasma concentrations at least 24 fold higher than the currently anticipated effective plasma concentration (mean area under curve [AUC] and C_{max}) based on PK modelling.

In a drug–drug interaction study in monkeys, three doses of up to 1 mg/kg of NovoSeven® were administered at 2-h intervals, alone or in the presence of a steady state concentration of concizumab. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation. No notable clinical observations were made.

In clinical trials, except for one case of superficial thrombophlebitis in a healthy volunteer who received a single dose of 1mg/kg, no other thromboembolic events were observed. A phase 1

multiple dose trial was finalised in haemophilia A patients (0.8 mg/kg s.c. every 4 days for 6 weeks). In this clinical trial, marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range in patients with high plasma concentrations of concizumab. These changes were not judged as clinically significant by the investigators and were not followed by thromboembolic AEs or an increase in the number of bleeding episodes in the explorer™3 trial.

A potential risk identified in non-clinical studies is vascular vessel wall changes due to immune complex deposition causing localized vascular vessel wall changes such as hypertrophy and inflammatory cell infiltration. Concizumab is a foreign protein to animals and it is generally recognized that animal studies are limited in their ability to predict human immune responses to a therapeutic protein product. The concentrations of concizumab in plasma in animals in the non-clinical studies have reached levels far above the anticipated effective concentration. Humans are expected to have a very low immunogenic response towards a humanised mAb. The antibodies towards concizumab have not been observed so far in clinical trials. Furthermore, even if antibodies towards concizumab occur, the risk for the rate of immune complex formation exceeding the clearance capacity is considered low. Please refer to the Investigator's Brochure for further information.

If antibodies against concizumab develop, they might also inhibit the function of the administered drug. The consequence of this could be that the patient may not be able to benefit from the drug in the future. Antibody development against concizumab is not expected to reduce the effect of other treatment options.

Theoretical risks include bleeding due to consumption of coagulation factors and adverse reactions due to potentiation of inflammatory reactions or tissue damage due to impairment of tissue repair mechanisms[33 34]. TFPI is an important inhibitor of TF which, in addition to its role in haemostasis, is implicated in tissue repair processes and in a variety of physiological and pathophysiological states where repair mechanisms are activated. These include sepsis, DIC, inflammation, atherosclerosis, cancer and crush injuries[35 36, 37].

There may be a risk of allergic reactions, including severe (anaphylactic) reactions, in connection with concizumab administration. Severe allergic reactions may potentially be life-threatening and thus, the trial products will be administered to the trial patients at the site under the surveillance of medically trained trial site staff in the beginning of the trial.

Overall the anticipated benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki [2].

Before any trial-related activity, the investigator must give the patient verbal and written information about the trial and the procedures involved in a form that the patient can read and understand.

The patients must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the patient before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

Only applicable for Japan: As a minor is unable to provide legally binding consent, informed consent must be sought from the parent(s)/LAR(s) on the child's behalf prior to enrolling a child in the trial, according to local requirements.

18.3 Data handling

If the patient withdraws from the trial or is lost to follow up, then the patient's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to patients during 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided and protocol waivers are not acceptable under any circumstances.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances are likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated (potential serious breach) and if it should be reported to the Regulatory Authorities as a serious breach of GCP and/or the protocol.

In addition, 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.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The below process will be in place to prevent missing data in this trial.

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 is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. 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).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

An Investigator Portal (Global Haemophilia Network [GHN]) will be used as primary media for exchange and handling of investigator trial master file documents between Novo Nordisk and the site and for electronic storage of these documents during trial conduct.

Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- SmPC or similar labelling of eptacog alfa (rFVIIa)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- Description of research facility obtained (applicable for sites outside the US)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

For local laboratory parameters the following will be collected:

- Laboratory normal ranges
- Laboratory certification, QA scheme or similar documentation
- Laboratory assay methods (only non-standard assays) and/or analytical methods

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP [1] applicable regulatory requirements and the Declaration of Helsinki [2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 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.

At least investigator must be trained in the current protocol version at a Novo Nordisk Investigator meeting or by the most recent version of the web training. It is recommended that all site staff completes the web protocol training.

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 will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [38].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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 subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure how-we-disclose-trial-information.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. 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.

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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[38] (sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Patients' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

Only applicable for Spain: 25 years retention according to the Spanish Royal Decree 1090/2015.

The files from the trial site/institution must be retained for 15 years after EOT as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

This trial will involve collection of human biosamples at visit 1 (screening visit) and at visit 17 (EOT) and these samples are to be stored maximum 15 years from EOT. In addition, samples which have been drawn as back-up samples during the conduct of the trial and have not been analysed will be captured and stored under the same conditions.

Storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and

participate, while refusing permission for biological specimens to be stored for future exploratory analysis.

- Human biosamples will be stored at the central laboratory
- 1.0 mL citrated plasma, 1.2 mL serum and/or 2.0 mL whole blood (DNA for genotyping) will be obtained
- The intended use of the stored human biosamples e.g.: 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 human biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- Human biosamples may be transferred to third parties e.g. research consortia
- The human biosamples will be transferred and stored after the EOT at a designated central laboratory
- Confidentiality and personal data protection will be ensured during storage after the EOT
- The human biosamples may be transferred to other countries (not applicable if local regulations prohibit export of human biosamples)
- The human biosamples will be destroyed at the latest 15 years from EOT
- The patient may request the stored human biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used
- Novo Nordisk and laboratory will have access to the stored human biosamples
- Potential consequences for the patient and their relatives: In the event that the collected human biosamples (plasma, serum and/or DNA for genotyping) 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 human biosamples obtained from their own body, see Section 5.1.

24.2.1 Antibody samples

Antibody samples will be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

The retained antibody samples may be used 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 assays, and will not be reported in this trial. The samples will be stored at a central bio-repository after EOT and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from EOT after which they will be destroyed.

The patients' identity will remain confidential and the antibody samples will be identified only by patient number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Patients can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC (not applicable for Japan).

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the patients.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

26 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.

Novo Nordisk accepts liability in accordance with:

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. II Nr. 105/2015

Only applicable for 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 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 or the fault 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".

Only applicable for Poland: Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal pf Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigators are covered by the Insurance Policy issued according to applicable Polish law.

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Protocol

NN7415-4310

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

Trial phase: 2

Includes: Protocol Version 1 (15 March 2017); Protocol Amendment no 1 (05 May 2017) for all participating countries; Protocol Amendment no 2 (15 November 2017) and Protocol Amendment no 3 (21 August 2018) for all participating countries.

Protocol originator

[redacted], International Trial Manager
Biopharm Trial Ops 1

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List of abbreviations

ABI	ankle-brachial index
ABR	annualised bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under curve
BP	blood pressure
BU	Bethesda Unit
CCDS	company core data sheet
CLAE	clinical laboratory adverse event
C_{max}	maximum plasma concentration
CNS	central nervous system
concizumab B	the name concizumab is being used as an abbreviation for concizumab B. B is the formulation

CPoC	clinical proof of concept
CRF	case report form
CRO	contract research organisation
CRP	c-reactive protein
CT	computerized tomography
cTn	cardiac troponin
CTR	clinical trial report
DFU	direction for use
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
DRC	data request correction
DUN	dispensing unit number
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eITMF	electronic investigator trial master file
ELISA	enzyme-linked immunosorbent assay

EMA	european medicines agency
EOT	end of trial
ePRO	electronic patient reported outcome
eptacog alfa	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to rFVIIa,'NovoSeven®, and 'NiaStaseRT®'
ETP	endogenous thrombin potential
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	U.S. Food and Drug Administration Amendment Act
FIX	coagulation factor IX
FPFV	first patient first visit
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FVIII:C	plasma activity of factor VIII
FX	coagulation factor X
FX_a	activated coagulation factor X
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHN	global haemophilia network

HCP	host cell protein
Hemo-TEM	Hemophilia Treatment Experience Measure
IB	investigator's brochure
IC	informed consent
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	independent ethics committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
INN	International Non-Proprietary Names for Pharmaceutical Substances
IRB	institutional review board
ISRQ-SIAQ	Injection Site Reaction Questionnaire – Self-Injection Assessment Questionnaire
ISTH	International Society on Thrombosis and Haemostasis
IT	information technology
i.v.	intravenous(-ly)
IWRS	interactive web response system

LBBB	left bundle branch block
LPFV	last patient first visit
LPLV	last patient last visit
mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NIMP	non investigational medicinal product
PCD	primary completion date
PD	pharmacodynamics
PEF	peak expiratory flow
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome

PT	prothrombin time
Q	Inter compartmental clearance
QA	quality assurance
Q4D	every 4th day
eptacog alfa (rFVIIa)	the name 'eptacog alfa (rFVIIa)' will be used throughout the protocol and the product is identical to 'NovoSeven®'
sABR	spontaneous annualised bleeding rate
SAE	serious adverse event
SAS	safety analysis set
sBE	spontaneous bleeding episodes
s.c.	subcutaneous(-ly)
SDS	Sheehan Disability Scale
SF-36v2	36-Item Short Form Health Survey
SI	international system of units
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
TAT	thrombin-antithrombin complex
TEAE	treatment emergent adverse events
TIA	transient ischemic attack

TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	thrombin generation
TMM	trial materials manual
TSQM	Treatment Satisfaction Questionnaire for Medication
TVP	trial validation plan
UTN	Universal Trial Number
VERITAS-PRN®	Validated Hemophilia Regimen Treatment Adherence Scale

1 Summary

The main objective for the phase 2 trial NN7415-4310, explorer™4, is to assess the efficacy of concizumab administered s.c. once daily to prevent bleeding episodes in haemophilia A and B patients with inhibitors. Furthermore, this trial aims to assess the longer-term efficacy and safety of concizumab in haemophilia A and B patients with inhibitors and to establish the safety of treating breakthrough bleeding episodes with recombinant factor VIIa (rFVIIa) in these patients.

Objective(s) and endpoint(s)

Primary objective

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors.

Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

Primary endpoint

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

Key secondary endpoints

- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset
- Number of treatment emergent adverse events (TEAEs) during at least 24 weeks from treatment onset

Time frames for evaluation of Objectives/Endpoints

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of dosing treatment with trial product (or has withdrawn). The extension part of the trial will provide additional safety and long-term efficacy data.

Trial design

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. We expect 16 patients to complete treatment in concizumab arm (concizumab prophylaxis) and 8 patients in comparator arm (rFVIIa on demand). The dose regimen is selected based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

For all patients treated with concizumab (concizumab arm and comparator arm extention part) a loading dose of 0,5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0,15 mg/kg. All patients in treatment with concizumab will in a non-bleeding state receive a single dose of 90 µg/kg eptacog alfa (rFVIIa) one week after dosing with concizumab. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at the site after 24h.

The total trial duration for the individual patient will be approximately 86-130 weeks, consisting of a 2-4 week screening period, a subsequent 76-118 week treatment period and an 8-week follow-up period. eptacog alfa (rFVIIa) for treatment of bleeding episodes during the trial will be provided by Novo Nordisk. The patient will not be provided with trial product or eptacog alfa (rFVIIa) after end of trial.

The trial is split into a main part which lasts at least 24 weeks for all patients in the trial and an extension part which lasts up to 94 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed at least of 24 weeks of concizumab prophylaxis and 8 patients have completed 24 weeks of treatment with eptacog alfa (rFVIIa) on-demand or have withdrawn. The analysis of the main part of the trial aims to substantiate the clinical proof of concept (CPoC) that concizumab has the potential to prevent bleeding episodes in patients with haemophilia and inhibitors. The extension part of the trial will provide additional safety and long-term efficacy data.

Trial population

Number of patients planned to be screened: 28
Number of patients planned to be started on trial product: 26
Number of patients expected to complete the trial: 24

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 the suitability for the trial
- Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
- Patients currently in need of treatment with bypassing agents

Key exclusion criteria

- Known or suspected hypersensitivity to trial product(s) or related products
- Known inherited or acquired bleeding disorder other than haemophilia
- Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX

Key Efficacy assessment

- Number of bleeding episodes during at least 24 weeks of treatment onset

Key Safety assessment

- Number of treatment emergent adverse events during at least 24 weeks of treatment onset

Trial products

The following products will be used in the trial:

- **Investigational Medicinal Products:**
  - concizumab B, 100mg/mL to be administered s.c. with NovoPen®4 and needles
  - eptacog alfa (rFVIIa), 5mg /vial and histidine (solvent). Reconstituted eptacog alfa (rFVIIa) is for intravenous administration and used in the trial at visit 3 and 9.1 for all patients with the purpose of investigating the safety of administering eptacog alfa (rFVIIa) to haemophilia patients
- **Non Investigational Medicinal Product**:
  - eptacog alfa (rFVIIa) 5 mg /vial and histidine (solvent). Reconstituted eptacog alfa is for intravenous administration and used in this trial for treatment of bleeding episodes

2 Flow chart

2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a, b]						Treatment extension [b]											Follow-up
Visit number [c]	**1**	**2**	**3**	**4-5**	**6**	**7-8**	**9**	**9.1**[d]	**9.2**[d]	**10**	**10.1**[d]	**11**	**11.1**[d]	**12**	**13-14**	**15, 15.1, 15.2, 15.n**[w]	**16**	**Unscheduled** [e]	**17**[x]
Timing of visits (d) [f]	**14 - 28 d before visit 2**	**1**	**8**	**29-57**	**85**	**113-141**	**169**	**176**	**197**	**225**	**253**	**281**	**309**	**337**	**393-449**	**505-785**	**Up to 827**	**When applicable**	**Up to 883**
Visit window (d)	**14 - 28 d before visit 2**	**0**	**+1**	**±7**	**±7**	**±7**	**±7**	**+1**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**Not applicable**	**-7**
Treatment week (w)		**0**	**1w**	**Every 4w**	**12w**	**Every 4w**	**24w**	**25w**	**28w**	**32w**	**36w**	**40w**	**44w**	**48 w**	**Every 8w**	**Every 8w**	**Up to 118w**	**-**	**Up to 126w**
PATIENT RELATED INFO/ASSESSMENTS																			
Informed consent/ Long-term storage consent	●																		
In/exclusion criteria	●	●[g]																	
Demography	●																		
Concomitant illness/Medical history	●																		
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Details of Haemophilia/Haemophilia treatment and bleed history	●																		
Withdrawal criteria/ Criteria for premature discontinuation of trial product		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Randomisation (IWRS)		●																	
EFFICACY																			
Bleeding episodes [h, i]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Thrombin generation (central lab)	●	●[l]	●[j, k, l]	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●[l]	●	●
Free TFPI (central lab)	●	●[l]	●[k, l]	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●[l]	●	●
SAFETY																			
Physical examination	●	●	●[k]				●	●						●			●	●	●
Body measurements	●	●[m]	●[k, m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]		●[m]	●[m]
Vital signs	●	●[n]	●[k, n]	●	●	●	●[n]	●[n]	●	●	●	●	●	●	●	●	●	●	●
ECG	●																		
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

explorer™4 trial periods	Screening	Treatment main [a, b]						Treatment extension [b]											Follow-up
Visit number [c]	1	2	3	4-5	6	7-8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13-14	15, 15.1, 15.2, 15.n[w]	16	Unscheduled [e]	17[x]
Timing of visits (d) [f]	14 - 28 d before visit 2	1	8	29-57	85	113-141	169	176	197	225	253	281	309	337	393-449	505-785	Up to 827	When applicable	Up to 883
Visit window (d)	14 - 28 d before visit 2	0	+1	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	Every 4w	12w	Every 4w	24w	25w	28w	32w	36w	40w	44w	48 w	Every 8w	Every 8w	Up to 118w	-	Up to 126w
Injection site reaction		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Urinalysis (local lab)	●																		
Haematology (local lab)	●	●[l]	●[j, k, l]	●	●	●	●[l]	●[j]	●	●	●	●	●	●	●	●	●[l]	●	●
Biochemistry (central lab)	●	●[l]	●[k, l]	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●[l]	●	●
FVIII/ FIX activity (central lab)	●						●[l]										●[l]		
Coagulation parameters (central lab)	●	●[l]		●	●	●	●[l]		●	●	●	●	●	●	●	●	●[l]	●	●
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			●[j, k, l]					●[j]											
FVIII/FIX inhibitors (central lab)	●						●[l]										●[l]		
Anti-concizumab antibodies (ADA) (special lab) [o]	●	●[l]	●[k, l, p]	●[p]	●[p]	●[p]	●[l, p]	●	●	●	●	●	●	●	●	●	●[l]	●	●
Concizumab ELISA (special lab)		●[l]	●[j, k, l, p]	●[p]	●[p]	●[p]	●[l, p]	●[j]	●	●	●	●	●	●	●	●	●[l]	●	●
FVII ELISA (special lab)			●[j,k, l]					●[j]											
Total TFPI (special lab)	●	●[l]	●[k, l]	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●[l]	●	●
TRIAL MATERIAL																			
IWRS call	●	●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●		●[k]		●		●	●		●		●		●	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]				●[d, s]	●									●[s]	●	
Administration of trial product (eptacog alfa)			●[k, t]					●[t]											
Drug accountability (concizumab)			●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New dose of trial product [e, u]				●	●	●	●		●	●	●	●	●	●	●	●		●	
PRO questionnaires	●	●	●[k]	●	●	●	●			●						●[z]	● [aa]		
REMINDERS																			
Human biological specimen for storage (central lab)	●																		●

explorer™4 trial periods	Screening	Treatment main [a, b]						Treatment extension [b]											Follow-up
Visit number [c]	1	2	3	4-5	6	7-8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13-14	15, 15.1, 15.2, 15.n[w]	16	Unscheduled [e]	17[x]
Timing of visits (d) [f]	14 - 28 d before visit 2	1	8	29-57	85	113-141	169	176	197	225	253	281	309	337	393-449	505-785	Up to 827	When applicable	Up to 883
Visit window (d)	14 - 28 d before visit 2	0	+1	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	Every 4w	12w	Every 4w	24w	25w	28w	32w	36w	40w	44w	48 w	Every 8w	Every 8w	Up to 118w	-	Up to 126w
Handout ID card	●																		
Training [v]	●	●					●	●										●	
Compliance: eDiary			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of treatment																	●		
End of trial																	●[y]		●[y]

The cells marked in 'red' are only for the patients randomised to eptacog alfa (rFVIIa) arm.

2.2 Explanatory descriptions

Footer	Description
a	There is staggered recruitment for the 4 first patients in the trial on the concizumab arm.
b	Concizumab administration is performed at home except for visit 2 and visit 3 for patients randomised to concizumab and visit 9 and 9.1 for patients randomised to eptacog alfa. Sampling for Free TFPI, Anti-concizumab antibodies, Concizumab ELISA and Total TFPI are done prior to concizumab administration.
c	The duration of the visits will last according to patient's individual training need on concizumab administration, NovoPen® 4, eDiary training etc. Visit 3 and visit 9.1 have a PK session of 24 hours and a safety follow up visit the following day.
d	Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment.Visit 9.1 should be performed 7 days (+ 1 day) after visit 9.
e	For patients being dose escalated on concizumab a phone call is recommended 1 week after first dose of concizumab.
f	Daily dosing preferably at the same time in the morning.
g	Evaluation of the laboratory results obtained from samples taken at screening.
h	Bleeding episodes occurring between visit 1 and visit 2 or at site should be registered in the eCRF. All bleeding episodes except for severe occurring after visit 2 at home should be registered in the eDiary. Severe bleeding episodes must be registered in the eCRF.
i	Eptacog alfa will be given to treat breakthrough bleeding episodes.
j	Sampling time schedule for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.
k	ONLY for patients randomised to concizumab arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
l	At visit 2, visit 3, visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.
m	Only body weight should be measured.
n	Vital signs should be evaluated before and after trial drug administration at visit 2 and visit 3 for concizumab arm and at visit 9 and visit 9.1 for patients in eptacog alfa arm switching to concizumab treatment.
o	In case clinical signs of e.g. hypersensitivity reactions or immune related events are seen, additional samples for ADAs may be taken. All antibody samples from the affected patient will be analysed on an ongoing basis. If antibodies are detected, additional blood samples will be taken and stored for characterisation of the antibodies.
p	Blood sampling for anti-concizumab antibodies and concizumab ELISA testing should only be collected for patients on concizumab.
q	If needed dispensing of eptacog alfa, histidine, trial injection kits and Direction For Use (DFU).
r	First treatment dose of concizumab is a loading dose and will be administered at visit 2 for the concizumab arm and visit 9 for the eptacog arm.
s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g.,

	eptacog alfa, FEIBA®) for treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2.
t	Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
u	Patient treated with concizumab should be dose escalated at next scheduled visit if he experiences ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab. If the investigator judges that next scheduled visit is too late an unscheduled visit should be performed for dose escalation.
v	Home treatment training must take place at visit 2 at the latest and whenever needed afterwards. Patients randomised to eptacog alfa will be re-trained in NovoPen®4 and s.c. administration at visit 9 and 9.1. If necessary training can be performed as needed at other visits. The eDiary will be provided to the patients at visit 2 if the patient feels capable in s.c. administration and using the eDiary. Further the patients will be trained in recognition of signs/symptoms of thrombosis.
w	Only for patients randomised to on-demand arm.
x	Visit repeated every 8 week until patient either discontinues, completes extension or is enrolled into phase 3 programme
y	For patients continuing in a subsequent trial End of Trial must be completed at visit 16. For patients declining participation in the prolongation, End of Trial must be completed at visit 17, 8 weeks after End of Treatment.
z	PRO questionnaires should only be completed at 15.1 for patients continuing in the prolongation of the trial.
aa	PRO questionnaires should only be completed at visit 16 for patients not continuing in the prolongation of the trial

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, ICH GCP [1], applicable regulatory requirements, in accordance with the Declaration of Helsinki [2] and ISO 14155 [3].

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

The INN name of the active pharmaceutical ingredient is concizumab (synonyms used during early development are NNC0172-2021, anti-TFPI, NN7415 or mab2021). Throughout this document "concizumab" is used as the name of the trial drug.

3.1 Background information

3.1.1 Haemophilia

Haemophilia is an inherited bleeding disorder characterised by an increased bleeding tendency, typically in weight bearing joints. Haemophilia A is caused by a partial or complete deficiency of blood coagulation factor VIII (FVIII). In haemophilia B, it is factor IX (FIX) that is deficient. Inheritance is chromosome X-linked; therefore the disease mainly affects males. The incidence of haemophilia A and B on average is estimated to be about 1 in 5000 live male births [4]. According to the World Federation of Haemophilia global survey of 2014[5], about 178,500 persons are diagnosed with haemophilia worldwide. Of these, about 80% have haemophilia A.

Haemophilia is classified as "severe", "moderate" or "mild" according to the plasma activity level of the affected coagulation factor [6]. 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 [7]. The haemostatic plug, if formed, in these patients 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 occurs spontaneously and is the most frequent symptoms 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 majority of children with severe haemophilia experience their first bleeding episode into a joint prior to age 4 year. Many children also bleed from other body sites before this age is reached [8]. For this reason, primary prophylaxis with regular FVIII or FIX injections in the non-bleeding state is the recommended treatment from early childhood.

In patients who have developed inhibitors towards FVIII or FIX, replacement therapy is rendered ineffective. Though prevalence studies and registry data indicate that the prevalence of inhibitors in the haemophiliac population overall has been reported to be between 5% and 7% [9], the prevalence

amongst patients with severe haemophilia (FVIII:C < 1%) is higher and has been reported to be up to 30% [9, 10]. These patients may be treated with bypassing agents, activated FVII (NovoSeven®) and activated prothrombin complex concentrate (FEIBA®) given as i.v. injections.

Current treatment options in haemophilia, replacement therapy or bypassing therapy, are hampered by the fact that these products must be given as i.v. injections. Furthermore, bypassing agents are characterized by relatively short half-lives, therefore prophylactic treatment is burdensome. It is also generally acknowledged that the efficacy profile of bypassing agents is inferior to replacement therapy. Consequently, delayed or sub-optimal treatment occurs in a significant number of patients with inhibitors. A new therapeutic agent that can be administered subcutaneously will represent a major improvement in the treatment of these patients in a prophylaxis setting.

3.1.2 Concizumab

The trial product, concizumab, is a humanised recombinant monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) isotype with a molecular weight of 149 kilo Dalton's. Like other antibodies, concizumab is composed of two light chains and two heavy chains linked together by disulfide bridges. To prevent formation of half-antibodies, the serine at position 241 in the heavy chain has been replaced with a proline (S241P (Kabat annotation)) [10]. The mechanism of action of concizumab is based on the concept of inhibiting the activity of a natural coagulation inhibitor, tissue factor pathway inhibitor (TFPI). TFPI is a potent inhibitor of the initiation phase of the coagulation process, i.e. the activation of (FX) to FXa by the tissue factor (TF)/factor VIIa (FVIIa) complex. TFPI first binds to and inhibits activated FXa and subsequently binds to and inhibits the TF/FVIIa complex, forming a TF/FVIIa/FXa/TFPI complex. Thus, concizumab prevents both inhibition of FXa and inhibition of FVIIa/TF by TFPI. In this manner, sufficient amounts of FXa to ensure effective haemostasis in the absence of a functional activated factor IX/activated factor VIII (FIXa/ FVIIIa) complex may be generated. This is a new concept that remains to be documented safe and efficacious in patients with haemophilia. More information about the physiological role of TFPI and the mode of action of concizumab is provided in the Investigator's Brochure.

Key differentiators of this new mode of action (MoA) and the key benefit of concizumab in patients with severe haemophilia A and B with inhibitors is reduced treatment burden due to subcutaneous administration potentially leading to better adherence, more patients on prophylactic treatment and ultimately better outcome.

Four clinical trials with concizumab have been completed thus far: the first human-dose trial (NN7415-3813, explorer™1) [11], a single dose trial in Japanese healthy subjects (NN7415-3981), two multiple dose trials (NN7415-3986, explorer™2) and (NN7415-4159, explorer™3). When the first cohort with 4 (four) healthy subjects in explorer™2 was completed, prior to the initiation of the 2nd cohort, the trial was halted, due to findings related to thrombosis in an ongoing 26-week toxicity study in primates. In this trial animal had concizumab plasma concentrations several hundred fold

above clinically relevant concentrations. Follow up investigations confirmed that the animal's condition was related to thrombosis in the lungs caused by exaggerated pharmacology at these high plasma concentrations. Before the initiation of the fourth phase 1 trial (NN7415-4159), explorer™3, a new 52 week non-clinical toxicology study was conducted in primates to investigate the findings in the previous study. The conclusion from this new non-clinical study was that the results from non-clinical studies support further clinical development of concizumab. Explorer™3 was a multiple dose clinical trial which aimed to investigate the safety, pharmacokinetics and pharmacodynamics of concizumab at five different dose levels in adult severe haemophilia A patients without inhibitors. In this trial multiple doses of concizumab were administered s.c. over a period of six weeks.

The explorer™3 trial was finalised following the completion of cohort 3 (0.8 mg/kg s.c. every 4 days for 6 weeks). Blinded preliminary safety and PK/PD data from the cohort was reviewed by the concizumab safety committee. Marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range. In addition, a substantial inter subject variation in pro-coagulant response to the drug was observed. Based on this, the Novo Nordisk safety committee (see Section 12.8.1) decided not to proceed to cohort 4 (1.1 mg/kg s.c. every 4 days for 6 weeks). No clinical consequences or serious adverse events were seen in the completed cohorts in explorer™3.

The PK results from explorer™3 showed exposure-response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL. Individual predicted PK profiles merged with recorded spontaneous and traumatic bleeding episodes are shown in Figure 3–1.

Figure 3–1 Individual predicted PK profiles based on data merged with recorded spontaneous (circles) and traumatic (triangles) bleeding episodes during the dosing period and follow-up period. All data originates from explorer™3 (N=24 patients). PK of concizumab is subdivided into three exposure levels of ≤ 20 ng/mL, 20-100 ng/mL, and > 100 ng/mL together with the number of contributing patients. LLOQ: lower limit of quantification.

[a] 'Time in trial' refers to the time that the patients spent on each concizumab exposure level, and the ≤ 20 ng/mL level therefore also includes the screening period (not shown on this figure).

A large difference between the peak and trough plasma concentrations of concizumab were observed as well, especially in the highest dose group (0.80 mg/kg) of explorer™3. In patients who received 0.25, 0.5 and 0.8 mg/kg doses a significant overlap in plasma concentrations of concizumab was seen due to high between-patient variability in concizumab.

Single doses of concizumab up to 9 mg/kg have been administered to haemophilia patients in the first human dose trial with concizumab, explorer™1. These doses resulted in plasma concentrations of concizumab that were significantly higher than the ones that are modelled to be reached in the highest escalated daily dose (0.25 mg/kg) of explorer™4.

In a drug–drug interaction study in monkeys (NN215431), three doses of up to 1 mg/kg of NovoSeven® were administered at 2h intervals, alone or in the presence of a steady state concentration of concizumab. No notable clinical observations were made, no treatment-related

adverse findings were seen, i.e. no thrombi or other signs of excessive coagulation. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation.

For an assessment of benefits and risks of the trial, see Section 18.1.

For further information, please refer to the Investigator's Brochure.

3.2 Rationale for the trial

Four phase 1 clinical studies with concizumab have been finalised. Key safety and preliminary efficacy results from these phase 1 studies support further development of concizumab in haemophilia patients. Therefore, the main objective in the phase 2 of concizumab development is to assess efficacy and safety and provide data that will guide for the confirmatory phase 3 concizumab trials.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

4.1.1 Primary objective

To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors

4.1.2 Secondary objectives

- To assess the longer-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors

4.2 Endpoint(s)

4.2.1 Primary endpoint

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

4.2.2 Secondary endpoints

4.2.2.1 Supportive secondary endpoints

Supportive secondary efficacy endpoints

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

Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from treatment onset
- Number of TEAEs during at least 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence of anti-concizumab antibodies during at least 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during at least 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset

- Change from baseline of D-dimer during at least 76 weeks from treatment onset
- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during at least 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during at least 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset
- Change from baseline of APTT during at least 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT after at least 76 weeks from treatment onset

Supportive secondary pharmacokinetic endpoints

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

Supportive secondary pharmacodynamic endpoints

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

4.2.3 Exploratory endpoints

4.2.3.1 Exploratory safety endpoints

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

4.2.3.2 Exploratory patient reported outcome endpoints

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

All endpoints referring to a time frame of either 24 weeks, or of at least 24 weeks, will be evaluated in the main part of the trial.

All endpoints referring to a time frame of at least 76 weeks will be evaluated in the extension part of the trial.

5 Trial design

5.1 Type of trial

The trial is a multi-centre, randomised (2:1), open-label, controlled trial, aiming to evaluate the efficacy and safety of concizumab 0.15 mg/kg (with potential dose escalation) administered daily s.c. in haemophilia patients with inhibitors. The selected dose regimen is based on relevant PK and TFPI data as well as PK/PD modelling of the results from the preceding explorer™ trials. Only on-demand patients will be eligible for the trial.

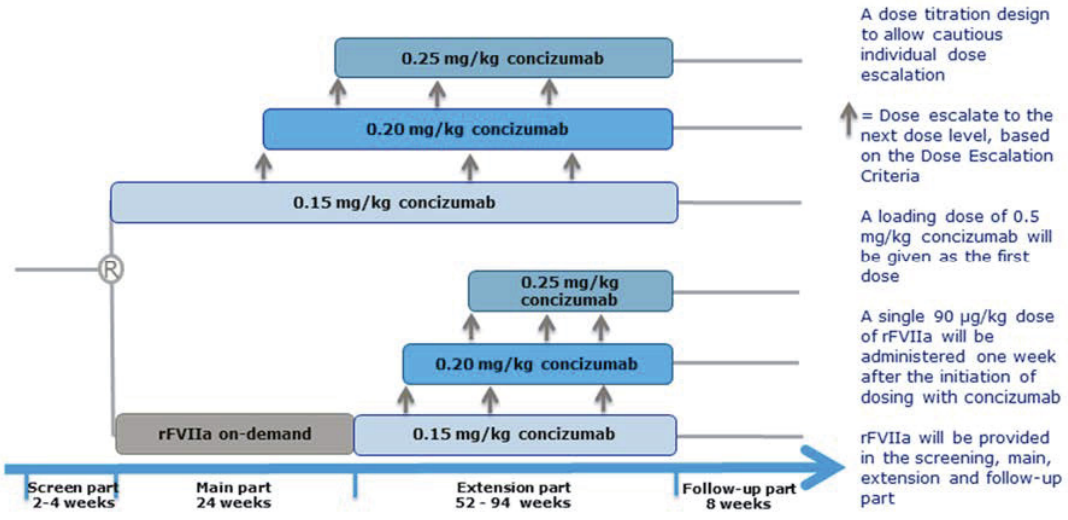


Figure 5–1 Schematic diagram of the trial design

The total trial duration for the individual patient will be approximately 86-130 weeks, including a 2-4 week screening period, a 76-118 week treatment period, and a follow-up period of 8 weeks, see Figure 5–1

The trial is split into a main part which lasts at least 24 weeks for all patients in the trial and an extension part which lasts up to 94 weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn.

In the concizumab arm bleeding episodes occurring during the trial will be treated with eptacog alfa (rFVIIa). In all patients treated with concizumab a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state one week after dosing with concizumab has been

initiated. The investigator will evaluate if there are any safety concerns 24 hours post eptacog alfa (rFVIIa) administration. Furthermore, the scheduled administration of eptacog alfa (rFVIIa) for the first 4 patients entering the trial with concizumab will be staggered.

In the comparator arm, in the main part, patients will receive eptacog alfa (rFVIIa) on-demand treatment. After completion of the main part, the patients will continue the trial in the extension part being treated with prophylactic concizumab 0.15 mg/kg (with potential dose escalation) s.c. daily administration.

Human biosamples (plasma, serum, and/or DNA for genotyping) will be collected in this trial for future exploratory analysis to pursue a deeper insight into the biology of TFPI, coagulation, and effect of concizumab on joint health. That may include coagulation parameters and markers of joint status and damage. Acceptance of storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for human biosamples to be stored for future exploratory analysis, see Section 8.1.1.

An independent data monitoring committee (DMC) will be established for this trial. The DMC will review all safety data from the ongoing trial with concizumab exposure, see Section 12.8.2.

5.1.1 Surgery

Minor surgery is allowed in this trial. Major surgery conducted earlier than one month (30 days) prior to trial start is allowed, see exclusion criteria no 6.

Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. Examples of minor surgery include implanting of central venous access devices (ports, CVC, pumps and other CVADs) in subcutaneous tissue, skin biopsies or simple dental procedures.

5.2 Rationale for trial design

Explorer™4 is a phase 2, clinical proof of concept (CPoC), and safety trial. The trial aims to substantiate CPoC that concizumab has the potential to prevent bleeding episodes in haemophilia patients with inhibitors. A dose escalation design will allow cautious dose escalation in order to identify an efficacious and safe concizumab dose for the individual patient. A comparator arm is included to assess if concizumab is superior to on-demand treatment. Furthermore, the trial will give a possibility to assess safety of co-administration of eptacog alfa (rFVIIa) to the patients exposed to the concizumab treatment.

The duration of at least 24 weeks for the main part of the trial is deemed necessary in order to obtain information on the annualised bleeding rate on concizumab prophylaxis. The duration of the extension part of the trial will be up to 94 weeks and provide further information on efficacy, i.e.

annualised bleeding rate, and also provide additional safety data upon 76-118 weeks treatment with concizumab.

Patients participating in NN7415-4310 will be offered screening for eligibility to participate in the subsequent clinical trials for concizumab, following their participation in NN7415-4310 and provided that either the site participates in the subsequent trial with concizumab or if possible the patient can be transferred to a participating site. It is expected that the majority of the participating patients will join subsequent trial and thus may continue prophylactic treatment with concizumab.

A total of 26 patients previously on-demand (OD) treatment will be randomised into one of the two arms, with 16 patients in the concizumab arm and 8 patients in the comparator arm see Figure 5–1. Concizumab will be administered s.c. daily for patients randomised to the concizumab arm in the main and the extension part of the trial. For patients in the comparator arm in the extension part treatment will be changed from on-demand with rFVIIa to prophylaxis with concizumab.

The concizumab dose regimens will be starting with 0.15 mg/kg with the possibility to escalate to 0.20 mg/kg and 0.25 mg/kg based on bleeding frequency, see Section 5.3.3.

Daily dosing with concizumab 0.15 mg/kg aims to ensure steady-state levels of concizumab plasma concentrations above 100 ng/mL for the majority of the patients starting on this dose. The PK results from explorer™3 showed exposure response in terms of fewer bleeding episodes recorded for patients who reached plasma concentrations of concizumab above 100 ng/mL, see Figure 3–1 . The minority of patients which are predicted to have steady-state plasma concentrations below this threshold are expected to experience bleeding episodes and therefore will have the opportunity to be dose escalated to the dose of 0.2 mg/kg. A further dose escalation to 0.25 mg/kg per day is permitted, again based on the bleeding rate, see Section 5.3.3.

Figure 5–2 Individual predicted concizumab concentration profiles for all concizumab-treated patients in explorer™2 (n=4 patients) and explorer™3 (n=18 patients). The horizontal lines indicate 100 ng/mL, and the shaded areas represent the full range (min-max) of the individual predicted profiles.[1]

Due to the high between patient variability in concizumab concentration observed in explorer™3, a significant overlap in plasma concentrations of concizumab in patients who received 0.25, 0.5 and 0.8 mg/kg doses was seen, see Figure 5–2. Therefore, choosing three doses that would lead to reasonably distinct mean plasma concentrations of concizumab, and thus different efficacy at each

[1] Plasma concentrations in the same range as those in explorer™3 are expected to be reached in this trial with daily dose administration. The starting dose for all patients will be 0.15 mg/kg daily. The plasma steady-state exposure for a typical subject at this dose level is predicted to fourfold lower compared to a typical subject on 0.8 mg/kg Q4D (cohort 3 of explorer3) in terms of both Cmax and AUC 0-24h. For 0.20 mg/kg daily and 0.25 mg/kg, the plasma steady-state exposure levels for a typical subject are predicted to be less than 40% and 70% respectively, compared to the typical subject exposure in the 3rd cohort of explorer™3 (AUC and Cmax). The maximum predicted plasma exposure levels (Cmax and AUC 0-24h) for the 0.15 mg/kg daily dose level is predicted to be more than 8 fold lower than for 0.80 mg/kg Q4D. For 0.20 mg/kg daily both Cmax and AUC 0-24h are predicted to be more than 3 times lower than for 0.80 mg/kg Q4D. For 0.25 mg/kg daily, the maximum Cmax and AUC 0-24h are predicted to be 35% lower than for 0.80 mg/kg Q4D.

dose level was not deemed possible. For this reason, a traditional parallel arm design was not chosen for the phase 2 trials. In contrast, the titration trial design allows patients to start on a low dose, which is expected to ensure prophylaxis but not marked changes in coagulation parameters, for the majority of patients. Escalation to the next dose level will only occur in the case of lack of efficacy (≥ 3 spontaneous bleeding episodes within the preceding 12 weeks). In addition, the PK of concizumab is heavily influenced by target mediated drug disposition, which means that small differences in concizumab dose ultimately leads to large differences in plasma concentrations. Therefore, daily dosing is proposed for the phase 2 trial, explorer™4. Daily dosing will allow for the increase in trough levels and thus better efficacy may be expected with a lower dose.

A loading dose of 0.5 mg/kg concizumab will be given as the first dose, followed by one week of concizumab dosing 0.15 mg/kg in order to ensure steady-state levels at the time of eptacog alfa (rFVIIa) administration. eptacog alfa (rFVIIa) will be administered one week after initiation of dosing with concizumab in a non-bleeding state to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment.

Embryonic exposure in pregnant female partners of men treated with concizumab is highly unlikely and there is no need for protocol requirements for use of contraception in phase 2 and 3 trials.

5.3 Treatment of patients

The following products will be administered in the trial.

Table 5–1 List of products provided by Novo Nordisk

Compound Name	Strength	Dosage form	Route of administration	Treatment period
concizumab B [a]	100 mg/mL	solution for s.c. injection in a 3 mL cartridge [b]	Subcutaneous administration using NovoPen®4	For prophylactic treatment for at least 76 weeks (for concizumab arm in the main part and extension part). For prophylactic treatment for at least 52 weeks (for comparator arm in the extension part).
eptacog alfa (rFVIIa) [a, c]	5 mg/vial	Powder for solution for i.v. injection	Intravenous administration	For treatment of breakthrough bleeding episodes at the discretion of the

histidine solvent (5 mL)		Prefilled syringes for solution for i.v. injection		investigator (screening, main, extension and follow up part). [c] Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. For on-demand treatment at the discretion of the investigator in 24 weeks for comparator arm in the main part. In the concizumab arm and comparator arm after switching to concizumab in the extension part of the study a single 90µg/kg dose for initial safety assessments in a non-bleeding state. [a] Will be provided for as long as patients participate in the trial (screening, main, extension and follow up part)

[a] Investigational medicinal product (IMP)
[b] Not to be confused with the daily injected volume (~150 µL, depending on dose strength and body weight)
[c] Non-investigational medicinal product (NIMP)

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with national legislation and a copy of the label can be found in the Trial Materials Manual, see Section 9.

5.3.1 Concizumab arm

5.3.1.1 Concizumab prophylactic treatment (main and extension part)

Concizumab will be given s.c. once daily 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg). The dose escalation criteria are described, see Section 5.3.3. The first dose of concizumab will be given at the trial site under medical supervision.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 2 in order to ensure steady state levels at the time of the administration of eptacog alfa (rFVIIa) in a non-bleeding state at visit 3, see Section 5.3.4.

The patients will be trained in s.c. administration of concizumab with NovoPen®4 at the screening visit and at the first scheduled treatment visit.

5.3.2 Comparator arm (eptacog alfa (rFVIIa))

5.3.2.1 On-demand treatment (main part)

During the main part of the trial, patients will receive eptacog alfa (rFVIIa) for treatment of bleeding episodes, with a dose regimen at the discretion of the investigator.

5.3.2.2 Concizumab prophylactic treatment (extension part)

After completion of the main part, the patients will continue the trial in the extension part and will switch to prophylactic treatment with s.c. daily administration of concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) s.c. daily administration.

The same dose escalation criteria as described below (for the initial concizumab arm) will apply.

A loading dose of 0.5 mg/kg will be given as the first concizumab dose at visit 9 in order to ensure steady state levels at the time of the administration of rFVIIa in a non-bleeding state at visit 9.1.

5.3.3 Dose escalation

The dose escalation criteria as described below will apply to all treatment arms.

Bleeding episodes will be assessed during the trial both at scheduled visit and also between visits. The first 2 weeks of the treatment with concizumab 0.15 mg/kg is considered as a run-in period. Hence, bleeding episodes occurring during first 2 weeks should not influence a dose escalation decision.

All spontaneous bleeding episodes (sBEs) are counted from 2 weeks after visit 2 (or visit 9 when switching from eptacog alfa (rFVIIa) to concizumab) (first treatment visit) until visit 16 (end of treatment visit), i.e. a total of up to 116 weeks. Dose escalation will be based on the number of spontaneous treated bleeding episodes in patients within preceding 12 weeks. However, before dose escalation can occur, to ensure the safety of the patients, the investigator must take into account the full clinical picture the patient is presenting with and all available laboratory results, including coagulation parameters.

Dose 0.15 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE). If yes, and if investigator deems it safe, the patient will be dose escalated from 0.15 to 0.20 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.20 mg/kg:
When sBE occurs, the investigator will determine if ≥3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.20 mg/kg treatment period. If yes, and if investigator deems it safe, the patient will be dose escalated from 0.20 to 0.25 mg/kg at the next scheduled visit. If the investigator judges that this visit is scheduled too late, he/she should contact the patient for an unscheduled visit sooner.

Dose 0.25 mg/kg:
Patients are not dose escalated further regardless of the number of sBEs. When an sBE occurs, the investigator will determine if ≥ 3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.25 mg/kg treatment period. If yes, then the patient must be discontinued due to lack of efficacy, see Section 6.4.

The possibility of dose escalation at unscheduled visits is necessary in order to avoid bleeding episodes at inadequate dose level: e.g. if the dose escalation eliciting bleeding episode occurs soon after a scheduled visit, the patient will avoid to wait 8 weeks for the next scheduled visit (in the extension part).

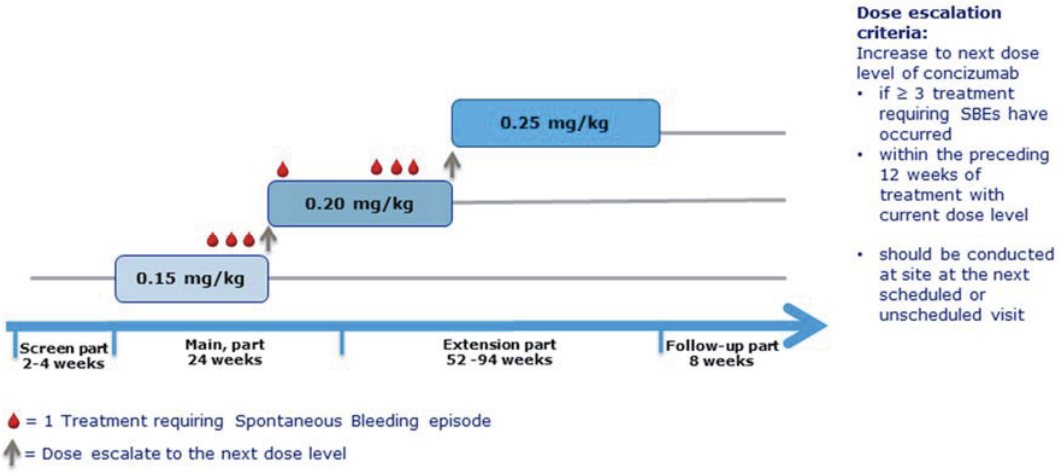


Figure 5–3 Dose escalation for one individual patient in the concizumab arm

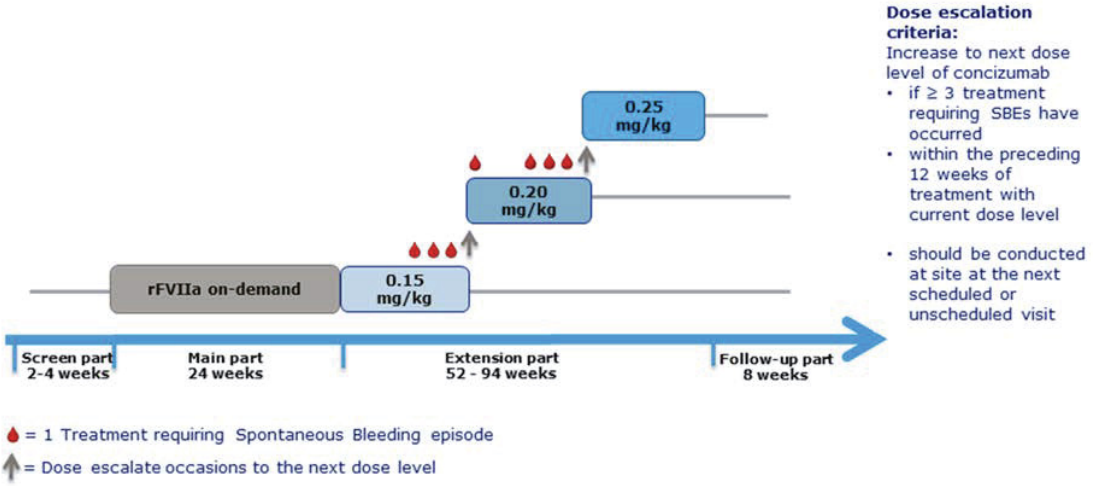


Figure 5–4 Dose escalation for one individual patient in the comparator arm

5.3.4 Co-administration of eptacog alfa (rFVIIa)

eptacog alfa (rFVIIa) will be used for treating breakthrough bleeding episodes in this trial; one week after initiation of dosing with concizumab, a single 90 µg/kg dose of eptacog alfa (rFVIIa) will be administered in a non-bleeding state at the trial site under medical supervision to assess safety of treatment with eptacog alfa (rFVIIa) in patients exposed to concizumab treatment. Hereafter, patients will be closely clinically observed at the site for potential safety issues for at least 12h and evaluated again at site after 24h. Between 12h and 24h, the patient must either stay at the site or at a hotel or at home if he lives nearby to be able to continue visit 3 or 9.1 the day after. Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to concizumab arm will be staggered so that the period between eptacog alfa (rFVIIa) administrations from one patient to another is at least 48 hours. If no safety concerns are observed (for example signs and symptoms of thromboembolism, such as swelling, pain and redness of the leg, shortness of breath, and chest pain) by the investigator in the period between the administration of eptacog alfa (rFVIIa) and when the next daily concizumab dose is to be given, the investigator allows the individual patient to administer concizumab prophylactically at home and if needed, treat breakthrough bleeding episodes at home with eptacog alfa (rFVIIa). The patients will receive prophylactic doses of concizumab 0.15 mg/kg daily throughout the main part (at least 24 weeks) and the extension part (up to 94 weeks), unless dose escalation criteria are fulfilled, see Section 5.3.3.

In case safety concerns are raised by an investigator after eptacog alfa (rFVIIa) administration and these concerns meet the described criteria for putting enrolment of additional patients on hold, dosing in the individual patients will be halted and further recruitment in the trial will be halted, see Section 12.7. In case safety concerns that do not meet the criteria for putting enrolment of additional patients on hold are observed by the investigator, dosing in that individual patient will be halted

until further evaluation. In such cases, all available data will be assessed by the Data Monitoring Committee (DMC), see Section 12.8.2.

5.3.5 Treatment of bleeding episodes during the trial

Breakthrough bleeding episodes between visit 1 and visit 2 can be treated with any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) up to a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to first concizumab administration at visit 2. Novo Nordisk will provide eptacog alfa (rFVIIa) throughout the trial. The patient can treat himself and then he must call the site. The bleeding episode must be recorded in the eCRF.

Breakthrough bleeding episodes between visit 2-3 in the concizumab arm and visit 9-9.1 in the comparator arm must be treated with eptacog alfa (rFVIIa). Upon breakthrough bleeding episodes in this period the patient must first call the site. The investigator should instruct the patient about whether he should go to the site to receive treatment or if he can administer a single dose of eptacog alfa (rFVIIa) which is not higher than 90µg/kg without delay to treat the breakthrough bleeding episode. If the patient is instructed to administer the eptacog alfa (rFVIIa) dose at home, following the administration, the patient should immediately go to the site for further clinical evaluation. The bleeding episode must be recorded in the electronic Diary (eDiary).

Breakthrough bleeding episodes between visit 3 and visit 16 in the concizumab arm must be treated with eptacog alfa (rFVIIa). The patient can treat himself without delay but must inform the site that a bleeding episode has occurred. Doses of eptacog alfa (rFVIIa) those are lower than 90µg/kg may be used to treat breakthrough bleeding episodes at the discretion of the investigator. Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. If a single dose of eptacog alfa (rFVIIa) is not sufficient to stop a bleeding episode, the patient should inform the site and in agreement with the investigator may administer a second dose of eptacog alfa (rFVIIa) not higher than 90µg/kg 2-3h after the first dose has been administered. The same procedure should be repeated in case the second dose of eptacog alfa (rFVIIa) is not sufficient to stop the bleeding episode. If more than three 90µg/kg doses of eptacog alfa (rFVIIa) are needed to stop a bleeding episode, the patient should go to the site without delay. The definition and diagnostic criteria of DIC, acute myocardial infraction, stroke, deep vein thrombosis, pulmonary embolism and peripheral artery occlusion is provided in section 12.1.6. The bleeding episodes must be recorded in the eDiary.

Breakthrough bleeding episodes between visit 16 and visit 17 (follow-up part) may be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator. The patient can treat himself with eptacog alfa (rFVIIa) at home without delay. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The bleeding episodes must be recorded in the eDiary.

See Table 5–1 and Table 8–3.

5.3.6 Prohibited medication

- Treatment with anti-fibrinolytics (e.g. tranexamic acid, aminocaproic acid)*
- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anticoagulants (DOACs)
- Home treatment (between visit 2 and visit 16) with activated prothrombin complex concentrates (FEIBA®)

* Local/topical use is allowed. Use of single systemic doses in severe bleeding episodes, after careful benefit risk evaluation, is allowed.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products (visit 16 or earlier), the patient should be switched to a suitable marketed product at the discretion of the investigator. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk. The patient will not be provided with concizumab or eptacog alfa (rFVIIa) after end of trial (EOT) (visit 17) by Novo Nordisk.

5.5 Rationale for treatment

Concizumab is a monoclonal antibody and as such offers the possibility of s.c. administration. S.c. administration of an effective prophylactic drug has potential to reduce the treatment burden compared to the currently approved prophylactic drugs which have to be administered i.v. Furthermore, the current treatment options for prophylaxis in inhibitor patients do not reduce the frequency of breakthrough bleeding episodes to the same extent as prophylaxis with replacement therapy in non-inhibitor patients. Concizumab may therefore show a better efficacy profile compared to current treatment options in haemophilia A and B patients with inhibitors.

The treatment period during at least 24 weeks (the main part of the trial) is considered necessary for providing robust data that allow demonstration of clinical proof of concept and to support decision making regarding a phase 3 confirmatory trial. Dosing for up to 94 additional weeks will provide valuable long term efficacy and safety data.

Breakthrough bleeding episodes occur in prophylactic regimens with both bypassing agents and replacement therapy. Therefore, it is expected that breakthrough bleeding episodes will occur during prophylaxis with concizumab even if clinical proof of concept is demonstrated. Consequently, eptacog alfa (rFVIIa) will be provided by Novo Nordisk in this trial for treatment of breakthrough bleeding episodes. In order to minimize the likelihood of any unforeseen adverse events associated with administration of eptacog alfa (rFVIIa) in these circumstances, administration of eptacog alfa (rFVIIa) in a controlled setting will be performed at visit 3 or 9.1. Please refer to the Investigator's Brochure for further information.

6 Trial population

6.1 Number of patients

Number of patients planned to be screened: 28

Number of patients planned to start on trial product: 26

Number of patients expected to complete the trial: 24

- Preferably 21 haemophilia A patients
- Preferably 3 haemophilia B patients

Discontinued patients will not be replaced.

6.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered "yes".

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 the suitability for the trial
2. Male haemophilia A or B patients with inhibitors aged ≥ 18 years at the time of signing informed consent
3. Patients currently treated on-demand with a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening
4. Documented history of high-titer inhibitors towards FVIII or FIX, defined as ≥ 5 Bethesda Units
5. Patients currently in need of treatment with bypassing agents

6.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within the last 30 days or 5 half-lives (whichever is longer) from the last drug administration before screening
4. Any disorder which in the investigator's opinion, might jeopardise patient's safety or compliance with the protocol
5. Known inherited or acquired bleeding disorder other than haemophilia
6. Major surgery conducted within one month prior to the initiation of trial activities or major surgery planned to occur during the trial

7. Previous history of thromboembolic disease. Current clinical signs of thromboembolic disease or patients who in the judgement of the investigator are considered at high risk of thromboembolic events
8. Mental incapacity, unwillingness to cooperate or language barrier precluding adequate understanding and cooperation
9. Patients who, at screening, have a significant infection or known systemic inflammatory condition which requires systemic treatment according to the investigator's judgement
10. Hepatic dysfunction defined as elevated liver transaminases (ALT) >3 times the upper limit of normal laboratory reference ranges at screening
11. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m^2 for serum creatinine measured at screening for patients without evidence of renal damage
12. Platelet count ≤ $100x10^9$/L at screening
13. Fibrinogen level < the lower limit of normal
14. Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX
15. Antithrombin levels below the normal reference range at screening

6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation 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. Anaphylactic reaction
5. Thromboembolic event
6. Event of Disseminated Intravascular Coagulation
7. Lack of efficacy due to neutralizing antibodies
8. Lack of efficacy defined as ≥ 3 treated sBEs within the previous 12 weeks in patients being treated with the highest dose level (0.25 mg/kg) of concizumab.

See Section 8.1.4 for procedures to be performed for patients discontinuing trial product prematurely.

6.5 Withdrawal from trial

The patient may withdraw consent at will at any time.
See section 8.1.5 for procedures to be performed for patients withdrawing consent.

6.6 Patient replacement

Patients who discontinue trial product prematurely will not be replaced.

6.7 Rationale for trial population

The most important reason for choosing the trial population, haemophilia with inhibitors, is that there is a significant unmet medical need in this patient population for

1. A more effective treatment and
2. A treatment which reduces treatment burden.

In addition to this, since most of these patients are likely to have been treated and therefore familiar with eptacog alfa (rFVIIa) on-demand treatment, this trial population is considered the most suitable for assessing the safety of administering eptacog alfa (rFVIIa) to patients in whom plasma TFPI levels are inhibited. Finally, the trial population reflects the patient population that will be selected in a potential subsequent phase 3 trial in which the efficacy and safety of concizumab are to be confirmed.

7 Milestones

Planned duration of recruitment period (FPFV-LPFV): 28 weeks

FPFV: 16-Aug-2017
FPFT: 30-Aug-2017
LPFV: 28-Feb-2018
Planned LPLV: 31-Jan-2020

The total duration of concizumab treatment in this trial is at least 76 weeks for an individual patient randomised to concizumab prophylaxis treatment at visit 2.

The total duration of concizumab treatment in the trial is at least 52 weeks for an individual patient randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2.

EOT is defined as last patient last visit (LPLV).

Recruitment

The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further patients may be screened and the IWRS will be closed for further screening. All patients screened during the recruitment period and found eligible for randomisation can be randomised in a 2:1 allocation to either the concizumab or the comparator arm within the timelines specified in the flow chart (see Section 2).

Trial registration:

Information of the trial will be disclosed at clinicaltrials.gov, novonordisk-trials.com and clinicaltrials.jp. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure, how-we-disclose-trial-information, it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE), [12] the Food and Drug Administration Amendment Act (FDAAA), [13] European Commission Requirements, [14 15] 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.

Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this protocol LPFT (visit 2) + 24 weeks corresponding to visit 9. If the last patient is withdrawn early the PCD is the date when the last patient would have completed visit 9. The PCD determines the deadline for results disclosure at ClinicalTrials.gov according to FDAAA.[13]

8 Methods and assessments

Assessments to be performed at the scheduled and at the unscheduled visits in the trial are described in this section, Figure 8–1, Figure 8–2 and in Section 2.

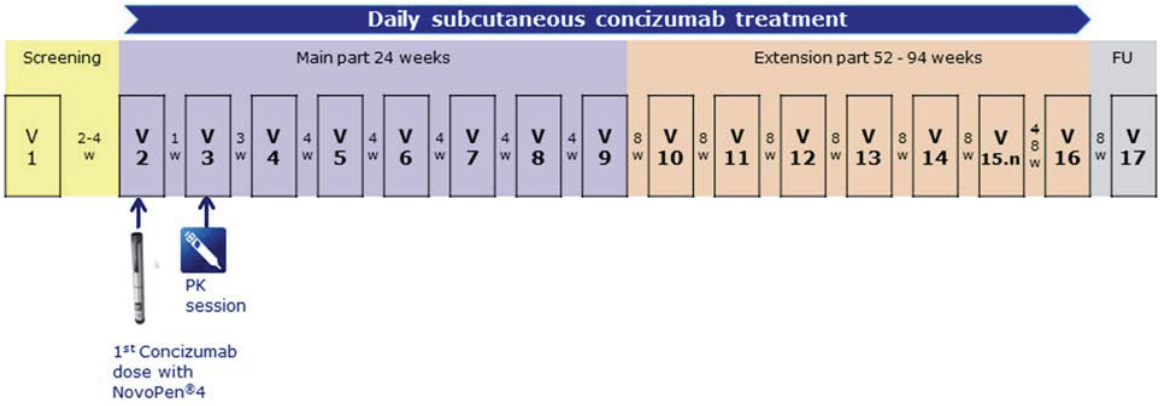


Figure 8–1 Visit schedule – concizumab arm.

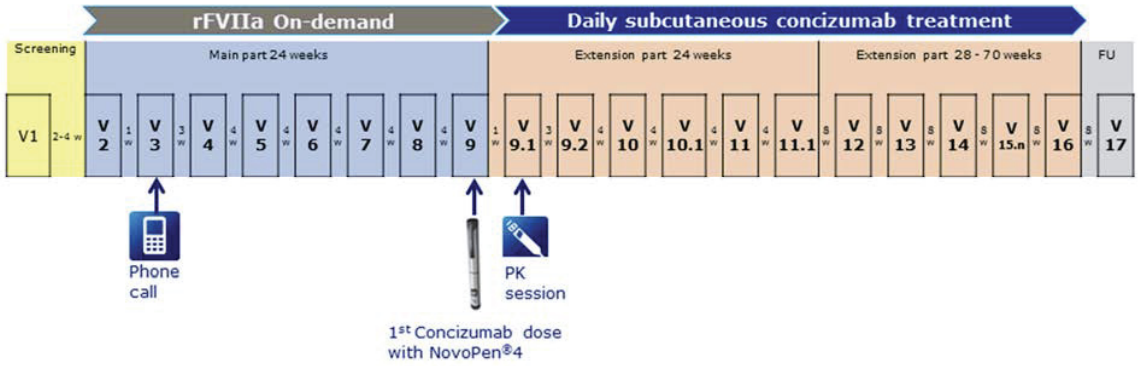


Figure 8–2 Visit schedule – eptacog alfa (rFVIIa) arm later switching to concizumab.

8.1 Visit procedures

For each patient the trial can consist of the following scheduled parts and visits depending upon which arm the patient is randomised to:

Screening Part:

- Visit 1 (screening visit)

Main Part:

- Visit 2 (Randomisation and 1st treatment visit with concizumab at site for patients randomised to the concizumab-arm)
- *Home treatment with concizumab daily*
- Visit 3 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site only for patients randomised to the concizumab-arm - phone visit for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 4 (Assessment visit, patients treat themselves at home)
- Visit 5 (Assessment visit, patients treat themselves at home)
- Visit 6 (Assessment visit, patients treat themselves at home)
- Visit 7 (Assessment visit, patients treat themselves at home)
- Visit 8 (Assessment visit, patients treat themselves at home)
- Visit 9 (Assessment visit, after the visit patients treat themselves at home – 1st treatment visit with concizumab at site for patients randomised to the eptacog alfa (rFVIIa) arm)

Extension Part:

- Visit 9.1 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 9.2 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 10 (Assessment visit, patients treat themselves at home)
- Visit 10.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 11 (Assessment visit, patients treat themselves at home)
- Visit 11.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on demand-arm)
- Visit 12 (Assessment visit, patients treat themselves at home)
- Visit 13 (Assessment visit, patients treat themselves at home)
- Visit 14 (Assessment visit, patients treat themselves at home)
- Visit 15 – 15.n (Assessment visit, patients treat themselves at home)
- Visit 16 (Assessment visit, no treatment at home before the visit and End of Treatment)

Follow-up Part:

- Visit 17 (Assessment visit and End of Trial)

Unscheduled Part:

- Unscheduled visits can occur e.g. for dispensing of trial product, dose escalation or when an assessment of bleeding episodes is necessary at site or at the discretion of the investigator.

The duration of the visits (V1-V17) will depend on the assessments and the patient's individual training and/or discussion need on concizumab and eptacog alfa (rFVIIa) administration, NovoPen®4, usage of eDiary, completion of the PRO etc.

8.1.1 Informed consent, genotyping and long-term storage consent

Informed consent must be obtained before any trial related activity at visit 1, see Section 18.2.

The trial includes a separate informed consent for long-term storage of human biosamples, see Section 24.2.

Storage of human biosamples and/or genotyping is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and participate, while refusing permission for biological specimens and/or genotyping to be stored for future exploratory analysis.

8.1.2 Screening log, enrolment log, trial card and patient number

The investigator must keep a patients screening log, a patients identification code list and a patients enrolment log. Only patients who have signed the informed consent form should be included on the logs. The patients screening log and patients enrolment log may be combined in one log.

At screening, patients will be provided with a card stating that they are participating in a trial and given contact address(es) and telephone number(s) of relevant trial clinic staff. Patients should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each patient will be assigned a unique 6-digit patient number which will remain the same throughout the trial.

8.1.3 Screening failures and re-screening

For screening failures the screening failure form in the electronic case report form (eCRF) must be completed with the reason for not continuing in the trial.

Serious and non-serious adverse events from screening failures must be transcribed by the investigator into the eCRF. Follow-up on serious adverse events (SAEs) must be carried out according to Section 12. A screening failure session must be made in the IWRS. The case book must be signed in the eCRF.

Re-screening is NOT allowed if the patient has failed one of the inclusion or exclusion criteria; this includes re-sampling if the patient has failed one of the inclusion or exclusion criteria related to laboratory parameters.

8.1.4 Premature discontinuation of trial product

If a patient prematurely discontinues trial product, the investigator must undertake procedures similar to those for visit 9 (the last treatment in the main part) or visit 16 (the last treatment visit in the extension part) as soon as possible. The follow up visit (visit 17) must be performed 8 weeks (window minus 7 days) after last dose of trial drug.

The primary reason for premature 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.

The patients who permanently prematurely discontinue trial product at Investigator's discretion due to a safety concern after completion of the main part of the trial may have visit 17 scheduled 8 weeks after visit 16. Furthermore additional unscheduled visits will be conducted at least every 8 weeks for safety assessments (see Section 8.4 and 8.5.2), PK and PD markers. The patients who permanently prematurely discontinue trial product due to safety concerns may have the safety follow up period extended at Investigator's discretion until the safety concern have been resolved, but no later than Last Patient Last Visit as defined in Milestones (Section 7 of the protocol).

Permanent premature discontinuation of treatment with trial product will lead to patient withdrawal from the trial.

8.1.5 Withdrawal from trial

If a patient withdraws consent, the investigator must aim to undertake procedures similar to those for visit 9 (the last visit in the main part) or visit 16 (the last visit in the extension part) as soon as possible depending on where the patient is in the trial schedule.

The end-of-trial form must be completed, and 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 and the case book must be signed in the eCRF.

Although a patient is not obliged to give his reason(s) for withdrawing consent, 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 withdrawing consent must be specified in the end-of-trial form in the eCRF.

8.1.6 Review/ evaluation of clinical outcome

Novo Nordisk has constituted an internal concizumab safety committee and established an external DMC to perform ongoing safety surveillance of safety data relevant to concizumab, see Section 12.8.

Review of eDiary data and laboratory reports etc. must be documented either on the documents or in the patient's medical record.

If unclear entries or discrepancies in the eDiary or ePRO are identified and a clarification is needed, the patient must be asked for clarification and a conclusion made in the patient's medical record. Care must be taken not to bias the patient.

8.1.7 Visit 1 (Screening part)

Informed consent must be obtained before any trial related activity, see Section 18.2

All assessments to be performed at screening are listed in Section 2.

After informed consent is given, patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- Hemo-TEM,
- VERITAS-PRN®

Assessment results from physical examination and body measurements, as well as measurements of vital signs, urinalysis and ECG and details of any contemporary adverse events, must be entered into the eCRF.

A screening confirmation call must be performed in the IWRS, at the day of the visit.

The investigator must review all information obtained from the screening procedures. If a patient does not meet all inclusion criteria or meets one or more of the exclusion criteria for the trial the patient does not qualify to be enrolled.

For bleeding episodes that occur in the period from Screening visit (Visit1) to randomisation visit (Visit 2), information about the bleeding episode is to be entered in the eCRF at visit 2.

Patients will be provided with eptacog alfa (rFVIIa), trial injection kits and direction for use (DFU) to cover the potential eptacog alfa (rFVIIa) treatment after the screening part of the trial and investigator will ensure that the patients are capable of treating themselves with eptacog alfa (rFVIIa).

Dispensing of eptacog alfa (rFVIIa) should be performed in IWRS.

The patient must be instructed to call the site if any bleeding episodes, questions or issues arise after he has left the site.

8.1.8 Training of patients at visit 1, visit 2 and visit 9

During visit 1 and visit 2 and visit 9 (comparator arm) patients must be trained in self-administration of concizumab in the home setting using NovoPen®4. The dose of concizumab to be administered must be communicated to the patient at visit 2 (if they are randomised to concizumab) or at visit 9 (if they are randomised to eptacog alfa (rFVIIa) and switching to concizumab at visit 9). Furthermore, patients must be instructed and trained in the importance of reporting all the home treatments with concizumab, details of the bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes in the eDiary. The patient should call the site if bleeding episodes occur between visit 1 and 2 for the site to register in the eCRF.

Patients should be trained on how to recognize signs of thromboembolic events, so that the patient contacts the site without delay.

The site and patient can arrange for additional training whenever needed during the remaining time of the trial.

8.1.9 Treatment period at home

Home treatment is defined as self-administration of trial product, performed independently by the patient, preferably in the morning. Home treatment starts after visit 2 (concizumab arm) or when the patient is comfortable self-administrating trial product subcutaneously (concizumab) and intravenously (eptacog alfa (rFVIIa)).

8.1.10 Staggered recruitment

Dosing of eptacog alfa (rFVIIa) in the first 4 patients randomised to the concizumab arm will be staggered until the 4th patient randomised to the concizumab arm has completed visit 3 without any safety concerns raised by the investigator. Until this time point, enrolled patients will not be randomised until the previous patient randomised to concizumab has completed visit 3 without any safety concerns raised by the investigator. Novo Nordisk will as sponsor control and communicate the staggered recruitment process.

8.1.11 Treatment period – Main part

8.1.11.1 Visit 2 (Randomisation)

Visit 2 should be scheduled 14 to 28 days after visit 1. The date of visit 2 will be considered as trial day 1.

It is important to verify the in/exclusion criteria again and review central laboratory tests from screening.

The patients must be in a non-bleeding state and should not have received any bypassing agent (e.g., eptacog alfa (rFVIIa), FEIBA®) for treatment of bleeding episodes within a period of 24 hours (for eptacog alfa (rFVIIa)) or 48 hours (for FEIBA®) prior to the potential first concizumab administration (depending on the treatment arm). After visit 2 only treatment with eptacog alfa (rFVIIa) for bleeding episodes is allowed.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments listed in 2, must be performed before potential administration of concizumab (depending on the treatment arm). Vital signs must be assessed both before (within 1 hour) and after concizumab administration. Pre-dose blood sampling must take place no more than 1 hour before concizumab administration.

Assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

A randomisation and dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the Trial Materials Manual (TMM) on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

For patients randomised to the concizumab arm, the first treatment with the loading dose of concizumab will be given.

The time point at which the completion of the first dose takes place corresponds to 'Time on treatment' = 0 and must be recorded in the eCRF.

The patient must be observed at the trial site for at least 2 hours after the administration of the first dose of concizumab.

At the visit the patient will be provided with trial product concizumab and/or eptacog alfa (rFVIIa) and trial injection kits and an eDiary device to be able to conduct and report home treatment and bleeding episodes until next scheduled visit.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for eptacog alfa (rFVIIa), if applicable according to section 9.4. Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site. If the patient on concizumab needs to treat a bleeding episode with eptacog alfa (rFVIIa) at home, then he must visit the site immediately after.

8.1.11.2 Visit 3 (Phone call for eptacog alfa (rFVIIa) on-demand arm and PK visit for concizumab arm)

eptacog alfa (rFVIIa) on-demand arm:

Visit 3 for eptacog alfa (rFVIIa) on-demand arm is a phone call scheduled 7 days after visit 2 (with a visit window of +1 day).

All relevant assessments listed in Section 2, must be discussed.

Assessment results from concomitant medication and details of adverse events must be entered into the eCRF.

concizumab arm:

Visit 3 is to be scheduled 7 days after visit 2 (with a visit window of +1 day) and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- PGI-C
- Hemo-TEM

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) administration.

The concizumab dose should be administered first followed by eptacog alfa dose. eptacog alfa (rFVIIa) should be administered to the trial patients at the site under the surveillance of medically trained trial site staff. The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min.

Samples for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

The investigator must ensure that all assessments are performed as described in Section 2, The Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF prior to administration of the next dose of concizumab.

Recruitment of the first four patients will be staggered according to section 8.1.9.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.11.3 Visit 4, 5, 6, 7 and 8

Patients should treat themselves at home according to their individual dosing schedule regardless of when visits 4, 5, 6, 7 and 8 are scheduled.

Visits 4, 5, 6, 7 and 8 are to be scheduled on trial day 29 (4 weeks), day 57 (8 weeks), day 85 (12 weeks), day 113 (16 weeks) and day 141 (20 weeks) respectively with a visit window of ±7days.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM

All assessments are to be performed according to Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visits the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until the next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 8 patients should be reminded that treatment with concizumab (concizumab arm) must take place after the blood sampling at visit 9.

8.1.11.4 Visit 9

Visit 9 is to be scheduled on trial day 169 (24 weeks) with a visit window of ±7days.

Patients randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2 will now be switched to concizumab treatment. At this visit the first treatment (loading dose) with concizumab will take place.

Treatment with concizumab must take place after the blood sampling for both the patients on the concizumab arm as well as patients on the eptacog alfa (rFVIIa on-demand) arm.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1:

- PGI-C
- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are to be performed according to Section 2, and the assessment results from physical examination, concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through the available access to collected data from the e-Diary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients randomised to concizumab arm at visit 2, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in Section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12 Treatment period – Extension part

8.1.12.1 Visit 9.1 (PK visit and ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.1 is to be scheduled on trial day 176 (25 weeks) with a visit window of +1 day and the visit takes two days.

All assessments are listed in Section 2, and must be performed accordingly and recorded in the eCRF.

Pre-dose blood sampling must take place no more than 1 hour before eptacog alfa (rFVIIa) administration. Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) administration.

The concizumab dose should be taken first followed by eptacog alfa dose. eptacog alfa (rFVIIa) should be administered at the site under the surveillance of medically trained trial site staff. The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min. A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

Samples for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9 h (± 10 min) and 12h (±20 min) and 24h (±20 min).

The Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF prior to administration of the next dose of concizumab.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.2 Visit 9.2 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 9.2 is to be scheduled on trial day 197 (28 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.3 Visit 10

Visits 10 is to be scheduled on trial day 225 (32 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1.

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.4 Visit 10.1 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Visit 10.1 is to be scheduled on trial day 253 (36 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.5 Visit 11

Visit 11 is to be scheduled on trial day 281 (40 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's

current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.6 Visit 11.1 (ONLY patients previously on the rFVIIa on-demand arm)

Visit 11.1 is to be scheduled on trial day 309 (44 weeks) with a visit window of ±7days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must, for patients initiating concizumab treatment at visit 9, evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

8.1.12.7 Visit 12, 13, 14 and 15, 15.1, 15.2, 15.n

Visits 12, to15.n are to be scheduled with an interval of 8 weeks with a visit window of ±7 days until the patient either discontinues treatment or completes visit 16.

If patient declines participation in the prolongation of the extension, visit 16 should be conducted 4 weeks after visit 15 (see Section 8.1.12.8)

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 15.1 only patients in the prolongation will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1;

- Hemo-TEM

- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

At the last visit (visit 15 or 15.n) before visit 16 (End of treatment) patients should be reminded that treatment with concizumab must take place after the blood sampling at visit 16.

8.1.12.8 Visit 16

Visit 16 is to be scheduled:

- on trial day 533 (for patients declining participation in the prolongation of the trial)
- or later (for patients continuing in the extension or enrolled in a subsequent trial)

with a visit window of ± 7days. Further visit 16 should be scheduled to be conducted at the last day of treatment with concizumab.

Patients **not** continuing in the prolongation will be asked to complete the PRO questionnaires before any other trial related activities are performed according to section 8.6.1;

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF. Treatment with concizumab must take place after the blood sampling at this visit.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary.

For patients not continuing in the prolongation of the trial a completion session must be made at Visit 16 in the IWRS. In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat any bleeding episodes. Eptacog alfa (rFVIIa) may be requested via IWRS. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period. If necessary, the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

For patients continuing in the prolongation of the trial and are enrolled in a subsequent trial as completion session must be made at visit 16 in the IWRS, but no additional trial product (eptacog alfa) will be provided to the patient

For patients continuing in the prolongation of the trial but not enrolled in a subsequent trial a completion session must be made at Visit 16 in the IWRS. In the period from visit 16 to visit 17 the patient can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat any bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period. If necessary, the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes) arise after he has left the site.

The End-of-Trial information must be entered in the End-of-Trial form in the eCRF at visit 16 for all patients continuing in a subsequent trial with concizumab.

8.1.13 Visit 17 (End of trial) - Follow-up part

For patients not enrolled into a subsequent trial with concizumab visit 17 is to be scheduled 8 weeks after visit 16 with a visit window of minus 7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, physical examination, body measurements (weight only), vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data. Patients should be asked if their female partner has become pregnant, see Section 12.5.1.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), unused histidine syringes, eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

End-of-Trial information must be entered in the End-of-Trial form in the eCRF at visit 17 for all patients **not** continuing in a subsequent trial with concizumab.

If eptacog alfa (rFVIIa) was requested at visit 16 drug accountability should be performed in IWRS, see Section 10.

8.1.14 Unscheduled Visit

Unscheduled visits can be performed at any time during the trial as listed in Section 2. Unscheduled visits may be performed after visit 17 at the discretion of the investigator for patients who has permanently prematurely discontinue trial product due to a safety concern (see Section 8.1.4). The purpose of the unscheduled visit must be documented in the eCRF.

During unscheduled visits assessments and blood sampling must be performed according to Section 2. Assessment results must be recorded in the eCRF. Assessments and blood sampling can be omitted if the only reason for the unscheduled visit is dispensing of trial product or replacement of eDiary or NovoPen®4.

If trial product administration or dispensing is required, dispensing of trial product must be performed via IWRS.

The following forms can be found in the unscheduled visit in the eCRF:

- Bleeding episodes
- Dosing with eptacog alfa (rFVIIa), concizumab including dose escalation, see Section 5.3.3.
- Surgery
- Local, special and central laboratory (re-)sampling/results
- Body measurements

8.2 Patient related information/assessments

8.2.1 Demography

Demography will be recorded at screening and consists of:

- Date of birth (according to local regulation)
- Sex
- Ethnicity (according to local regulation)
- Race (according to local regulation)

8.2.2 Concomitant illness and medical history other than haemophilia

A **concomitant illness** is any illness, other than haemophilia, 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 first exposure to trial product. All concomitant illnesses should be reported in the concomitant illness forms in the eCRF except information on haemophilia with inhibitors which is to be reported in the haemophilia medical history section of the eCRF.

Medical history is a medical event, other than haemophilia, which the patient has experienced in the past. Only relevant medical history should be reported.

The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

It must be possible to verify the patient's medical history in source documents such as patient's medical record, see Section 6.2 and 6.3.

If a patient is not from the investigators own practice; the investigator must make a reasonable effort to obtain a copy of the patient's medical record from relevant party e.g. primary physician. The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who has been contacted.

8.2.3 Concomitant medication

A **concomitant medication** is any medication, other than the concizumab and eptacog alfa (rFVIIa), which is taken during the trial, including the screening and follow-up period.

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur.

The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date or continuation.

If a change is due to an AE, then this must be reported according to Section 12. If the change influences the patient's eligibility to continue in the trial, the monitor must be informed.

8.2.4 Details of Haemophilia, Haemophilia treatment and bleed history

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

- Diagnosis of haemophilia (date)
  - Classification of haemophilia type (haemophilia A/B)
  - Severity of haemophilia (severe, moderate or mild)
  - Aetiology of haemophilia (congenital or acquired)
- Family history of
  - Haemophilia (Y/N)
  - Inhibitors (Y/N)
  - Prothrombotic disorders (Y/N)
  - Thromboembolism (Y/N)

- Inhibitor tests taken (Y/N)
  - Date (dd-mmm-yyyy)
  - Result (BU)
- Cut-off for positive inhibitor result
- Deficiency factor level

The following information on bleeding episodes one year prior to screening should be recorded in the eCRF:

- Type of treatment
  - 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
- Dosing frequency during prophylaxis
- Approximate dose to treat a bleeding episode
- Approximate number of doses to treat a bleeding episode
- Target joint listing (definition: a target joint is a joint in which 3 or more spontaneous bleeding episodes have occurred within a consecutive 6-month period)
  - Location
  - Position (left/right)
  - Number of bleeding episodes

8.3 Efficacy assessments

8.3.1 Bleeding episodes

All bleeding episodes treated with eptacog alfa (rFVIIa) and symptoms related to the underlying disease must be captured in the eDiary by the patient or in the eCRF by the investigator. The trial site should be informed of the details of all bleeding episodes, including those that are treated outside of the trial site.

All information captured during visits to the trial site will be collected in the eCRF.

When home treatment is initiated at visit 2 all bleeding episodes and injections with concizumab and eptacog alfa (rFVIIa) injection occurring outside the trial site should be entered in the eDiary by the patient, Section 13.3.

The completed eDiary is considered source data.

For reporting of bleeding episodes as AEs/SAEs, please refer to Section 12. In case of life-threatening bleeding episode, it should always be reported as an SAE, see Section 12.1.2.

The following must be recorded for any bleeding episode, including bleeding episodes that do not require treatment with eptacog alfa (rFVIIa):

- Start date and time
- Stop date and time (see Table 8–1)
- Anatomical location
    - Position (left/right)
- Cause (see Table 8–2)
    - spontaneous
    - traumatic
    - post-surgical
- Severity (see Table 8–3)
    - mild/moderate, severe
        - classification and recording of severe bleeding episodes is the responsibility of the investigator
- Treatment, if any
    - eptacog alfa (rFVIIa) administration or other product administration
        - dose, date, stop time
    - other medicinal treatments related to the bleeding episode (pain relieving medication, non-medical therapy etc.)
        - record as concomitant medication (section 8.2.3)
- Symptoms during bleeding episode(s)
    - Pain
    - 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 if fatal, life threatening or evaluated as related to trial product, see Section 12.1.1 and 12.1.2.

Table 8–1 Definition of stop of bleeding episode

Stop time is:	When the patient experiences/observes signs of cessation of the active bleeding episode 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 8–2 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 8–3 Definition of bleeding episode severity and treatment recommendation

Category	**Definition**	**Treatment recommendation**
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeding episodes (joint, muscular bleeding episodes without compartment syndrome), mucosal- or subcutaneous bleeding episodes Mild/moderate bleeding episodes may occur in other anatomical locations	Mild/moderate bleeding episodes: • patient must call the site between visit 1-2 and visit 3-16 (see 2-3 and 9-9.1 below) • patient must call the site between visit 2-3 or visit 9-9.1 (eptacog alfa arm) and if treated at home, go to the site immediately after • patient can treat themselves at home between visit 16 and visit 17

Category	Definition	Treatment recommendation
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeding episodes; muscle bleeding episodes with compartment syndrome; bleeding episodes associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeding episodes may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes	Severe bleeding episodes must be treated immediately
Instruction for patients	The patient must be instructed to contact the site immediately if in doubt regarding treatment of a bleeding episode and to discuss what other actions may need to be taken	

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.

Dosing for bleeding episodes with eptacog alfa (rFVIIa) should be documented in the eCRF (visit 1 to visit 2) and eDiary (visit 2 to visit 17). After visit 2 bleeding episodes must be recorded either in the eDiary (if treated at home) or in the eCRF (if treated at the trial site), see section 13.3.

Investigator must instruct the patient not to perform preventive treatment with eptacog alfa (rFVIIa) after bleeding stop as defined in Table 8–1.

Investigator must instruct the patient to use eptacog alfa (rFVIIa) as rescue medication to treat bleeding episode between visit 2 and visit 16, see Section 5.3.5.

Furthermore investigator must instruct the patient to contact the site when a bleeding episode occurs. It is the responsibility of the investigator to instruct the patient about the timelines for timely completion of the eDiary.

Furthermore the investigator must review the bleeding and treatment data collected by the eDiary according to Section 13.3.

For in-between visit administrations of trial drug, patients will self-administer concizumab (and eptacog alfa (rFVIIa) as rescue medication) and will record treatment in the eDiary, which will be reviewed during periodic calls to/contact with the patient and at each visit by trial site staff and the sponsor staff.

8.4 Safety assessments

8.4.1 Physical examination

Performed as standard physical examination and include the following.

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

The investigator must evaluate the results of the examination and classify them 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 Medical History (Section 8.2.2)
    - If observed after screening: report an AE/SAE (Section 12)

Measurements will be reported in the eCRF.

8.4.2 Body measurements

- Height (cm), at screening
- Body weight (kg), (with one decimal)

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

Measurements will be reported in the eCRF.

8.4.3 Vital Signs

Before measurement of vital signs the patient should preferably rest comfortably for at least five minutes and all measurements should, if possible, be performed using the same method and in a sitting position throughout the trial.

Measurements at visits must be performed prior to any trial product administration unless otherwise specified.

- Body temperature (°C)
- Systolic and diastolic blood pressure, sitting (BP) (mmHg)
- Pulse, sitting (beats/min)
- Respiratory rate

Exception: At visits 2 and visit 3 (for patients randomised to concizumab) and at visit 9 and visit 9.1 (for patients initiating concizumab treatment at visit 9), the measurements are also performed after concizumab administration.

The investigator must evaluate the vital signs 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, section 8.2.2
    - If observed after screening: report an AE/SAE, section 12

Measurements will be reported in the eCRF.

8.4.4 Electrocardiogram

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 Medical History, section 8.2.2
    - If observed after screening: report an AE/SAE, section 12

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.

8.4.5 Adverse events

Adverse events (AEs) must be reported at each visit in accordance with the procedures outlined in Section 12.

8.4.5.1 Medication error

If a medication error is observed during the trial, the following information is required and a specific event form must be completed in the eCRF in addition to the AE form:

- Trial product involved
- Classification of medication error
- Whether the patient experienced any adverse event(s) as a result of the medication error
- Suspected primary reason for the medication error

For definition of medication errors, see Section 12.1.4.

8.4.5.2 Adverse events requiring additional data collection

For some AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form.

In case any of these events fulfil the criteria for a serious adverse event, please report accordingly, see Section 12.

For the following AEs additional data collection is required and specific event forms must be completed in the eCRF in addition to the AE form:

Injection site reaction

Investigation of injection site reactions will be performed locally at all visits after visit 2 until visit 16 based on patient feedback and by following visual inspections of injection sites for concizumab administration:

Symptoms e.g.

- Pain
- Numbness
- Itching
- Burning

Signs e.g.

- Redness (mm x mm)
- Induration (mm x mm)

- Swelling
- Dimpling
- Macula
- Haematoma
- Bleeding
- Other (visual reactions)

Any injection site reaction symptom (evaluated at visit 2-16) should be recorded in the AE form and the injection site reaction form, see Section 12.1.5.

A separate AE should be recorded for each injection site reaction symptom. The affected area should also be evaluated for redness and induration in mm using a ruler. To ensure all local injection site assessments are performed at the injection site, the area around the site will be marked with a pen prior to injection.

In the event of a local reaction, additional visual assessments (as described above) 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.

Hypersensitivity reaction

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

All events of hypersensitivity reactions must be reported and the following information must be obtained if available on the hypersensitivity reaction form:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed, see Section 8.5.2.7
- Treatment given for the reaction
- Previous history of similar reactions
- Association with the trial product(s)
- Relevant risk factors associated with the event
- Storage condition of the trial product
- Total number of doses, from first day on trial product, up to the time of this event

8.5 Laboratory assessments

An approximate total blood volume of 768 mL will be taken from each patient on the concizumab arm and 868 mL from each patient on the eptacog alfa (rFVIIa) arm.

A laboratory manual will be provided for detailed description of obtaining and processing blood samples.

All laboratory blood samples collected for this trial except for haematology samples at all visits and coagulation parameters at visits 3 and 9.1 are to be shipped for analysis at central laboratories or further distribution to special laboratories. Haematology samples (all visits) and coagulation parameters (visit 3 and 9.1) are to be analysed locally. Ports cannot be used for blood sampling.

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

Laboratory reports listing results from centrally analysed samples will be made available for the investigator. Investigator must review and evaluate the results and report AEs for results which are clinically significant. Laboratory reports will where possible indicate normal ranges.

Categorisation of clinical significance for out of range results may not be required for the following laboratory parameters and the investigator is therefore not required to perform a categorisation even though these parameters are listed in the laboratory report: FVIII/FIX activity, FVIII/FIX inhibitor

test, Thrombin generation, Free TFPI (TFPI not bound to concizumab), concizumab concentration in plasma, anti-concizumab antibodies, Total TFPI and FVII antigen concentration.

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 and report these according to Section 8.2.3 and Section 12.

Only laboratory samples specified in the protocol must 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 except for biomarkers and anti-drug antibodies (anti-concizumab IgE antibodies and anti-concizumab antibodies).

Laboratory samples will be destroyed no later than at finalisation of the clinical trial report (CTR).

Antibody samples and human biosamples, if applicable, will be stored as described in Section 24.2. The investigator may not be able to review the results of antibody measurements in relation to AEs as these are often analysed after LPLV.

8.5.1 Laboratory assessments for efficacy

8.5.1.1 Thrombin generation

The Thrombin Generation Assay (TGA) will be collected at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

The TGA is included as an exploratory PD assessment.

The generation of thrombin is a fundamental part of the haemostatic system, and is a key measurable parameter of the formation of a clot under bleeding or thrombotic conditions. The thrombin burst is crucial for the formation of a stable fibrin clot.

The Calibrated Automated Thrombogram (CAT) method (used by Thrombinoscope BV) will be used to measure thrombin generation (TG). This method uses a slow acting fluorogenic substrate that allows continuous measurement of thrombin generation in double centrifuged citrated plasma.

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.

The thrombin generation endpoints are defined but not limited to:

- The Endogenous Thrombin Potential (ETP) – the area under the curve
- Peak thrombin generation
- Velocity Index

8.5.1.2 Free TFPI

Free TFPI (TFPI not bound to concizumab) will be collected at all visits, pre-dose at visit 2 and 3 (concizumab arm), visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16.

The free TFPI assay is an enzyme immunoassay measuring levels of free TFPI from [redacted] (named and referred to [redacted] TOTAL TFPI) and will be used for PD assessments.

8.5.2 Laboratory assessments for safety

8.5.2.1 Urinalysis

- pH
- Protein
- Glucose
- Bilirubin

This is a semi qualitative measurement which will be performed (locally) at the screening visit by the site by using the appropriate reagent strips for urinalysis. The results will be recorded in the eCRF.

The investigator must evaluate the results and record the outcome as:

- Normal or abnormal
- If abnormal the investigator must:
    - Record if the result is clinically significant? (Yes/No)
    - If observed before or at screening: record as concomitant illness (section 8.2.2)

8.5.2.2 Haematology

Haematology samples are to be sampled and analysed locally at all visits.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa), 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9 h (± 10 min), 12h (± 20 min) and 24h (± 20 min).

- Haemoglobin
- Erythrocytes (cell count)
- Thrombocytes (platelet count)

- Leucocytes (cell count)
- Differential leucocytes cell count
    - Lymphocytes
    - Monocytes
    - Neutrophils
    - Eosinophils
    - Basophils

The investigator must evaluate the results and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Haematology results are to be entered into the eCRF.

8.5.2.3 Biochemistry

Biochemistry samples are to be sampled and analysed centrally at all visits.

- Creatinine
- Albumin
- Bilirubin; total, direct, indirect
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma glutamyltransferase (GGT)
- Alkaline phosphatase
- C-reactive protein (CRP)

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

8.5.2.4 FVIII/FIX activity

FVIII/FIX activity is to be sampled and analysed centrally at visit 1, visit 9 and visit 16.

- FVIII activity level (IU/mL) or
- FIX activity level (IU/mL)

8.5.2.5 Coagulation parameters

Coagulation parameters will be performed centrally at all visits with the exception of visit 3 and visit 9.1 where the PT, APTT, and Fibrinogen will be performed locally.

Further at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) samples are taken pre- and post-dose eptacog alfa (rFVIIa) at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (±10 min) and 12h (±20 min) and 24h (± 20 min) locally.

- Fibrinogen – centrally and locally
- Prothrombin time (incl. INR) (PT) centrally and locally
- D-dimer – only centrally
- Prothrombin fragment 1+2 – only centrally
- Activated partial thromboplastin time (APTT) – centrally and locally
- Antithrombin (AT) activity – only centrally

The investigator must evaluate the results of the examination and record the outcome 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 concomitant illness (section 8.2.2)
    - If observed after screening: report an AE/SAE (section 12)

Coagulation parameters analysed locally are to be entered into the eCRF.

8.5.2.6 FVIII/FIX inhibitors

FVIII/FIX inhibitor level will be measured by the Nijmegen method at visit 1, visit 9 and visit 16.

- FVIII inhibitors (BU) or
- FIX inhibitors (BU)

8.5.2.7 Anti-concizumab antibodies

Samples for the determination of anti-drug antibodies collected during the treatment period must be drawn at all visits and prior to administering concizumab at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

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, CDR region or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a modified TFPI functionality assay (neutralising ADA assay). All antibody assays are validated according to international guidelines and recommendations.

The following analyses will be available:

- Anti-concizumab antibodies assay
- Specificity assay (Anti-concizumab antibodies cross reacting with IgG4 backbone, CDR region or S241P mutation)
- Anti-concizumab neutralising antibodies assay

The binding ADA samples will be analysed in batches during the trial and results will be available to the data monitoring committee approximately every third month after the first patient has been dosed. Neutralising antibodies will be analysed and reported at the EOT. A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

Investigators will be notified in case their patient is shown to have developed binding and/or neutralising antibodies against concizumab.

In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit. The ADA positive patients will be called for additional visits, e.g. every 4 to 6 weeks, for safety assessment and blood sampling for binding ADA and PD markers (free TFPI and Thrombin generation). The ADA positive patients will be followed no longer than one year after End-of-Trial.

Hypersensitivity

If suspicion of a hypersensitivity reaction occurs, patients should be instructed to contact the site staff as soon as possible for further guidance, see Section 12.1.5.

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 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 months post 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.

Results from the following additional tests will be reported to Novo Nordisk Safety Operations for inclusion in the ARGUS database and included in the narratives, if measured.

Test to be performed in case of severe hypersensitivity

- Anti-concizumab IgE antibodies
- Anti-concizumab antibodies (additional to scheduled time points)

Additional testing may be performed if deemed relevant e.g.

- Anti-Host Cell Proteins (HCP) antibodies
- Anti-HCP IgE antibodies
- Basophil activation results
- Prick test/intra-dermal test
- Complement test results

Furthermore, it is recommended locally to test for

- Tryptase (total and/or mature tryptase)

8.5.2.8 Concizumab ELISA

Concizumab ELISA will be collected at all visits where patients are in treatment with concizumab. Samples will be collected pre-dose at visit 2 for concizumab arm and visit 9 for eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

At visit 3 for concizumab arm and visit 9.1 for eptacog alfa arm samples for concizumab ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

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 correlates 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.

8.5.2.9 FVII ELISA

FVII ELISA will be collected at visit 3 (concizumab arm) and 9.1 (eptacog alfa (rFVIIa) arm) pre-dose eptacog alfa (rFVIIa) and post-dose at 10 min (±2 min), 1h (±10 min), 3h (±10 min), 6h (±10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa (rFVIIa) administration.

FVII in plasma will be quantified using a validated enzyme-linked immunosorbent assay (ELISA). The FVII ELISA will detect the total sum of FVII in a sample, including endogenous FVII, eptacog alfa (rFVIIa) and FVII in complex with other molecules e.g. antithrombin. The ELISA has been validated for measuring FVII in human citrated plasma samples. Validation follows current guidelines for bioanalytical method validation. Bioanalytical data will be reported in a bioanalytical report.

8.5.2.10 Total TFPI

Total TFPI ELISA will be collected at all visits. Samples will be collected pre-dose at visit 2 and 3 (concizumab arm) and visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) and visit 16 for both arms.

The total TFPI level (free and concizumab bound) will be included as an exploratory biomarker assessment.

The assay is an ELISA, where TFPI is captured by a polyclonal anti-TFPI antibody, distanced from the binding site of concizumab; meaning that both free TFPI and concizumab bound TFPI will be captured. Detection will be obtained with a monoclonal antibody against TFPI, which does not bind to the concizumab epitope.

Data will be reported in ng/mL TFPI.

8.5.3 Human Biosamples

If patient permission is obtained plasma, serum and/or DNA for genotyping samples are to be taken for long term retention, see Section 2. The blood samples can be stored up to 15 years, for future potential exploratory purposes please refer to section 24.2.

Antibody samples storage and retention, see Section 24.2.1. The investigator is not able to review the results of antibody measurements in relation to AEs as these are analysed after LPLV. Plasma and serum is taken at visit 1 and 17. DNA for genotyping is only taken at visit 1.

8.6 Other assessments

8.6.1 Patient reported outcomes

A newly developed disease-specific electronic PRO (ePRO) the Hemophilia Treatment Experience Measure (Hemo-TEM) - is being validated in this trial. In order to assess the psychometric properties of Hemo-TEM, other questionnaires will be provided; see further appendix 1.

The following ePRO questionnaires will be used in the trial:

- Hemophilia Treatment Experience Measure (Hemo-TEM)
- Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®) [16]
- 36-Item Short Form Health Survey (SF-36v2) (4 week recall)[17]
- Patient's Global Impression of Change (PGI-C)
- Sheehan Disability Scale (SDS) [18]
- Treatment Satisfaction Questionnaire for Medication (TSQM, version II) [19] [20] [21]
- Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)[22]

The ePROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, VERITAS-PRN®)
- visit 2 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 3 (PGI-C, Hemo-TEM)
- visit 4 (PGI-C, Hemo-TEM)
- visit 5 (PGI-C, Hemo-TEM)
- visit 6 (PGI-C, Hemo-TEM)
- visit 7 (PGI-C, Hemo-TEM)
- visit 8 (PGI-C, Hemo-TEM)
- visit 9 (PGI-C, Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 10 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 15.1 or 16 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)

At visit 1: before any visit-related activities all patients should complete Hemo-TEM and VERITAS-PRN®.

At visit 2: before any visit-related activities all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 3-8: before any visit-related activities the patient should complete the PGI-C before the Hemo-Tem. These are the rules that apply:

- If the patient responds "1" to question 1 in the PGI-C, the patient should also complete the Hemo-TEM. In this case the patient should not fill in the PGI-C any more in the trial and the Hemo-TEM only again at visits 9, 10 and 15.1 or 16.
- If the patient responds "0" or "2" to question 1 in the PGI-C, the patient should not complete any other questionnaires at this visit, but should repeat the procedure at next visit.

Exception: Patients randomised to eptacog alfa (rFVIIa) on-demand should not complete the ePRO at visit 3 as this is a phone visit.

At visit 9 if the patient has responded "0" or "2" in the PGI-C at all previous visits, the patient should complete PGI-C. All patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

At visit 10 and 15.1 or 16 all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

The investigator must check the ePROs for completeness. The completed ePROs should be transmitted at each visit to the PRO database by the Investigator.

8.6.2 Training

The patients must be trained in how to handle bleeding episodes and how to recognize the signs and symptoms of thrombosis. The training must be documented in the medical record.

8.6.2.1 Concizumab and NovoPen®4

Direction for use (DFUs) will be available as a hand out for patients at visit 2. Training in NovoPen®4 can start at screening (visit 1) and s.c administration of concizumab using the NovoPen®4 can start at the first dose at the trial site (visit 2). Patients must be instructed that injections are to be performed subcutaneously, not intravenously. Concizumab and NovoPen®4 will be dispensed to the patients at visit 2. Training must be performed at site until patients feel comfortable using the device or performing the treatment. The training must be documented in the medical records.

Detailed instructions can be found in the DFUs.

8.6.2.2 eptacog alfa (rFVIIa)

A direction for use (DFU) will be available as hand out for patients at visit 1. Training must be performed at site until patients feel comfortable performing the treatment. The training must be documented in the medical records.

The following should be emphasised for eptacog alfa (rFVIIa):

- eptacog alfa (rFVIIa) should be slowly injected intravenously over 2 to 5 minutes

Detailed instructions can be found in the DFU

8.6.2.3 eDiary

Training on the use of the eDiary can start at visit 1. The eDiary will be provided to the patients at visit 2.

Training must be repeated at the site until patients feel comfortable using the device. The training must be documented in the medical records.

During the home treatment period the patient must ensure that all home treatments of concizumab, details of bleeding episodes and the eptacog alfa (rFVIIa) treatments associated with these bleeding episodes are captured in the eDiary as instructed and trained by investigator or delegated staff.

It will be the responsibility of the investigator or delegated staff to assess the eDiary data throughout the conduct of the trial and to ensure data entry compliance (timely entry, no duplicate data, no missing data etc.) and retraining if necessary.

For patients completing the trial or in case of withdrawal, the eDiary will be collected at the EOT.

8.6.3 Surgery

Minor surgery can be performed within this trial at the investigator's discretion according to local guidelines. Definition of minor surgery, see Section 5.1.1. Major surgery is not allowed, see exclusion criteria no 6.

For minor surgery the following should be recorded in the eCRF:

- Date, stop time and dose of preventive treatment with eptacog alfa (rFVIIa) before surgery, if this was deemed necessary by the investigator
- Indication for surgery
- Location of surgery
- Date of surgery
- Start and stop time of surgery

8.7 Patient 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.

8.8 Treatment compliance

Treatment compliance will be monitored and documented through timely review of eDiary data and drug accountability.

Concizumab will be administered at the trial site at visit 2 for the concizumab arm supervised by medically trained trial staff and administration at home can be initiated after visit 2 if the patient feels comfortable with the s.c. administration. Administration of eptacog alfa (rFVIIa) for bleeding episodes will be administered at the trial site by a medically trained trial staff or at home by the patient, see Section 8.3.1.

Drug accountability will be performed and will be used to assess patient compliance together with the patients' adherence to trial procedures.

Compliance check includes a cross check between records in EDC/eDiary (number of administrations and bleeding episodes) and the used/returned cartridges/vials.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the TMM.

The trial product, concizumab B, appears as clear to slightly opalescent and colourless to slightly yellow. The trial product must not be used if it contains visible particles or discoloration.

The reconstituted eptacog alfa (rFVIIa) solution appears clear and colourless. Do not use the reconstituted solution if it contains visible particles or if it is discoloured.

Trial products must not be dispensed to any person not included in the trial.

9.1 Trial products

The following trial products will be provided by Novo Nordisk, Denmark:

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
concizumab B (IMP)	100 mg/mL	Solution for injection	s.c. injection	3 mL cartridge
eptacog alfa (IMP [a] and NIMP [b])	5 mg/vial	Powder for solution for injection	i.v. injection	Vial
histidine 5 mL	N/A	Solvent for solution for injection	i.v. injection	prefilled syringe

[a] Investigational Medicinal Product (IMP) given as IMP for a single dose at visit 3 and 9.1.
[b] Non-Investigational Medicinal Product (NIMP) given as NIMP for bleeding episodes

The NovoPen®4 injector will be supplied by Novo Nordisk and used for the s.c. administration of concizumab. It will be labelled in accordance with the EMA directive on medical devices annex I [23] and similar national legislation. A description of how to use the device is given in the DFU.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13 [24], local regulations and trial requirements.

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 enrolment and randomisation.

The investigator must document that DFUs are given to the patient orally and in writing at the first dispensing visit (see Section 2).

9.3 Storage

Table 9–2 Storage conditions

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time [a]
concizumab B 100 mg/mL	Store in refrigerator (2°C-8°C) Do not freeze Protect from light	Store at room temperature (below 30°C) Do not refrigerate Protect from light	Use within 4 weeks (28 days)
eptacog alfa 5mg	Store between 2°C-25°C Do not freeze Protect from light	For single use Do not freeze Protect from light To be used immediately after reconstitution	If not used immediately, store in refrigerator (2°C-8°C) for up to 3 hours
histidine 5 mL	Store between 2°C-25°C Do not freeze Protect from light	For single use	N/A

[a] In-use time for concizumab starts when first dose is administered from an individual cartridge and for eptacog alfa (rFVIIa) when the product is reconstituted

The investigator must ensure that trial product is kept under proper storage conditions and record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range). Additional details regarding handling of temperature deviations can be found in the TMM.

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 must take appropriate action to ensure correct storage.

Investigator must instruct the patient to use and store trial product according to the label.

9.4 Drug accountability and destruction

Drug accountability of all trial products (concizumab and eptacog alfa (rFVIIa) received at site is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial product during the trial as instructed by the investigator, except for used histidine syringes which should be discarded at home and not accounted for. Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

All cartridges (concizumab) and vials (eptacog alfa (rFVIIa)) must be accounted for as used, partly used or unused.

The investigator will perform drug accountability using the IWRS Drug Accountability module.

Returned trial product (used/partly used and/or unused), expired or damaged trial product can be stored at room temperature and must be stored separately from non-allocated trial product.

Non-allocated trial product including expired or damaged products must be accounted as unused at the latest at closure of the trial site.

Destruction of concizumab and eptacog alfa (rFVIIa) can be performed on an on-going basis and will be done according to local procedures after accountability is finalised and reconciled by the monitor. Destruction of products must be documented in the IWRS.

For Japan only: Responsibility for storage and drug accountability of the trial drug product at the trial site rests with the head of the trial site. The head of the trial site could assign some or all of the responsibilities for accountability of the trial drug product at the trial sites to a trial product storage manager (a pharmacist in principle). The trial product storage manager should control and take accountability of the trial drug product in accordance with procedures specified by Novo Nordisk. The head of the trial site or the trial product storage manager must ensure the availability of proper storage conditions, and record and evaluate the temperature.

9.5 Auxiliary supplies

Novo Nordisk will provide the auxiliaries for this trial:

- For concizumab administration: NovoPen®4, needles and DFUs
- For eptacog alfa (rFVIIa) reconstitution and administration: Trial Injection Kit and DFU

Only needles and trial injection kit provided by Novo Nordisk must be used for administration of trial product.

For further guidance please see the TMM.

10 Interactive voice/web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Dispensing verification
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure and breaking of blinded codes

11.1 Randomisation

Randomisation will be handed by the IWRS.

All patients included in the screening period and eligible for the trial will enter the trial and be randomised at visit 2 in a 2:1 allocation to either concizumab prophylaxis arm or eptacog alfa (rFVIIa) on-demand arm.

11.2 Breaking of blinded codes

Not applicable for this trial.

12 Adverse events, and technical complaints

12.1 Definitions

12.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality 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.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other trial procedures performed before exposure to trial product (pre-existing conditions should be reported as medical history or 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
- Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. All bleeding episodes and other findings related to underlying disease will be captured in the eCRF/eDiary.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild –** no or transient symptoms, no interference with the patient's daily activities
  - **Moderate** – marked symptoms, moderate interference with the patient's daily activities
  - **Severe** – considerable interference with the patient's daily activities; unacceptable
- **Causality**

Relationship between an AE and the relevant trial product(s):

- **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

- **Final 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 fatal outcome must be reported as an SAE
  - **Unknown** - This term is only applicable if the patient is lost to follow-up

12.1.2 Serious adverse event

A serious adverse event (SAE) is an experience that at any dose results in any of the following:

- Death
- A life-threatening [a] experience
- In-patient hospitalisation [b] or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity [c]
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening [a] or require hospitalisation [b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE [d]

a. The term "life threatening" in the definition of SAE 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 was more severe.

[b.] The term "hospitalisation" is used when a patient:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. 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.

[c.] A substantial disruption of a patient's ability to conduct normal life functions (e.g. following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his body function or structure, physical activity and/or quality of life).

[d.] For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The following adverse events must always be reported as an SAE 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 ALT or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

12.1.3 Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

12.1.4 Medication errors

A medication error concerning trial products is defined as:

- Administration of wrong drug

  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration
- Administration of an overdose with the intention to cause harm (e.g. suicide attempt), misuse or abuse of trial product
- 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

Medication errors must be reported on an AE form and a specific event form, see Section 8.4.5.1

12.1.5 Adverse events 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.

In this trial the following AEs require the completion of specific event forms in the eCRF:

- Injection site reaction, see Section 8.4.5.2
- Hypersensitivity type reactions, incl. anaphylactic reactions, see Section 8.4.5.2

Injection site reactions:
Any injection site reaction symptom must be recorded on the AE form and the injection site reaction form.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction are present, blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. In the event of an immediate systemic hypersensitivity reaction to the trial product, it is recommended to also test for tryptase (total and/or mature tryptase) within 3 hours of the reaction. Moreover, a baseline tryptase measurement is necessary ~1 week after the immediate severe hypersensitivity reaction due to individual to individual variation in tryptase baseline concentration. Tryptase concentrations (if measured) must be interpreted and considered in the context of a complete workup of each patient.

Special 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 type 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 cases where there is a suspicion of hypersensitivity reaction that requires systemic treatment, additional sampling for the purpose of measuring ADA will be performed.

Definition of anaphylaxis [25]
Anaphylaxis is highly likely when **any one of the following 3 criteria** is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
    a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

- **Two or more of the following** that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours): Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP.

If a patient fulfils any of the three criteria of anaphylaxis outlined above, the patient should receive epinephrine/adrenalin immediately. Dose regimen should be according to hospital operating procedure, and the patient should be transferred to an emergency department or intensive care unit, if clinically warranted.

Events not fulfilling the criteria for an anaphylactic reaction and other allergic reactions must be treated at the discretion of the treating physician. If according to the investigators judgement, hypersensitivity type reactions that require systemic treatment are suspected, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

12.1.6 Adverse Events of special interest

An adverse event of special interest (AESI) is an event, which in the evaluation of safety, has a special focus. In this trial, the following AEs fulfil the AESI criteria:

- Thromboembolic events including but not limited to,
    - disseminated intravascular coagulation (DIC) (A),
    - clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction (B),
    - pulmonary embolism (C),
    - stroke (D),
    - deep vein thrombosis (E),
    - other clinically significant thromboembolic events (F) and peripheral artery occlusion (see below G), see definitions below

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

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 × 10^9/L = 0, <100 × 10^9/L = 1, <50 × 10^9/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) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction" [26]
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.

C) 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 [(27)].

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

D) 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" [(28)].

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:

- 1. pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
- 2. 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 [(29)].

E) 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 DVT in the lower extremities[27]. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

F) 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 is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

G) 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, 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 [30].

12.1.7 Technical complaints

A technical complaint is any written, electronic or oral communication that alledges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

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

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until visit 16 (end of treatment) for patients enrolling into a subsequent trial with concizumab and at the end of the post-treatment follow-up period (visit 17) for patient not enrolling into a new trial. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the patient must be asked about AEs and technical complaints, for example by asking: “Have you experienced any problems since the last contact?”

All AEs, either observed by the investigator or patient, must be reported by the investigator and evaluated. All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

AESIs regardless of the seriousness must be reported using the AE form and safety information form.

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.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the CRF/eCRF within the specified timelines:

- **SAEs:** The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE.

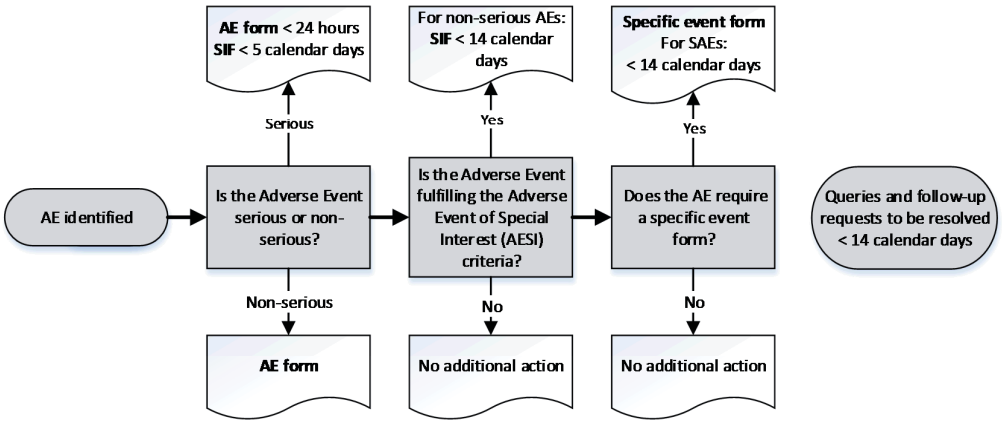
Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.

For SAEs requiring reporting on a specific event form: In addition to the above the specific event form within **14 calendar days** from the investigator's first knowledge of the AE.

- **Non-serious AEs fulfilling the AESI criteria:** The AE form and safety information form **within 14 calendar days** of the investigator's first knowledge of the event.

If the eCRF is unavailable, the concerned AE information must be reported on a paper AE form and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the form into the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.



Timelines are for the completion of forms from the time of investigator's awareness
AEs requiring specific event forms are described in Section 12.1.5 *and 12.1.6*

AE: Adverse event **AESI:** Adverse event of special interest **SIF:** Safety information form

Figure 12–1 Reporting of AEs

Novo Nordisk assessment of AE expectedness:

Novo Nordisk assessment of expectedness is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto.

When eptacog alfa (rFVIIa), NovoSeven® is used as IMP, expectedness is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto.

Reporting of trial product-related SUSARs by Novo Nordisk:

Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and ICH GCP [1]. In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the IRBs/IECs of trial product-related SUSARs in accordance with local requirement and ICH GCP [1], unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication or non-investigational medicinal product:

If an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as non-investigational medicinal product (eptacog alfa (rFVIIa)) or 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.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.

Follow-up information must be reported to Novo Nordisk according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

  The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

- **Non-serious AEs fulfilling the AESI criteria:** Non-serious AE fulfilling the AESI criteria must be followed as specified for non-serious AEs. Follow-up information on AESIs should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the AESI criteria.

The investigator must ensure that the recording of the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product occurring to a patient after the patient has ended the trial, the investigator should report this SAE within the same timelines as for SAEs during the trial.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Concizumab B 100 mg/mL, solution for injection in a 3 mL cartridge
- NovoPen®4
- Novo Nordisk needles
- Eptacog alfa (rFVIIa) 5 mg/vial, powder for solution for injection in a vial
- Histidine 5 mL, solvent for solution for injection in a prefilled syringe
- Novo Nordisk trial injection kit

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Centre, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, AESI and/or SAEs.

Technical complaints must be reported on a separate technical complaint form:

- One technical complaint form must be completed for each affected DUN
- If DUN is not available, a technical complaint form for each batch, code or lot number must be completed

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints **within 5 calendar days**

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 Centre, 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.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Centre, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A copy of the technical complaint form must be included in the shipment of the sample. If several samples are returned in one shipment, the individual sample and the corresponding technical complaint form must be clearly separated.

The investigator must ensure that the technical complaint sample contains the batch, code or lot number and, if available, the DUN. All parts of the DUN should be returned.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

12.5 Pregnancies

12.5.1 Pregnancies in female partners of male patients

Male patients must be instructed to notify the investigator if their female partner becomes pregnant during the trial, except in the screening period (from visit 1 to dosing with concizumab at visit 2 or visit 9 depending on the arm). At the last scheduled visit (visit 17), male patients must be asked if their female partner has become pregnant.

If a female partner has become pregnant during the trial, the investigator must follow-up on the pregnancy outcome and until the newborn infant is one month of age, irrespective of whether the trial is completed or not. The investigator must ask the male patient and assess if the pregnancy outcome is normal or abnormal.

When the pregnancy outcome is **normal** this information is recorded in the patient's medical record only, no further information is collected and reported to Novo Nordisk. When the pregnancy outcome is **abnormal** (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), the following must be reported by the investigator to Novo Nordisk electronically (e.g. in PDF format) or by fax.

1. **Reporting of pregnancy information**
   Information from the male patient has to be reported on the Paternal Form. Furthermore, information from the female partner (including information about the pregnancy outcome and health status of the infant until the age of one month) has to be reported on the Maternal Forms 1A, 1B and 2, after an informed consent has been obtained from the female partner.

   Initial reporting and follow-up information must be reported within **14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The following AEs in the foetus and newborn infant have to be reported:
   - Non-serious AEs evaluated as possible/probably related to the father's treatment with the trial product(s)
   - SAEs in the foetus and newborn infant - whether or not related to the father's treatment with the trial product(s). This includes an abnormal outcome - such as foetal death (including spontaneous abortion) and congenital anomalies (including those observed at gross examination or during autopsy of the foetus)

<u>Forms and timelines for reporting AEs:</u>
Non-serious AEs:

- Paper AE form[a] **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE

SAEs:

- Paper AE form[a] **within 24 hours** of the investigator's first knowledge of the SAE
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information

[a] It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the patient, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Dose limiting toxicities of concizumab have not been investigated in clinical trials.

There have been no reports about overdosing of concizumab and therefore no experience with overdose and overdose reactions exists. In case of a concizumab overdose, symptomatic medical treatment according to the clinical condition should be applied. No antidote exists in case of concizumab overdose.

Any overdose should be reported as an AE, with or without clinical manifestations. Overdoses are considered medication errors.

Treatment should be as appropriate and in accordance with hospital practice and guidelines.

12.7 Rules for putting enrolment on hold

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee. A substantial amendment with relevant data must be submitted to the regulatory authorities to support restart of the trial.

- Significant thromboembolic event
- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product
- Two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements
- Trends in AEs, clinical observations or laboratory parameters which raise concerns about the safety of continued treatment.

12.8 Committees related to safety

12.8.1 Novo Nordisk safety committee

Novo Nordisk has constituted an internal concizumab safety committee to perform ongoing safety surveillance of safety data relevant to concizumab. The safety committee is a cross functional group within Novo Nordisk.

12.8.2 Data monitoring committee

The 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 in order to protect the safety of the patients and to evaluate the benefit-risk balance. The DMC will have access to the data, and will provide recommendations on trial continuation, modification or termination.

In case there is any safety concern, data will be compiled and the DMC will review these data. Their recommendation will go to the Novo Nordisk Safety committee for final decision of what next step is in this trial.

The DMC members will only have direct contact with the Novo Nordisk Global Safety department through the safety surveillance representatives, and will have no direct interaction with those in trial management. The DMC recommendations should be addressed directly to the Novo Nordisk Global Safety department and the internal Novo Nordisk safety committee for concizumab. It is the responsibility of the Novo Nordisk internal safety committee for concizumab to take action(s) for patient safety based on the DMC recommendations.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

13 Case report forms

For this trial a combination of electronic case report forms (eCRFs) and paper CRFs will be used.

Novo Nordisk will provide a system for the electronic case report forms (eCRF). This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms
- Technical complaint forms
- AE forms
- Safety information forms

The paper version of the technical complaint form, AE form, and safety information form must only be used to ensure timely reporting when/if the electronic CRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing “ND” (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing “NA” (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

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 the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

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

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

13.3 Electronic diary

Novo Nordisk will provide the patient with an eDiary for electronic recording of details of their home treatment, bleeding episodes and treatment of bleeding episodes (i.e. use of eptacog alfa (rFVIIa)).
The eDiary and related support services will be supplied by a vendor working under the direction and supervision of Novo Nordisk.

Patients will be instructed in the use of the eDiary by the investigator or delegated person before entering of any data. The eDiary will be dispensed to the patient at visit 2. After visit 2 and onwards, data will be entered by the patient in the eDiary device during home treatment.

The eDiary will be returned by the patient at the EOT visit.

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

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.

Investigator review of eDiary data

It is the responsibility of the Investigator or delegated staff to review the eDiary data reported by the patient. As a minimum it must be verified that the eDiary data is complete, consistent and according to the requirements defined in this protocol. This also includes that the number of doses reported in the eDiary is reviewed against the number of vials/cartridge accounted for as used by the patient. Upon review the Investigator must document that the review has taken place and any actions required e.g. retraining of the patient or decision to amend or correct the data reported by the patient.

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

14 Monitoring procedures

Monitoring will be conducted using a risk based approach including risk assessment, monitoring plans, centralised monitoring and visits to trial sites. During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. Monitoring visits should be scheduled as frequently as needed to support the first 6 patients recruited in the trial. The monitoring visit intervals will depend on the outcome of the centralised monitoring of the eCRFs (remote assessment of data by Novo Nordisk), the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks until LPLV at the trial site. This only applies to sites with scheduled, ongoing and/or discontinued patients.

The monitor must be given direct access to all source 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 or text message).

All data must be verifiable in source documentation other than the eCRF. eDiary data is entered by the patient and will also be treated as source data.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

For historical data such as medical history, details of haemophilia and haemophilia treatment history, a reasonable effort must be made by the investigator, considering local requirements, to obtain this information from external sources, if not known by the patient. It is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document. This means that for laboratory results (e.g. biochemistry and haematology) a signed printout of the electronic results must be available.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The monitor will ensure that the eCRFs are completed and paper CRFs (if any) collected, that ePROs and eDiaries are completed and reviewed by the investigator at the relevant scheduled visits and needed action has been taken and documented, if any.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Inclusion and exclusion criteria
- Screen failure reason if possible
- Date patient left the trial
- Data relating to AEs if applicable
- Demography, see section 8.2.1
- Date of visit

Monitors will review the patient's medical records and other source data (e.g. the eDiaries and ePROs) to ensure consistency and/or identify omissions compared to the eCRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a CRO.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of patient data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide all laboratory reports to the investigator for filing at the trial site. The laboratory report must be signed and dated by the investigator or delegated person and stored at the trial site as source data.

The patient and any biological material obtained from the patient will be identified by patient number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients in all presentations and publications as required by local, regional and national requirements.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

Novo Nordisk will use the Global Haemophilia Network Investigator Portal to distribute and share trial-related documents and information with the participating sites. After trial completion, Novo Nordisk will supply each trial site with long-life CDs or other relevant archiving containing the electronic Investigator Trial Master File (eITMF) for each trial site. These CDs or other relevant archiving will contain site-specific trial documentation as well as trial specific news and other relevant trial information, including audit trail on documents and site staff users. The GHN Portal software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1, 31]

Novo Nordisk will provide electronic tablets for reporting of all PROs questionnaires described in section 8.6.1 and in Appendix 1. In case the electronic tablet is revoked the questionnaires will be available in paper.

The eDiary and ePRO software and hardware implementation are compliant with the requirements of FDA 21 CFR Part 11 and ICH E6 (EU directive for personal data protection).[1], [31] After trial completion, each trial site will be supplied with long-life CDs. These CDs will contain site-specific patient records including the patient's eDiaries and audit trail including any data additions and corrections made on each form. The eDiary vendor will furthermore retain and securely store copies of all archived documents and data for 15 years or as required by local data retention laws for trial data.

17 Statistical considerations

All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. Please refer to Figure 17–1 for further information.

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

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. Further, the endpoints will not include re-bleed. A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping treatment of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping treatment, the bleed is defined as a new bleeding episode.

Data collected among permanently prematurely discontinued from trial product due to a safety concern patients after visit 17, in the possible extended safety follow-up period (ref section 8.1.4) will be listed only.

Clinical proof of concept

The statistical analysis of the collected data aims to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia patients with inhibitors. The objective will be assessed when the last of the 24 patients has completed 24 weeks of dosing (or has withdrawn before that).

Two criteria will be evaluated in a hierarchical fashion in support of CPoC comprising a comparison of the ABR of all patients in the concizumab group, irrespective of individual dose titration, with the ABR of the patients in the on-demand arm using different sets of observations. The primary CPoC criterion aims at evaluating the effect of concizumab when given at the last dose level reached for the patient. Hence, for this evaluation, only observations from the period where patients are on their end dose at time of analysis will contribute to the analysis. Furthermore, observations from the 2 week run-in period will not be included. Since this evaluation disregards a subset of data collected post randomisation, the result should be viewed taking into account the potential bias. The second CPoC criterion aims at evaluating the effect of concizumab when given

as an escalation regimen. Hence, this will compare the ABR of patients in the concizumab arm with the ABR of the patients in the on-demand arm using all data collected after randomisation. The second CPoC criterion will only be evaluated if the first one succeeds.

The referred comparisons will be made using a negative binomial model with log of exposure time in main part as offset and regimen as factor (concizumab vs. on-demand). For each criterion, evidence of effect will be concluded if the 95% confidence interval of the treatment ratio is below 1.

Clinical arguments for the hierarchical test approach

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

17.1 Sample size calculation

The estimand will be defined as the "if all patients had adhered" estimand.

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

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

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

Sufficient inference on bleeding episodes for the primary CPoC criterion is judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm. It is expected that the treatment duration of the main part allowing for escalation time for some patients is on average 6 months in the below calculations.

When evaluating the power of the negative binomial analysis referred above, annual bleeding rates of 24 and 6 are assumed for the on-demand patients and the end dose concizumab regimen, respectively. Assuming further over-dispersion of 7, the power for concluding superiority of the concizumab regimen becomes approximately 80%. The power under varying values of true ABR and over-dispersion for the primary CPoC criterion are shown below in Table 17–1.

Table 17–1 Power in superiority comparison between concizumab prophylaxis and on-demand treatment under different assumptions of ABR for concizumab and over-dispersion (assuming on-demand ABR=24).

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

For the secondary CPoC criterion that includes data prior to potential dose escalation, it is expected that the treatment duration of the main part is on average 8 months with an average ABR of 7.6 for the concizumab regimen. This yields a marginal power of approximately 70% for the secondary CPoC criterion.

In prior Novo Nordisk trials conducted in haemophilia patients, the typical 1-year over-dispersion for non-inhibitor patients on prophylaxis with FVIII or FIX has been in the range 4-8, implying 24 weeks over-dispersion of 3-5 (e.g. in NN7008-3543, NN7088-3859 and NN7999-3747). In the NN7128-1907 trial in inhibitor patients, larger 1-year over-dispersion values of approximately 21 and 18, respectively, were observed during an initial 3-month on-demand period and a subsequent 3-month prophylaxis period. It is expected that the variation in the current trial will be smaller, partly due to the longer duration of the trial and partly due to an expected more homogenous patient population. Another published trial including inhibitor patients, comparing prophylaxis using FEIBA® with on-demand treatment, showed 6-month over-dispersion of 4-5 [32]. On that background, an over-dispersion of 7 over the 24 weeks in main part of the current trial is deemed realistic.

17.2 Definition of analysis sets

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

17.3 Primary endpoint

The primary endpoint is the number of bleeding episodes during at least 24 weeks from treatment onset.

The endpoint will be analysed when the main part of trial has been completed.

17.3.1 Estimand and primary statistical analysis

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

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

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

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time (the included observational period of the main part) as offset and regimen as factor. The offset for first CPoC criterion of patients in concizumab arm is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for subjects on 0.15 mg/kg. The offset for the second criterion of patients in concizumab arm is the log of the individual exposure time in the main part. For both criteria and patients in the on-demand arm, the offset is the log of the exposure time in the main part. The analysis provides an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is “missing at random”, i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

17.3.2 Sensitivity analysis

To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis will be performed where patients having discontinued before finalization of the main part are assumed to have a worse outcome compared to what was observed during the main part of the trial. This will be done by adding a value Δ to the observed bleeding episodes in the main part of the trial before analysing the data. The offset is maintained as being the exposure during the main part since it is not possible to identify the amount of missing observation time. The degree of worsening, Δ_i, will gradually be increased to evaluate at which point concizumab prophylaxis no longer is superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis will be considered robust if the tipping point is above what is considered clinically plausible.

17.3.3 Additional analysis

An additional evaluation of the primary endpoint will be made, including the actual concizumab dose level (interpreted as the patients last dose level) as additional factor in the primary analysis model specified above. Point estimates and 95% confidence interval will be provided for the ABR

at the different dose levels of concizumab (0.15, 0.20 and 0.25 mg/kg). Furthermore, series of analyses with individual steady state PK/PD assessments included as covariates in the negative binomial regression model as specified for the primary analysis of number of bleeding episodes will be performed in order to evaluate possible associations between PK/PD and ABR that potentially could guide dose-selection. The referred steady-state PK/PD assessments comprise the concizumab trough level, TFPI value prior to the last s.c. dose administration, peak thrombin generation (nM), Endogenous thrombin potential (nMxmin) and velocity index (nM/min).

17.4 Supportive secondary endpoints

17.4.1 Supportive secondary efficacy endpoints

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

The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset will be addressed in terms of the same estimand as for the primary endpoint. The estimand will be estimated using the same negative binomial regression model as for the primary endpoint.

Furthermore, an additional evaluation will be made, where actual concizumab dose is included as factors in the model.

The remaining supportive secondary efficacy endpoints will be summarised descriptively by treatment regimen. In addition, number of bleeding episodes during at least 76 weeks of treatment with prophylactic concizumab will be analysed using a negative binomial model with log of trial duration as offset, providing estimates of the ABR with confidence interval for that particular regimen.

17.4.2 Supportive secondary safety endpoints

- Number of treatment-emergent adverse events (TEAEs) during at least 24 weeks from treatment onset
- Number of TEAEs during at least 76 weeks from treatment onset
- Number of TEAEs within 24 hours of rFVIIa administration
- Occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset
- Occurrence of anti-concizumab antibodies during at least 76 weeks from treatment onset
- Change from baseline of fibrinogen during 24 weeks from treatment onset
- Change from baseline of fibrinogen during at least 76 weeks from treatment onset
- Change from baseline of D-dimer during 24 weeks from treatment onset
- Change from baseline of D-dimer during at least 76 weeks from treatment onset

- Change from baseline of prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset
- Change from baseline of F1 + 2 during at least 76 weeks from treatment onset
- Change from baseline of prothrombin time (PT) during 24 weeks from treatment onset
- Change from baseline of PT during at least 76 weeks from treatment onset
- Change from baseline of activated partial thromboplastin time (APTT) during 24 weeks from treatment onset
- Change from baseline of APTT during at least 76 weeks from treatment onset
- Change from baseline of anti-thrombin (AT) during 24 weeks from treatment onset
- Change from baseline of AT after at least 76 weeks from treatment onset

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

TEAE is defined as an event that has onset after randomisation until the last visit in the trial. Adverse events collected among permanently prematurely discontinued from trial product due to a safety concern patients after visit 17 in the possible extended safety follow-up period (ref section 8.1.4) are not considered treatment emergent. Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All adverse events will further be listed. Relations to Novo Nordisk marketed products used by patients in the trial, such as eptacog alpha, is reported as described in section 12.2 of the protocol and not reported in the report of the trial.

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

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

17.4.3 Supportive secondary pharmacokinetic endpoints

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

The pharmacokinetic endpoints will be summarised and listed.

17.4.4 Supportive secondary pharmacodynamic endpoints

- *Free TFPI concentration*
  - Value prior to the last dose administration at 24 weeks
  - Value prior to the last dose administration after at least 76 weeks
- *Thrombin generation*

- Peak thrombin generation (nM) prior to the last dose administration at 24 weeks
- Peak thrombin generation (nM) prior to the last dose administration after at least 76 weeks
- Endogenous thrombin potential (nM^xmin) prior to the last dose administration at 24 weeks
- Endogenous thrombin potential (nM^xmin) prior to the last dose administration after at least 76 weeks
- Velocity index (nM/min) prior to the last dose administration at 24 weeks
- Velocity index (nM/min) prior to the last dose administration after at least 76 weeks

The PD endpoints will be summarized and listed.

17.4.5 Exploratory endpoints

17.4.5.1 Exploratory safety endpoints

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

Adverse events related to technical complaints will be listed and summarised

17.4.5.2 Exploratory patient reported-outcome endpoints

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

VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change after 24 weeks of treatment onset for SF-36v2, SDS and TSQM from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

The PRO endpoints will be summarised using descriptive statistics and the remaining questionnaires (Hemo-TEM, PGI-C, SIAQ-ISRQ) will be summarised and listed using descriptive statistics.

17.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. For patients in the concizumab s.c. prophylaxis arm, main part is defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. For patients in the on-demand arm, the main part consists of observations from randomisation until transfer to concizumab s.c. prophylaxis treatment or withdrawal from trial, whichever comes first. All observations for these patients after transfer to concizumab treatment are regarded as extension part of the trial. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual CTRs might in such case be issued. A CTR describing results from the main and the extension part will be written when the last patient has either completed or withdrawn from the trial. All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 17–1.

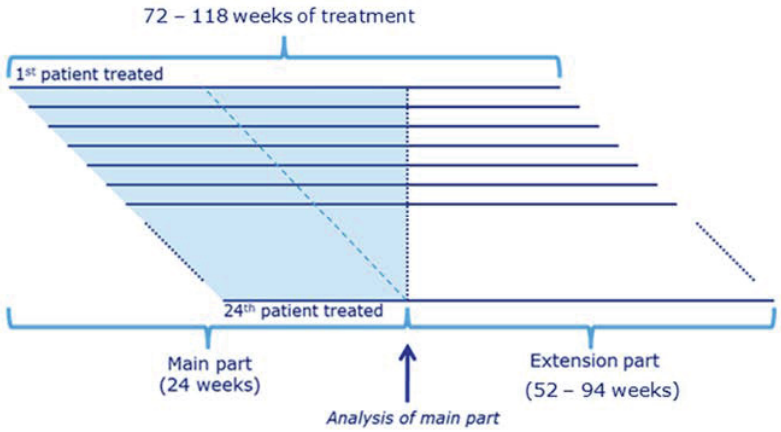


Figure 17–1 Definition of main and extension part

18 Ethics

18.1 Benefit-risk assessment of the trial

Benefits

Results from a multiple dose phase 1 trial where concizumab was dosed for approximately 6 weeks showed a trend towards efficacy in a limited number of patients who reached concizumab plasma concentrations above 100 ng/mL, see Section 3.1.2. Based on these results, it is expected that the majority of the patients randomised to the concizumab treatment with 0.15 mg/kg daily dose will be protected from bleeding episodes. Patients who experience excessive bleeding episodes on the lowest dose will have a possibility to be escalated to a higher dose where bleeding preventive efficacy of concizumab treatment is expected to improve. For haemophilia patients with inhibitors and who are treated on-demand, expected improved efficacy is considered to be a major benefit in participating in this trial. Also, concizumab is administered s.c. and might reduce the burden of frequent i.v. injections associated with current treatment options in haemophilia patients with inhibitors.

Information gained from this trial will contribute to gaining regulatory approval for a product that is anticipated to offer clinical advantages over currently available products.

Risks

No risks have been recognised as identified risks by review of safety data from the activities in the clinical development so far. However, the nonclinical toxicity studies have identified thromboembolic events as a potential risk when treating non-human primates with concizumab at high exposures.

As observed for other pro-coagulant compounds, there is a potential safety risk of thrombosis and vascular ischemia with reaching very high concizumab plasma concentrations. In non-clinical toxicity studies with concizumab, thrombi were observed at high doses. However, a no observed adverse effect level (NOAEL) for concizumab has been identified in non-haemophilic animals at plasma concentrations at least 24 fold higher than the currently anticipated effective plasma concentration (mean area under curve [AUC] and C_{max}) based on PK modelling.

In a drug–drug interaction study in monkeys, three doses of up to 1 mg/kg of NovoSeven® were administered at 2-h intervals, alone or in the presence of a steady state concentration of concizumab. Increased concentrations of thrombin–anti-thrombin (TAT) and D-dimer were seen, which tended to be additive when both concizumab and eptacog alfa (rFVIIa) were present in circulation. No notable clinical observations were made.

In clinical trials, except for one case of superficial thrombophlebitis in a healthy volunteer who received a single dose of 1mg/kg, no other thromboembolic events were observed. A phase 1

multiple dose trial was finalised in haemophilia A patients (0.8 mg/kg s.c. every 4 days for 6 weeks). In this clinical trial, marked changes in coagulation parameters were observed including a decrease from baseline in fibrinogen and a pronounced increase in D-dimer and F1+2 outside of normal range in patients with high plasma concentrations of concizumab. These changes were not judged as clinically significant by the investigators and were not followed by thromboembolic AEs or an increase in the number of bleeding episodes in the explorer™3 trial.

A potential risk identified in non-clinical studies is vascular vessel wall changes due to immune complex deposition causing localized vascular vessel wall changes such as hypertrophy and inflammatory cell infiltration. Concizumab is a foreign protein to animals and it is generally recognized that animal studies are limited in their ability to predict human immune responses to a therapeutic protein product. The concentrations of concizumab in plasma in animals in the non-clinical studies have reached levels far above the anticipated effective concentration. Humans are expected to have a very low immunogenic response towards a humanised mAb. The antibodies towards concizumab have not been observed so far in clinical trials. Furthermore, even if antibodies towards concizumab occur, the risk for the rate of immune complex formation exceeding the clearance capacity is considered low. Please refer to the Investigator's Brochure for further information.

If antibodies against concizumab develop, they might also inhibit the function of the administered drug. The consequence of this could be that the patient may not be able to benefit from the drug in the future. Antibody development against concizumab is not expected to reduce the effect of other treatment options.

Theoretical risks include bleeding due to consumption of coagulation factors and adverse reactions due to potentiation of inflammatory reactions or tissue damage due to impairment of tissue repair mechanisms[33 34]. TFPI is an important inhibitor of TF which, in addition to its role in haemostasis, is implicated in tissue repair processes and in a variety of physiological and pathophysiological states where repair mechanisms are activated. These include sepsis, DIC, inflammation, atherosclerosis, cancer and crush injuries[35 36, 37].

There may be a risk of allergic reactions, including severe (anaphylactic) reactions, in connection with concizumab administration. Severe allergic reactions may potentially be life-threatening and thus, the trial products will be administered to the trial patients at the site under the surveillance of medically trained trial site staff in the beginning of the trial.

Overall the anticipated benefits from participating in the trial outweigh the potential risks.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki [2].

Before any trial-related activity, the investigator must give the patient verbal and written information about the trial and the procedures involved in a form that the patient can read and understand.

The patients must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the patient before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the investigator must inform the patient in a timely manner, and a revised written patient information must be provided and a new informed consent must be obtained.

Only applicable for Japan: As a minor is unable to provide legally binding consent, informed consent must be sought from the parent(s)/LAR(s) on the child's behalf prior to enrolling a child in the trial, according to local requirements.

18.3 Data handling

If the patient withdraws from the trial or is lost to follow up, then the patient's data will be handled as follows:

- Data already collected and any data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the CTR.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to patients during 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.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If the trial is suspended or prematurely 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.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

19 Protocol compliance

19.1 Protocol deviations

Deviations from the protocol should be avoided and protocol waivers are not acceptable under any circumstances.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. The Sponsor will assess any protocol deviation and decide whether any of these non-compliances are likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated (potential serious breach) and if it should be reported to the Regulatory Authorities as a serious breach of GCP and/or the protocol.

In addition, 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.

Documentation on protocol deviations must be kept in the investigator trial master file and sponsor trial master file.

19.2 Prevention of missing data

The below process will be in place to prevent missing data in this trial.

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 is collected. If missing data does occur the reason will be collected via the protocol deviation process, see Section 19.1. 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).

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

An Investigator Portal (Global Haemophilia Network [GHN]) will be used as primary media for exchange and handling of investigator trial master file documents between Novo Nordisk and the site and for electronic storage of these documents during trial conduct.

Before a trial site is allowed to start screening patients, written notification from Novo Nordisk must be received and the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, patient information/informed consent form, any other written information to be provided to the patient and patient recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of Investigator's Brochure
- SmPC or similar labelling of eptacog alfa (rFVIIa)
- Signed and dated Agreement on Protocol
- Signed and dated Agreement on Protocol Amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)
- Description of research facility obtained (applicable for sites outside the US)

Only applicable for US trial sites:

- For US trial sites: verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the IND
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

For local laboratory parameters the following will be collected:

- Laboratory normal ranges
- Laboratory certification, QA scheme or similar documentation
- Laboratory assay methods (only non-standard assays) and/or analytical methods

By signing the protocol agreement, each investigator agrees to comply fully with ICH GCP [1] applicable regulatory requirements and the Declaration of Helsinki [2].

By signing the protocol agreement, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 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.

At least investigator must be trained in the current protocol version at a Novo Nordisk Investigator meeting or by the most recent version of the web training. It is recommended that all site staff completes the web protocol training.

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 will follow instructions from Novo Nordisk when processing data.

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 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).

23 Reports and publications

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 physicians 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 CTR for this trial.

One investigator will be appointed by Novo Nordisk to review and sign the CTR (signatory investigator) on behalf of all participating investigators. The signatory investigator will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications [38].

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a 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 subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure how-we-disclose-trial-information.

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CTR 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. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. 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.

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.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[38] (sometimes referred to as the Vancouver Criteria).

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre 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. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 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.

24 Retention of clinical trial documentation and human biosamples

24.1 Retention of clinical trial documentation

Patients' medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other patient data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems and/or electronic devices supplied by Novo Nordisk. These data must be retained by the trial site. If the provided 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.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for at least 20 years after discontinuation of the marketing authorisation, termination of the trial or cancellation of the research project whichever is longest.

Only applicable for Spain: 25 years retention according to the Spanish Royal Decree 1090/2015.

The files from the trial site/institution must be retained for 15 years after EOT as defined in Section 7, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

24.2 Retention of human biosamples

This trial will involve collection of human biosamples at visit 1 (screening visit) and at visit 17 (EOT) and these samples are to be stored maximum 15 years from EOT. In addition, samples which have been drawn as back-up samples during the conduct of the trial and have not been analysed will be captured and stored under the same conditions.

Storage of human biosamples is voluntary and will not affect the patients' participation in the trial. Therefore, patients will have the possibility to sign the informed consent for the trial and

participate, while refusing permission for biological specimens to be stored for future exploratory analysis.

- Human biosamples will be stored at the central laboratory
- 1.0 mL citrated plasma, 1.2 mL serum and/or 2.0 mL whole blood (DNA for genotyping) will be obtained
- The intended use of the stored human biosamples e.g.: 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 human biosamples may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial
- Human biosamples may be transferred to third parties e.g. research consortia
- The human biosamples will be transferred and stored after the EOT at a designated central laboratory
- Confidentiality and personal data protection will be ensured during storage after the EOT
- The human biosamples may be transferred to other countries (not applicable if local regulations prohibit export of human biosamples)
- The human biosamples will be destroyed at the latest 15 years from EOT
- The patient may request the stored human biosamples to be destroyed by withdrawing consent. The results obtained from any already performed analyses of the samples will still be used
- Novo Nordisk and laboratory will have access to the stored human biosamples
- Potential consequences for the patient and their relatives: In the event that the collected human biosamples (plasma, serum and/or DNA for genotyping) 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 human biosamples obtained from their own body, see Section 5.1.

24.2.1 Antibody samples

Antibody samples will be retained until drug approval by U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA).

The retained antibody samples may be used 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 assays, and will not be reported in this trial. The samples will be stored at a central bio-repository after EOT and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from EOT after which they will be destroyed.

The patients' identity will remain confidential and the antibody samples will be identified only by patient number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

Only Novo Nordisk staff and bio-repository personnel will have access to the stored antibody samples.

Patients can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the patients, new information that may affect adversely the safety of the patients or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the patients), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the CTR synopsis to the IRB/IEC (not applicable for Japan).

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the patients.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.

26 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.

Novo Nordisk accepts liability in accordance with:

Only applicable for Austria: Arzneimittelgesetz (BGBI. Nr. 185/1983) last amended with BGBl. II Nr. 105/2015

Only applicable for 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 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 or the fault 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".

Only applicable for Poland: Novo Nordisk carries liability for the Trial exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001 (uniform version Journal pf Laws of 2008 No. 45 item 271 with amendments). In order to support potential claims for liability attributable to the Trial, Novo Nordisk and Investigators are covered by the Insurance Policy issued according to applicable Polish law.

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Appendix 1

NN7415-4310

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

Trial phase: 2

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1 Hemophilia Treatment Experience Measure (Hemo-TEM)

Hemophilia Treatment Experience Measure (Hemo-TEM)

The following questions are about your **hemophilia treatment**. When answering these questions, please think about your CURRENT EXPERIENCE with your hemophilia treatment.

IF you regularly take prophylactic treatment (and may also use on demand treatment when you have a bleed), please think ONLY about your prophylactic treatment.

IF you only use on demand treatment OR mainly use on demand and only rarely use prophylactic treatment (for example, before a physical activity), please think ONLY about your on demand treatment.

There are no right or wrong answers.

Please choose only one response for each question.

1. How easy or difficult is it to ...	Not at all Difficult	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
Find a good place on your body to inject	☐	☐	☐	☐	☐
Put the needle correctly into your body	☐	☐	☐	☐	☐
Find a good place to give yourself a treatment when you are not at home	☐	☐	☐	☐	☐
Remember to give yourself a treatment	☐	☐	☐	☐	☐
Give yourself a treatment exactly as instructed by your healthcare provider (for example, how, when, amount, or how often)	☐	☐	☐	☐	☐

2. How often do you ...	Never	Rarely	Sometimes	Often	Always
Delay or postpone taking your injection on purpose	☐	☐	☐	☐	☐
Delay or postpone taking your injection by accident	☐	☐	☐	☐	☐
Miss a treatment on purpose	☐	☐	☐	☐	☐
Miss a treatment by accident	☐	☐	☐	☐	☐

3. Due to your injection (while injecting or after), how often do you have ...	Never	Rarely	Sometimes	Often	Always
Soreness	☐	☐	☐	☐	☐
Physical discomfort	☐	☐	☐	☐	☐
Pain	☐	☐	☐	☐	☐
Bruising	☐	☐	☐	☐	☐
Blown or ruptured veins	☐	☐	☐	☐	☐
Problems due to scarring or scar tissue	☐	☐	☐	☐	☐

[redacted]

4. How bothered are you by ...	Not at all	A little	Somewhat	Very	Extremely
The number of steps it takes to give yourself a treatment	☐	☐	☐	☐	☐
The amount of time it takes to prepare and give yourself a treatment	☐	☐	☐	☐	☐
Needing to store your medication and supplies (at home or work)	☐	☐	☐	☐	☐
Needing to carry your medication and supplies with you when you are out	☐	☐	☐	☐	☐
How often you need to give yourself a treatment	☐	☐	☐	☐	☐
Having to find time in your daily schedule to give yourself a treatment	☐	☐	☐	☐	☐

5. How much does your current treatment interfere with your ...	Not at all	A little	Somewhat	A lot	Extremely
Travel or vacations	☐	☐	☐	☐	☐
Social activities	☐	☐	☐	☐	☐
Daily activities (NOT including work or school)	☐	☐	☐	☐	☐
Work or school ☐ I do not currently work or go to school	☐	☐	☐	☐	☐

6. Because of your current treatment, how often do you feel ...	Never	Rarely	Sometimes	Often	Always
Anxious	☐	☐	☐	☐	☐
Frustrated	☐	☐	☐	☐	☐
Stressed	☐	☐	☐	☐	☐
Self-conscious	☐	☐	☐	☐	☐
Worried about getting an infection	☐	☐	☐	☐	☐
Worried about developing an (or another) inhibitor	☐	☐	☐	☐	☐
Worried about losing access to a vein	☐	☐	☐	☐	☐

7. Currently ...	Not at all	A little	Somewhat	Very	Extremely
How burdened are you by your current treatment	☐	☐	☐	☐	☐
How important do you think it is to take your treatment exactly the way you have been instructed by your healthcare provider	☐	☐	☐	☐	☐
How motivated are you to take your treatment exactly the way you have been instructed by your health care provider	☐	☐	☐	☐	☐
In general, how busy is your day	☐	☐	☐	☐	☐
In general, how stressful is your day	☐	☐	☐	☐	☐

[redacted]

8. **On average, how much time does it take to give yourself a treatment (prepare and take):**

   ___ hours ___ minutes

9. **Before entering this study, which treatment regimen were you on... (*Please only check the one that was your PRIMARY treatment)***

   ☐ Prophylaxis ☐ On demand

10. **What is your work status *(Check all that apply)*:**

    ☐ Work full time
    ☐ Work part time
    ☐ Student
    ☐ Not working (retired)
    ☐ Not working (disabled)
    ☐ Not working (other)

Please make sure that you have answered all the questions.

Thank you!

[redacted]

2 Validated Hemophilia Regimen Treatment Adherence Scale - PRN (VERITAS-PRN®)

VERITAS-PRN®

Managing hemophilia is a challenging task. The questions below ask about how you manage bleeds and infusions. We'd like to get an idea of how often you have done each of these things in the **past three months**. When answering these questions, think of an ***average*** joint or muscle bleed – a definite bleed, but not life-or limb-threatening. There are no right or wrong answers. The most important thing is that you answer each question honestly. Please answer each question using the following scale:

Always – all of the time, 100% of the time
Often – most of the time, at least 75% of the time
Sometimes – occasionally, at least 50% of the time
Rarely – not often, 25% of the time
Never – not at all, 0% of the time

Treating

1. I infuse when there are symptoms of bleeding.

   Always Often Sometimes Rarely Never

2. I infuse for the number of days recommended by the treatment center.

   Always Often Sometimes Rarely Never

3. I complete the recommended number of infusions when a bleed occurs.

   Always Often Sometimes Rarely Never

4. I follow the guidelines the treatment center has given me for managing hemophilia.

   Always Often Sometimes Rarely Never

Timing

5. When there are symptoms of bleeding, I stop activities and infuse right away.

   Always Often Sometimes Rarely Never

6. When there are symptoms of bleeding, I wait to infuse until it is convenient.

   Always Often Sometimes Rarely Never

7. I wait to infuse until a day or two after the symptoms of bleeding start.

   Always Often Sometimes Rarely Never

8. I infuse within three hours of noticing symptoms of a bleed.

   Always Often Sometimes Rarely Never

Dosing

9. I infuse the prescribed dosage for bleeds.

   Always Often Sometimes Rarely Never

10. I remember the doctor-recommended dose.

    Always Often Sometimes Rarely Never

[redacted]

1

11. I use the correct number of factor boxes to total my recommended dose.

Always Often Sometimes Rarely Never

12. Instead of calling the treatment center, I increase or decrease the infusion dose based on what I think is appropriate.

Always Often Sometimes Rarely Never

Planning

13. When a bleed occurs, I order factor for same-day delivery or go to the emergency room because there is no factor at home.

Always Often Sometimes Rarely Never

14. I have enough factor and supplies at home to infuse when needed.

Always Often Sometimes Rarely Never

15. I keep two or more doses of factor at home.

Always Often Sometimes Rarely Never

16. I keep track of how much factor and how many supplies there are at home.

Always Often Sometimes Rarely Never

Remembering

17. I forget to infuse when there are symptoms of bleeding.

Always Often Sometimes Rarely Never

18. I remember how much factor to infuse for bleeds.

Always Often Sometimes Rarely Never

19. I miss recommended infusions because I forget about them.

Always Often Sometimes Rarely Never

20. When a bleed occurs, I forget to follow treatment recommendations that the treatment center gives me.

Always Often Sometimes Rarely Never

Communicating

21. I call the treatment center for advice when there are symptoms of bleeding.

Always Often Sometimes Rarely Never

22. I call the treatment center when I cannot tell whether I need to infuse.

Always Often Sometimes Rarely Never

23. I make treatment decisions myself rather than calling the hemophilia center.

Always Often Sometimes Rarely Never

24. I call the treatment center before medical interventions, such as dental extractions, colonoscopies, visits to the emergency room, or hospital stays.

Always Often Sometimes Rarely Never

3 36-Item Short Form Health Survey (SF-36v2) (standard)

SF-36v2 Health Survey Single-Item Presentation Text Standard, United States (English)

Note: Item SF36v2_BP1 (Item #21) has 6 answers, not 5 answers; see entry for item at end of sheet for more detail.

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	Your Health and Well-Being						
		This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one response that best describes your answer.					
SF36v2_GH1	None	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
SF36v2_HT	None	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
SF36v2_PF01	The following question is about activities you might do during a typical day.	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF02	The following question is about activities you might do during a typical day.	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF03	The following question is about activities you might do during a typical day.	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF04	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF05	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF06	The following question is about activities you might do during a typical day.	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF07	The following question is about activities you might do during a typical day.	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		

4 Patient's Global Impression of Change (PGI-C)

Patient's Global Impression of Change (PGIC)

These questions are about the hemophilia treatment you are now taking as part of this study.
Please circle your response, and follow the arrows for your next step.

1. Compared to the hemophilia treatment you were taking BEFORE you started this study, would you say your current experience with taking your treatment is: *(Circle the number next to your answer)*

0 About the Same → **If you answered "About the same", please go to question 2.**
1 Better *(go to 1a)*
2 Worse *(go to 1b)*

1a. How much better is your experience with giving yourself injections?	1b. How much worse is your experience with giving yourself injections?
1 A LITTLE BETTER	1 A LITTLE WORSE
2 SOMEWHAT BETTER	2 SOMEWHAT WORSE
3 A GOOD DEAL BETTER	3 A GOOD DEAL WORSE
4 A GREAT DEAL BETTER	4 A GREAT DEAL WORSE
5 A VERY GREAT DEAL BETTER	5 A VERY GREAT DEAL WORSE

1c. Was this a meaningful or important change for you? *(Circle the number next to your answer)*
0 No
1 Yes

2. Compared to when you first started giving yourself injections as part of this study, would you say your **experience with giving yourself injections** is: *(Circle the number next to your answer)*

0 About the Same → **If you answered "About the same", you have completed this questionnaire. Please return this sheet to your study coordinator.**
1 Better *(go to 2a)*
2 Worse *(go to 2b)*

2a. How much better is your experience with giving yourself injections?	2b. How much worse is your experience with giving yourself injections?
1 A LITTLE BETTER	1 A LITTLE WORSE
2 SOMEWHAT BETTER	2 SOMEWHAT WORSE
3 A GOOD DEAL BETTER	3 A GOOD DEAL WORSE
4 A GREAT DEAL BETTER	4 A GREAT DEAL WORSE
5 A VERY GREAT DEAL BETTER	5 A VERY GREAT DEAL WORSE

2c. Was this a meaningful or important change for you? *(Circle the number next to your answer)*
0 No
1 Yes

3. In the past two months, have you had any major life events such as marriage, divorce, changing jobs, or moving?
0 No
1 Yes

[redacted]

5 Sheehan Disability Scale (SDS)

Sheehan Disability Scale

Please mark ONE circle for each scale.

WORK*/SCHOOL

How much has giving yourself your hemophilia treatment disrupted your work/school work in the last week:

Not at all **Mildly** **Moderately** **Markedly** **Extremely**

☐ I have not worked / studied at all during the past week for reasons unrelated to my treatment.
*Work includes paid, unpaid volunteer work or training.

SOCIAL LIFE

How much has giving yourself your hemophilia treatment disrupted your social life / leisure activities in the last week:

Not at all **Mildly** **Moderately** **Markedly** **Extremely**

FAMILY LIFE / HOME RESPONSIBILITIES

How much has giving yourself your hemophilia treatment disrupted your family life /home responsibilities in the last week:

Not at all **Mildly** **Moderately** **Markedly** **Extremely**

Days Lost

On how many days in the last week did your hemophilia treatment cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

Days Unproductive

On how many days in the last week did you feel so impaired by your hemophilia treatment, that even though you went to school or work, your productivity was reduced? _____

[redacted]

6 Treatment Satisfaction Questionnaire for Medication (TSQM, version II)

TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the hemophilia medication you are taking. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐2 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

[redacted]

1

5. How dissatisfied are you by side effects that interfere with your mental function (i.e., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

6. How dissatisfied are you by side effects that interfere with your moods or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

- ☐1 Extremely Dissatisfied
- ☐2 Very Dissatisfied
- ☐3 Dissatisfied
- ☐4 Somewhat Satisfied
- ☐5 Satisfied
- ☐6 Very Satisfied
- ☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

- ☐1 Extremely Dissatisfied
- ☐2 Very Dissatisfied
- ☐3 Dissatisfied
- ☐4 Somewhat Satisfied
- ☐5 Satisfied
- ☐6 Very Satisfied
- ☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

- ☐1 Extremely Dissatisfied
- ☐2 Very Dissatisfied
- ☐3 Dissatisfied
- ☐4 Somewhat Satisfied
- ☐5 Satisfied
- ☐6 Very Satisfied
- ☐7 Extremely Satisfied

7 Injection Site Reaction Questionnaire (ISRQ) domain of SIAQ (SIAQ-ISRQ)

PAIN AND SKIN REACTIONS DURING OR AFTER THE INJECTION (ISRQ)

The following questions ask about **pain and skin reactions** you may have experienced at the injection site.

Please answer each question below by checking the box that best represents your opinion (Check only one box per question).

1. How bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **pain**?	☐5	☐4	☐3	☐2	☐1
b. **burning sensation**?	☐5	☐4	☐3	☐2	☐1
c. **cold sensation**?	☐5	☐4	☐3	☐2	☐1

2. How bothered were you by:	Not at all	A little	Moderately	Very	Extremely
a. **itching** at the injection site?	☐5	☐4	☐3	☐2	☐1
b. **redness** at the injection site?	☐5	☐4	☐3	☐2	☐1
c. **swelling** at the injection site?	☐5	☐4	☐3	☐2	☐1
d. **bruising** at the injection site?	☐5	☐4	☐3	☐2	☐1
e. **hardening** at the injection site?	☐5	☐4	☐3	☐2	☐1

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

[redacted]

Global and country key Novo Nordisk staff

Attachments I and II (if applicable) to the protocol are located in the Trial Master File.

Content: Global key staff and Country key staff

Protocol Amendment

no 1
to Protocol, version 1
dated 15 March 2017

explorer™4

Trial ID: NN7415-4310

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted] - Senior International Trial Manager

Biopharm Trial Ops 1

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol amendment has been prepared to address VHP1081 requirements to clarify individual discontinuation criteria, holding rules for the trial, protocol deviations and patient eligibility in order to improve safety and rights of the patients.

In this protocol amendment:

- Any new text is written *in italics*.
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

Individual discontinuation criteria:

Section 5.3.3 Dose escalation

Dose 0.25 mg/kg:
Patients are not dose escalated further regardless of the number of sBEs. *When an sBE occurs, the investigator will determine if ≥ 3 sBEs have occurred within the preceding 12 weeks (including the current sBE), counting only new sBEs from the beginning of the 0.25 mg/kg treatment period. If yes, then the patient must be discontinued due to lack of efficacy, see Section 6.4.*

Section 6.4 Criteria for premature discontinuation of trial product

The patient may be prematurely discontinued from trial product at the discretion of the investigator due to a safety concern.

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

1. Included in the trial in violation of the inclusion and/or exclusion criteria and/or randomised in violation of the randomisation 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. Anaphylactic reaction
5. Thromboembolic event
6. Event of Disseminated Intravascular Coagulation
7. *Lack* ~~Loss~~ of efficacy due to neutralizing antibodies
8. *Lack of efficacy defined as ≥ 3 treated sBEs within the previous 12 weeks in patients being treated with the highest dose level (0.25 mg/kg) of concizumab.*

Holding rules for the trial:

Section 12.7 Rules for putting enrolment on hold.

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee. *A substantial amendment with relevant data must be submitted to the regulatory authorities to support restart of the trial.*

- Significant thromboembolic event*
- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product
- *Two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements*
- *Trends in AEs, clinical observations or laboratory parameters which raise concerns about the safety of continued treatment*.

Protocol deviations:

Section 19.1 Protocol deviations

Deviations from the protocol should be avoided *and protocol waivers are not acceptable under any circumstances*.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed. *The Sponsor will assess any protocol deviation and decide whether any of these non-compliances are likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated (potential serious breach) and if it should be reported to the Regulatory Authorities as a serious breach of GCP and/or the protocol.*

In addition, d~~D~~eviations must be documented …

Patient eligibility 6:

Section 1 Summary

Only ~~Both~~ on-demand ~~and prophylaxis~~ patients will be eligible for the trial.

Section 2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a,b]							
Visit number [c]	1	2	3	4	5	6	7	8	9
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w
Dispensing visit (eptacog alfa, histidine)[s]	▪	▪[w]	▪[k]			▪			▪

Section 2.2 Explanatory descriptions

s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g., eptacog alfa, FEIBA®) for ~~prophylaxis or~~ treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2
w	Only for patients randomised to on-demand arm.

Section 4.2.3.2 Exploratory patient reported outcome endpoints

Change in ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN® after 24 weeks from treatment onset
Change in ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN® after 76 weeks from treatment onset

Section 5.1 Type of trial

Only ~~Both~~ on-demand ~~and prophylaxis~~ patients will be eligible for the trial.

Section 5.2 Rationale for trial design

A total of 26 patients previously ~~on prophylaxis (PPX) or~~ on-demand (OD) treatment will be randomised into one of the two arms, with 16 patients in the concizumab arm and 8 patients in the comparator arm ..

Section 6.2 Inclusion criteria

3. ~~For p~~*P*atients *currently* treated on-demand *with*~~,~~ a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening

Section 8.1.7 Visit 1 (Screening part)

After informed consent is given, patients will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to Section 8.6.1:

- Hemo-TEM,

- ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN®

Section 8.6.1 Patient reported outcomes

The following ePRO questionnaires will be used in the trial:

- Hemophilia Treatment Experience Measure (Hemo-TEM)
- ~~Validated Hemophilia Regimen Treatment Adherence Scale - Prophylaxis (VERITAS-Pro®)~~ ~~or~~ Validated Hemophilia Regimen Treatment Adherence Scale (VERITAS-PRN®) [16]

The ePROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN®)

At visit 1: before any visit-related activities all patients should complete Hemo-TEM and ~~VERITAS-Pro® (if the patient at baseline receives prophylactic treatment) or~~ VERITAS-PRN® (~~if the patient at baseline receives on-demand treatment).~~

Section 17.4.5.2 Exploratory patient reported-outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset
- Change in Hemo-TEM after 76 weeks from treatment onset
- Change in ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN® after 24 weeks from treatment onset
- Change in ~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN® after 76 weeks from treatment onset

~~VERITAS-Pro®~~ ~~or~~ VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

Protocol Amendment

no 2

to Protocol, version 2 dated 05 May 2017

explorer™4

Trial ID:NN7415-4310

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

Trial phase: 2

Applicable to all countries

Protocol Amendment originator

[redacted] - Senior International Trial Manager

Biopharm Trial Ops 1

Table of Contents

1 Introduction including rationale for the protocol amendment

This protocol amendment has been prepared to address:

- Section 2.2, 8.1.11.2, 8.1.12.1 and 8.5.2.8 'Concizumab ELISA' updated due to concizumab PK has been added to the trial in order to obtain PK-profile of daily dosing with concizumab after initiation of multiple dosing
- Section 4.2.3.2 and Section 17.4.5.2 'Exploratory patient reported-outcome endpoints' updated as VERITAS-PRN is not assessed at visit 9 and visit 16 and PGI-C is not assessed at visit 1 and visit 16
- Section 5.3.6 'Prohibited medication' is updated because the use of anti-fibrinolytics is commonly local/topical use in dental procedures or dental surgery and thus not seen as compromising patient safety or trial conclusions.

  A single systemic dose may be needed: Tranexamic acid has been used to reduce bleedings during orthopaedic surgery and trauma bleed without causing additional major thrombotic risks. It is also used in haemophilia patients during severe bleeding episodes. It is therefore considered adequate to allow a single dose after careful benefit risk evaluation by the investigator.
- Section 8.5.2.7 'Anti-concizumab antibodies' updated to provide clarity on when a patient is considered to be positive for binding antibodies as this is difficult to interpret with current text in version 2.0 of the protocol if reader is not in possession of thorough knowledge on the different tests described
- Section 9.4 'Drug accountability and destruction' updated to ensure solvent does not reach expiry date in patient's custody this includes clarification in relevant visits described in section 8
  - 8.1.11.1; 8.1.11.2; 8.1.11.3; 8.1.11.4; 8.1.12.1; 8.1.12.2; 8.1.12.3; 8.1.12.4; 8.1.12.5; 8.1.12.6; 8.1.12.7; 8.1.12.8; 8.1.13
- Section 18.1 'Benefit-risk assessment of the trial' updated to specify the minimum difference in plasma concentration between the NOAEL in non-haemophilic animals and highest anticipated plasma concentration in phase 2
- Clarifications and corrections which are seen as being minor
  - List of abbreviations; Figure 8-1 and Figure 8-2; Section 2.1; 2.2; 3.1.1; 4.2.3.2; 8.1.11.2; 8.1.12.1; 8.1.12.8; 8.5; 8.5.1.2; 12.7

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through.~~

2 Changes

List of abbreviations

Hemo-TEM	*Hemophilia Treatment Experience Measure*
ISRQ-SIAQ	*Injection Site Reaction Questionnaire - Self-Injection Assessment Questionnaire*
PGI-C	*Patient's Global Impression of Change*
SDS	*Sheehan Disability Scale*
SF-36v2	*36-Item Short Form Health Survey*
TSQM	*Treatment Satisfaction Questionnaire for Medication*
VERITAS-PRN®	*Validated Hemophilia Regimen Treatment Adherence Scale*

Section 2.1 Visits and assessments

explorer™4 trial periods	Screening	Treatment main [a, b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Unscheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176 7 days after V9	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64w	72w	76w	-	84w
PATIENT RELATED INFO/ASSESSMENTS																						
Informed consent/ Genotyping and Long-term storage consent	•																					
In/exclusion criteria	•	•[g]																				
Demography	•																					
Concomitant illness/Medical history	•																					
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Details of Haemophilia/Haemophilia treatment and bleed history	•																					
Withdrawal criteria/ Criteria for premature discontinuation of trial product		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Randomisation (IWRS)		•																				
EFFICACY																						
Bleeding episodes [h, i]		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Thrombin generation (central lab)	•	•[l]	•[j, k, l]	•	•	•	•	•	•[l]	•[j]	•	•	•	•	•	•	•	•	•	•[l]	•	•
Free TFPI (central lab)	•	•[l]	•[k, l]	•	•	•	•	•	•[l]	•	•	•	•	•	•	•	•	•	•	•[l]	•	•
SAFETY																						
Physical examination	•	•	•[k]						•	•						•				•	•	•
Body measurements	•	•[m]	•[k, m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]		•[m]	•[m]
Vital signs	•	•[n]	•[k, n]	•	•	•	•	•	•[n]	•[n]	•	•	•	•	•	•	•	•	•	•	•	•
ECG	•																					
Adverse events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Injection site reaction		•	•[k]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	

explorer™4 trial periods	Screening	Treatment main [a, b]								Treatment extension [b]												Follow-up
Visit number [c]	1	2	3	4	5	6	7	8	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	13	14	15	16	Unscheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	57	85	113	141	169	176 7 days after V9	197	225	253	281	309	337	393	449	505	533	When applicable	589
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	±7	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	4w	8w	12w	16w	20w	24w	25w	28w	32w	36w	40w	44w	48w	56w	64 w	72 w	76w	-	84w
Urinalysis (local lab)	•																					
Haematology (local lab)	•	•[l]	•[j, k, l]	•	•	•	•	•	•[l]	•[j]	•	•	•	•	•	•	•	•	•	•[l]	•	•
Biochemistry (central lab)	•	•[l]	•[k, l]	•	•	•	•	•	•[l]	•	•	•	•	•	•	•	•	•	•	•[l]	•	•
FVIII/ FIX activity (central lab)	•								•[l]											•[l]		
Coagulation parameters (central lab)	•	•[l]		•	•	•	•	•	•[l]		•	•	•	•	•	•	•	•	•	•[l]	•	•
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			•[j, k, l]							•[j]												
FVIII/FIX inhibitors (central lab)	•								•[l]											•[l]		
Anti-concizumab antibodies (ADA) (special lab) [o]	•	•[l]	•[k, l, p]	•[p]	•[p]	•[p]	•[p]	•[p]	•[l, p]	•	•	•	•	•	•	•	•	•	•	•[l]	•	•
Concizumab ELISA (special lab)		•[l]	•[j, k, l, p]	•[p]	•[p]	•[p]	•[p]	•[p]	•[l, p]	•[j]	•	•	•	•	•	•	•	•	•	•[l]	•	•
FVII ELISA (special lab)			•[j, k, l]							•[j]												
Total TFPI (special lab)	•	•[l]	•[k, l]	•	•	•	•	•	•[l]	•	•	•	•	•	•	•	•	•	•	•[l]	•	•
TRIAL MATERIAL																						
IWRS call	•	•	•[k]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Dispensing visit (concizumab)[r]		•[k]	•[k]	•[k]	•[k]	•[k]	•[k]	•[k]	•	•	•	•	•	•	•	•	•	•	•		•	
Dispensing visit (eptacog alfa, histidine)[q]	•	•[w]	•[k]			•			•	•		•		•		•	•	•	•	•	•	
Administration of trial product (concizumab)[r]		•[k, s]	•[k]						•[d, s]	•										•[s]	•	
Administration of trial product (eptacog alfa)			•[k, t]							•[t]												
Drug accountability (concizumab)			•[k]	•[k]	•[k]	•[k]	•[k]	•[k]	•[k]	•	•	•	•	•	•	•	•	•	•	•	•	
Drug accountability (eptacog alfa)		•	•[k]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
New dose of trial product [e, u]				•	•	•	•	•	•		•	•	•	•	•	•	•	•	•		•	
PRO questionnaires	•	•	•[k]	•	•	•	•	•	•			•								•		
REMINDERS																						
Human biological specimen for storage (central lab)	•																					•
Handout ID card	•																					
Training [v]	•	•							•	•											•	
Compliance: eDiary			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
End of treatment																				•		
End of trial																						•

Section 2.2 Explanatory descriptions

Footer 'd': Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment. *Visit 9.1 should be performed 7 days (+ 1 day) after visit 9.*

Footer 'j': Sampling time schedule for thrombin generation, haematology, coagulation parameters, *concizumab ELISA* and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.

Footer 'k': ONLY for patients randomised to concizumab arm. *The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.*

Footer 'l': At *visit 2, visit 3,* visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.

Footer 't': Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm. *The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.*

Administration of trial product (concizumab): *Dot and 's' footnote added to visit 16*

Section 3.1.1 Haemophilia

Haemophilia is classified as "severe", "moderate" or "mild" according to the plasma activity *level* of the affected coagulation factor.

Section 4.2.3.2 Exploratory patient reported outcome endpoints

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

All endpoints referring to a time frame of either 24 weeks, or of at least *24 weeks,* will be evaluated in the main part of the trial.

Section 5.3.6 Prohibited medication

- Treatment with anti-fibrinolytics (e.g. tranexamic acid, aminocaproic acid)*
- Heparin, except for sealing of central venous access ports according to local practice
- Vitamin-K antagonists
- Direct oral anticoagulants (DOACs)
- Home treatment (between visit 2 and visit 16) with activated prothrombin complex concentrates (FEIBA®)

** Local/topical use is allowed. Use of single systemic doses in severe bleeding episodes, after careful benefit risk evaluation, is allowed.*

Section 8; Figure 8-1 and Figure 8-2.

Figure 8.1

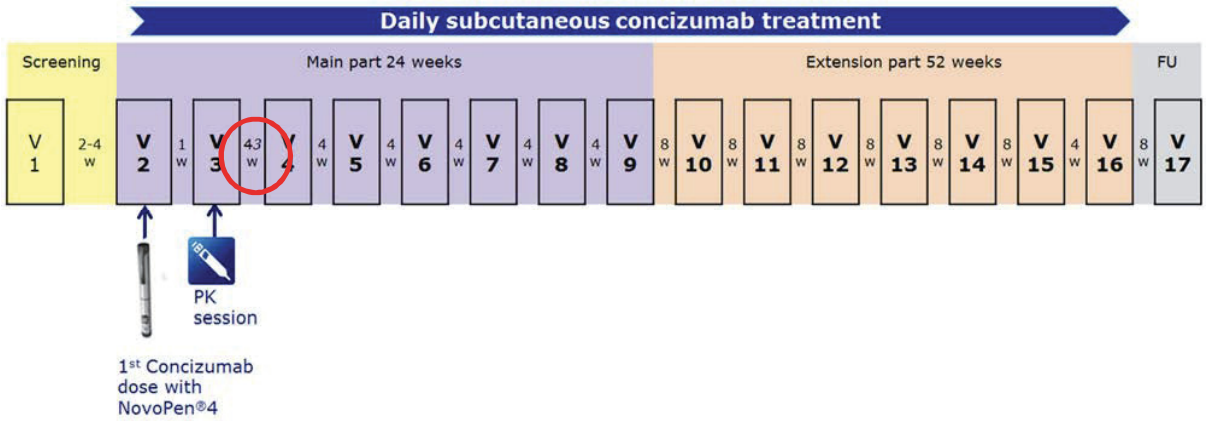
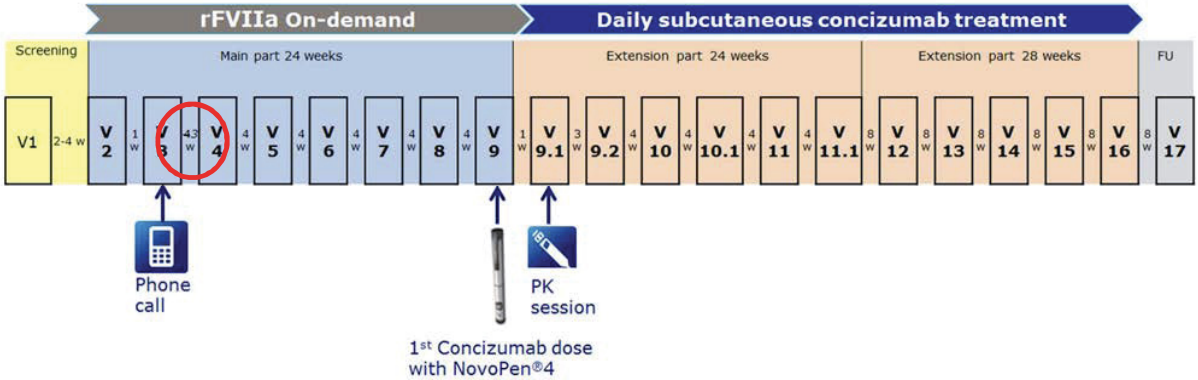


Figure 8.2



Section 8.1.11.1 Visit 2 (Randomisation)

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for eptacog alfa (rFVIIa), if applicable according to section 9.4. *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.11.2 Visit 3 (Phone call for eptacog alfa (rFVIIa) on-demand arm and PK visit for concizumab arm)

Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) *administration* ~~dosing~~. *The concizumab dose should be administered first followed by eptacog alfa dose.* eptacog alfa (rFVIIa) should be administered to the trial patients at the site under the surveillance of medically trained trial site staff. *The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min.* ~~Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.~~

Samples for thrombin generation, haematology, coagulation parameters, *concizumab ELISA* and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

The investigator must ensure *that* all assessments are performed as described in Section 2, *The* Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF *prior to administration of the* ~~before~~ next dose *of* ~~with~~ concizumab ~~is given the day after~~.

…

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.11.3 Visit 4, 5, 6, 7 and 8

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.11.4 Visit 9

The patient will be asked to return all used, partly used and unused concizumab and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.1 Visit 9.1 (PK visit and ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

Vital signs are assessed within 1 hour before and after eptacog alfa (rFVIIa) *administration* ~~dosing~~. *The concizumab dose should be taken first followed by eptacog alfa dose.* eptacog alfa (rFVIIa) should be administered at the site under the surveillance of medically trained trial site staff. *The interval between the concizumab and eptacog alfa dose administration should not exceed more than 30 min.* ~~Patient should continue his daily concizumab injections regardless of eptacog alfa (rFVIIa) administration.~~

…

Samples for thrombin generation, haematology, coagulation parameters, *concizumab ELISA* and FVII ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9 h (± 10 min) and 12h (±20 min) and 24h (±20 min).

The Investigator is requested to conclude after 24 hours if it is safe for the patient to continue in the trial and record the conclusion in the eCRF *prior to administration of* ~~before~~ the next dose of concizumab ~~is given the day after~~.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.2 Visit 9.2 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.3 Visit 10

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.4 Visit 10.1 (ONLY patients previously on the eptacog alfa (rFVIIa) on-demand arm)

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.5 Visit 11

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.6 Visit 11.1 (ONLY patients previously on the rFVIIa on-demand arm)

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.7 Visit 12, 13, 14 and 15

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.12.8 Visit 16

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF. *Treatment with concizumab must take place after the blood sampling at this visit.*

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 8.1.13 Visit 17 (End of trial) - Follow-up part

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), *unused histidine syringes*, eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

Section 8.5 Laboratory assessments

An approximate total blood volume of *625*~~725~~ mL will be taken from each patient on the concizumab arm and *725*~~625~~ mL from each patient on the eptacog alfa (rFVIIa) arm.

Section 8.5.1.2 Free TFPI

Free TFPI (TFPI not bound to concizumab) will be collected at all visits, pre-dose at visit 2 and 3 (concizumab arm), ~~and~~ visit 9 and 9.1 (eptacog alfa (rFVIIa) arm) *and visit 16*.

Section 8.5.2.7 Anti-concizumab antibodies

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, CDR region or the S241P mutation. Furthermore, positive samples will be characterised for neutralising activity using a modified TFPI functionality assay (neutralising ADA assay). All antibody assays are validated according to international guidelines and recommendations.

A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.
Investigators will be notified in case their patient is shown to have developed neutralising antibodies against concizumab.
In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit.

Section 8.5.2.8 Concizumab ELISA

Concizumab ELISA will be collected at all visits *where*~~except at screening~~ *patients are in treatment with* ~~only for the~~ concizumab ~~arm~~.
Samples will be collected pre-dose at visit 2 ~~and 3~~ for concizumab arm and visit 9 ~~and 9.1~~ for eptacog alfa (rFVIIa) arm) and visit 16 for both arms.
At visit 3 for concizumab arm and visit 9.1 for eptacog alfa arm samples for concizumab ELISA are taken pre-dose eptacog alfa (rFVIIa) (-1 hour) and post-dose eptacog alfa (rFVIIa): 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (±20 min) and 24h (±20 min).

Section 9.4 Drug accountability and destruction

Drug accountability of all trial products (concizumab and eptacog alfa (rFVIIa) received at site is the responsibility of the investigator. The patient will be asked to return all used, partly used and unused trial product during the trial as instructed by the investigator, except for *used* histidine *syringes* which should be discarded at home and not accounted for. *Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.*

Section 12.7 Rules for putting enrolment on hold

If one of below mentioned criteria is fulfilled, enrolment of additional patients in the clinical trial programme will be placed on hold. An urgent safety committee meeting will be scheduled to decide further actions. Dosing of patients on treatment may continue while further evaluation is made by the safety committee. A substantial amendment with relevant data must be submitted to the regulatory authorities to support restart of the trial.

- Significant thromboembolic event*

- Event of DIC
- Anaphylactic reaction related to trial drug administration
- Death of trial patient which may be related to the trial product
- Two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements
- Trends in AEs, clinical observations or laboratory parameters which raise concerns about the safety of continued treatment.

*Superficial thrombophlebitis or venous thrombosis associated with indwelling catheters is not considered a significant thromboembolic event unless evaluated as such by the investigator

~~If two or more other trial product related SAEs similar in nature have been reported and/or detected by laboratory measurements, or if trends in AEs, clinical observations or laboratory parameters raise concerns about the safety of continued treatment, the safety committee (see Section 12.8.1) will decide if further dosing of any patients in the clinical trial programme should be continued, paused or discontinued.~~

Section 17.4.5.2 Exploratory patient reported-outcome endpoints

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

Section 18.1 Benefit-risk assessment of the trial

Risks

However, a no observed adverse effect level (NOAEL) for concizumab has been identified in non-haemophilic animals at plasma concentrations *at least 24* ~~several~~ fold~~s~~ higher than the currently anticipated effective plasma concentration (mean area under curve [AUC] and Cmax) based on PK modelling.

Protocol Amendment

no 3
to Protocol, final version 3
dated 15 November 2017

Trial ID: NN7415-4310

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

Trial phase: 2

Applicable to all countries

Amendment originator:

[redacted], International Trial Manager

Biopharm Trial Ops 1

Table of Contents

1 Introduction including rationale for the protocol amendment and informed consent

The intention of this amendment is to provide patients current in an ongoing trial the option their participation in the trial being prolonged. During the prolongations the patients will be offered to be screened for eligibility for a subsequent clinical trial with concizumab. Further more additional clarification is made to the section of permanently premature discontinuation to ensure that patients with a safety concern are being followed until resolution or planned LPLV. Finally there is a change in the reporting to investigators about Anti-drug antibodies towards concizumab (ADA) to ensure that investigators are informed at an earlier time point than originally described.

Sections affected
Sections 1, 2, 5.1, 5.1 (Figure 5-1), 5.3 (Figures 5-3 and 5-4), 5.3.3, 5.3.4, 5.5, 7 and 17.5 (Figure 17-1) are updated to reflect the prolongation of the extension part to offer patients the possibility of being screened for eligibility to participate in the subsequent clinical trials for concizumab provided that either the study site participates in the subsequent trial programme or the patient can be transferred to a participating site.

Sections 4.2.2.1, 4.2.3.2, 17.4.1, 17.4.2, 17.4.3, 17.4.4 and 17.4.5.2 are updated to include the additional treatment weeks in the prolongation of the extension part. Currently the trial only accounts for 76 weeks of treatment therefore the endpoints have been updated to capture that patients are being treated at least 76 weeks in total.

Section 5.2, 'Rationale of the trial design' has been updated with an option ofor patients being screened for eligibility for a subsequent clinical trial based on site availability or if transferred to a participating site in the new trial.

Section 5.3 'Treatment of patients', Table 5-1 has been updated to reflect the extended use of concizumab based on the prolongation of the trial.

Section 8 (Figures 8-1 and 8-2), 8.1, 8.1.12.7, 8.1.12.8, 8.1.13 and 8.5 are updated to include the additional visits and blood volume that have been added to the trial. Between visit 15 and visit 16 (End of Treatment) additional visits have been added with 8 week intervals. Visit numbering is as following: 15, 15.1, 15.2, 15.n up to a maximum of 5 additional visits or until a subsequent clinical trial with concizumab is open for recruitment. When the patient can be enrolled in the trial the patient is scheduled for visit 16 and can from here be enrolled in the new trial.

Section 8.1.4 and 8.1.14'Premature discontinuation of trial product' has been updated as well as 'Unscheduled Visit' to provide the option of following patients who has permanently prematurely discontinue trial product due to a safety concern after visit 17 (End of trial). The purpose of the

visits is to collect additional safety information, if applicable. The additional follow up period may not be continued after the planned LPLV in Section 7, Milestones as described in section 8.1.4.

Section 8.1.12.7 and 8.6.1 have been updated as a result to the additional visits between visit 15 and visit 16. The ePROs have been added to visit 15.1 for patients participating in the prolongation of the extension. Whereas patients declining participation will continue to complete their last ePRO questionnaires at visit 16.

Section 8.5.2.7 'anti-concizumab antibodies' is updated to ensure that investigators are informed about any positive results of binding antibodies against concizumab and not only of neutralising antibodies towards concizumab as binding ADAs can affect PK of concizumab and thus efficacy and safety as well.

Section 8.6.1 'Patient reported outcome' the requirement of the investigator to review the ePROs for AEs and SAEs after completion has been removed as it is not possible for the patient to add own text to the ePROs.

Section 12.1.1 'Adverse event' has been updated due to a leftover in the standard text from former trials where i.v. administration was the treatment being investigated. As current trial is investigating a new route of administration, subcutaneous, injection site reactions including haematomas are AEs requiring additional data collection.

12.2 'Reporting of adverse events' has been updated to specify the AE reporting requirements if the patients will be enrolled in a subsequent trial with concizumab or not. Furthermore the section has been updated to accommodate the latest requirements in regards to Novo Nordisk assessment of AE expectedness. For patients enrolling into a new trial with concizumab any AEs reported after visit 16 will be reported in the new trial.

Section 12.7 'Rules for putting enrolment on hold' has per request from the Safety Committee been updated by removing the footnote. The footnote was not clear enough in regards to if thromboembolic events are considered significant or not

Section 17, 17.3.1 and 17.3 'Statistical considerations' has been updated due to technical details related to selection of bleeds and estimation of offset has been added

Section 17.4.5.2, Exploratory patient reported-outcome endpoints, are updated as the questionnaire VERITAS-PRN is only assessed at visit 1 and therefore no change in outcome can be analysed.

Main Informed consent is updated for give the patient the option of continuing in the trial after 76 weeks of treatment has passed. By consenting the patient may stay in the trial for up to 118 weeks of treatment and be given the possibility to participate in a subsequent trial with concizumab if he is

eligible and site continues in the trial or he can be transferred to a participating site. Furthermore has the GDPR (patient confidentiality) standard text been added as required.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Protocol

Section 1 Summary
Time frames for evaluation of Objectives/Endpoints
All endpoints referring to the time frame of at least 24 weeks will be evaluated in the main part of the trial, defined to end when the last patient has completed a minimum of 24 weeks of dosing treatment with trial product (or has withdrawn). ~~In addition, number of bleeding episodes during *at least* 76 weeks of treatment with prophylactic concizumab will be analysed.~~ The extension part of the trial will provide additional safety and long-term efficacy data.

Section 1 Summary
Trial design
The total trial duration for the individual patient will be approximately 86~~-88-~~*130* weeks, consisting of a 2-4 week screening period, a subsequent 76-*118* week treatment period and an 8-week follow-up period. eptacog alfa (rFVIIa) for treatment of bleeding episodes during the trial will be provided by Novo Nordisk. The patient will not be provided with trial product or eptacog alfa (rFVIIa) after end of trial.

The trial is split into a main part which lasts *at least* 24 weeks for all patients in the trial and an extension part which lasts *up to 94* ~~52~~ weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed ~~a minimum~~ *at least* of 24 weeks of concizumab prophylaxis and 8 patients have completed ~~a minimum of~~ 24 weeks of *treatment with* eptacog alfa (rFVIIa) on-demand or have withdrawn. The analysis of the main part of the trial aims to substantiate the clinical proof of concept (CPoC) that concizumab has the potential to prevent bleeding episodes in patients with haemophilia and inhibitors. The extension part of the trial will provide additional safety and long-term efficacy data.

Section 2 Flow chart with deletions (strike through)

~~explorer~~[2&3] trial periods	Screening	Treatment main [a,b]									Treatment extension [b]													Follow-up
Visit number [c]	1	2	3	4	~~5~~	6	7	~~8~~	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	~~13~~	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	~~57~~	85	113	~~141~~	169	176	197	225	253	281	309	337	~~393~~	449	505	~~533~~	When applicable	~~589~~
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	~~±7~~	±7	±7	~~±7~~	±7	+1	±7	±7	±7	±7	±7	±7	~~±7~~	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	~~4w~~	~~8w~~	12w	~~16w~~	~~20w~~	24w	25w	28w	32w	36w	40w	44w	~~48w~~	~~56w~~	64w	~~72w~~	~~76w~~	-	~~84w~~
PATIENT RELATED INFO/ASSESSMENTS																						
Informed consent/ Long-term storage consent	●																					
In/exclusion criteria	●	●[g]																				
Demography	●																					
Concomitant illness/Medical history	●																					
Concomitant medication	●	●	●	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
Details of Haemophilia/Haemophilia treatment and bleed history	●																					
Withdrawal criteria/ Criteria for premature discontinuation of trial product		●	●	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
Randomisation (IWRS)		●																				
EFFICACY																						
Bleeding episodes [h, i]		●	●	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
Thrombin generation (central lab)	●	●[j]	●[j, k, l]	●	◆	●	●	◆	●[j]	●[j]	●	●	●	●	●	●	◆	●	●	●[j]	●	●
Free TFPI (central lab)	●	●[j]	●[k, l]	●	◆	●	●	◆	●[j]	●	●	●	●	●	●	●	◆	●	●	●[j]	●	●
SAFETY																						
Physical examination	●	●	●[k]						●	●						●				●	●	●
Body measurements	●	●[m]	●[k, m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]		●[m]	●[m]
Vital signs	●	●[n]	●[k, n]	●	◆	●	●	◆	●[n]	●[n]	●	●	●	●	●	●	◆	●	●	●	●	●
ECG	●																					
Adverse events	●	●	●	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
Injection site reaction		●	●[k]	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	
Urinalysis (local lab)	●																					
Haematology (local lab)	●	●[j]	●[j, k, l]	●	◆	●	●	◆	●[j]	●[j]	●	●	●	●	●	●	◆	●	●	●[j]	●	●
Biochemistry (central lab)	●	●[j]	●[k, l]	●	◆	●	●	◆	●[j]	●	●	●	●	●	●	●	◆	●	●	●[j]	●	●
FVIII/ FIX activity (central lab)	●								●[j]											●[j]		
Coagulation parameters (central lab)	●	●[j]		●	◆	●	●	◆	●[j]		●	●	●	●	●	●	◆	●	●	●[j]	●	●
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			●[j, k, l]							●[j]												
FVIII/FIX inhibitors (central lab)	●								●[j]											●[j]		
Anti-concizumab antibodies (ADA) (special lab) [o]	●	●[j]	●[k, l, p]	●[p]	◆[p]	●[p]	●[p]	◆[p]	●[j, p]	●	●	●	●	●	●	●	◆	●	●	●[j]	●	●
Concizumab ELISA (special lab)		●[j]	●[j, k, l, p]	●[p]	◆[p]	●[p]	●[p]	◆[p]	●[j, p]	●[j]	●	●	●	●	●	●	◆	●	●	●[j]	●	●
FVII ELISA (special lab)			●[j, k, l]							●[j]												
Total TFPI (special lab)	●	●[j]	●[k, l]	●	◆	●	●	◆	●[j]	●	●	●	●	●	●	●	◆	●	●	●[j]	●	●
TRIAL MATERIAL																						
IWRS call	●	●	●[k]	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	◆[k]	●[k]	●[k]	◆[k]	●	●	●	●	●	●	●	●	◆	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●	●[w]	●[k]			●			●	●		●		●		●	◆	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]						●[g, s]	●										●[s]	●	
Administration of trial product (eptacog alfa)			●[k, t]							●[t]												
Drug accountability (concizumab)			●[k]	●[k]	◆[k]	●[k]	●[k]	◆[k]	●[k]	●	●	●	●	●	●	●	◆	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	◆	●	●	◆	●	●	●	●	●	●	●	●	◆	●	●	●	●	●
New dose of trial product [g, u]				●	◆	●	●	◆	●		●	●	●	●	●	●	◆	●	●		●	
PRO questionnaires	●	●	●[k]	●	◆	●	●	◆	●			●								●		
REMINDERS																						
Human biological specimen for storage (central lab)	●																					●

~~explorer[2/3/4]~~ trial periods	Screening	Treatment main [a,b]								Treatment extension [b]													Follow-up
Visit number [c]	1	2	3	4	~~5~~	6	7	~~8~~	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	~~13~~	14	15	16	Un-scheduled [e]	17
Timing of visits (d) [f]	14 to 28 d before visit 2	1	8	29	~~57~~	85	113	~~141~~	169	176	197	225	253	281	309	337	~~393~~	449	505	~~533~~	When applicable	~~589~~
Visit window (d)	14 to 28 d before visit 2	0	+1	±7	~~±7~~	±7	±7	~~±7~~	±7	+1	±7	±7	±7	±7	±7	±7	~~±7~~	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	~~4w~~	~~8w~~	12w	~~16w~~	~~20w~~	24w	25w	28w	32w	36w	40w	44w	~~48w~~	~~56w~~	64w	~~72w~~	~~76w~~	-	~~84w~~
Handout ID card	•																					
Training [x]	•	•							•	•											•	
Compliance: eDiary			•	•	◆	•	•	◆	•	•	•	•	•	•	•	•	◆	•	•	•	•	•
End of treatment																				•		
End of trial																						•

Section 2 Flow chart with updates (italics)

4310 trial periods	Screening	Treatment main [a, b]						Treatment extension [b]										Follow-up
Visit number [c]	1	2	3	*4-5*	6	*7-8*	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	*13*-14	*15, 15.1, 15.2, 15.n*[w]	16	Unscheduled [e]	*17*
Timing of visits (d) [f]	14 - 28 d before visit 2	1	8	*29-57*	85	*113-141*	169	176	197	225	253	281	309	337	*393*-449	*505-785*	*Up to 827*	When applicable	*Up to 883*
Visit window (d)	14 - 28 d before visit 2	0	+1	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	*Every 4w*	12w	*Every 4w*	24w	25w	28w	32w	36w	40w	44w	48 w	*Every 8w*	*Every 8w*	*Up to 118w*	-	*Up to 126w*
PATIENT RELATED INFO/ASSESSMENTS																			
Informed consent/ Long-term storage consent	•																		
In/exclusion criteria	•	•[g]																	
Demography	•																		
Concomitant illness/Medical history	•																		
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Details of Haemophilia/Haemophilia treatment and bleed history	•																		
Withdrawal criteria/ Criteria for premature discontinuation of trial product		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Randomisation (IWRS)		•																	
EFFICACY																			
Bleeding episodes [h, i]		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Thrombin generation (central lab)	•	•[j]	•[j, k, l]	•	•	•	•[j]	•[j]	•	•	•	•	•	•	•	•	•[j]	•	•
Free TFPI (central lab)	•	•[j]	•[k, l]	•	•	•	•[j]	•	•	•	•	•	•	•	•	•	•[j]	•	•
SAFETY																			
Physical examination	•	•	•[k]				•	•						•			•	•	•
Body measurements	•	•[m]	•[k, m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]	•[m]		•[m]	•[m]
Vital signs	•	•[n]	•[k, n]	•	•	•	•[n]	•[n]	•	•	•	•	•	•	•	•	•	•	•
ECG	•																		
Adverse events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Injection site reaction		•	•[k]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Urinalysis (local lab)	•																		
Haematology (local lab)	•	•[j]	•[j, k, l]	•	•	•	•[j]	•[j]	•	•	•	•	•	•	•	•	•[j]	•	•
Biochemistry (central lab)	•	•[j]	•[k, l]	•	•	•	•[j]	•	•	•	•	•	•	•	•	•	•[j]	•	•
FVIII/ FIX activity (central lab)	•						•[j]										•[j]		
Coagulation parameters (central lab)	•	•[j]		•	•	•	•[j]		•	•	•	•	•	•	•	•	•[j]	•	•
Coagulation parameters (PT, APTT and Fibrinogen (local lab))			•[j, k, l]					•[j]											
FVIII/FIX inhibitors (central lab)	•						•[j]										•[j]		
Anti-concizumab antibodies (ADA) (special lab) [o]	•	•[j]	•[k, l, p]	•[p]	•[p]	•[p]	•[j, p]	•	•	•	•	•	•	•	•	•	•[j]	•	•

***4310* trial periods**	Screening	Treatment main [a, b]						Treatment extension [b]											Follow-up
Visit number [c]	1	2	3	*4-5*	6	*7-8*	9	9.1[d]	9.2[d]	10	10.1[d]	11	11.1[d]	12	*13-14*	*15, 15.1, 15.2, 15.n*[m]	16	Unscheduled [e]	17[c]
Timing of visits (d) [f]	14 - 28 d before visit 2	1	8	*29-57*	85	*113-141*	169	176	197	225	253	281	309	337	*393-449*	*505-785*	*Up to 827*	When applicable	*Up to 883*
Visit window (d)	14 - 28 d before visit 2	0	+1	±7	±7	±7	±7	+1	±7	±7	±7	±7	±7	±7	±7	±7	±7	Not applicable	-7
Treatment week (w)		0	1w	*Every 4w*	12w	*Every 4w*	24w	25w	28w	32w	36w	40w	44w	48 w	*Every 8w*	*Every 8w*	*Up to 118w*	-	*Up to 126w*
Concizumab ELISA (special lab)		●[l]	●[j,k,l,p]	●[p]	●[p]	●[p]	●[k,p]	●[j]	●	●	●	●	●	●	●	●	●[j]	●	●
FVII ELISA (special lab)			●[j,k,l]					●[j]											
Total TFPI (special lab)	●	●[l]	●[k,l]	●	●	●	●[l]	●	●	●	●	●	●	●	●	●	●[l]	●	●
TRIAL MATERIAL																			
IWRS call	●	●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Dispensing visit (concizumab)[r]		●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●		●	
Dispensing visit (eptacog alfa, histidine)[q]	●		●[k]		●		●	●		●		●		●	●	●	●	●	
Administration of trial product (concizumab)[r]		●[k, s]	●[k]				●[d, s]	●									●[s]	●	
Administration of trial product (eptacog alfa)			●[k, t]					●[t]											
Drug accountability (concizumab)			●[k]	●[k]	●[k]	●[k]	●[k]	●	●	●	●	●	●	●	●	●	●	●	
Drug accountability (eptacog alfa)		●	●[k]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New dose of trial product [s, u]				●	●	●	●		●	●	●	●	●	●	●	●		●	
PRO questionnaires	●	●	●[k]	●	●	●	●			●						●[r]	●[m]		
REMINDERS																			
Human biological specimen for storage (central lab)	●																		●
Handout ID card	●																		
Training [v]	●	●					●	●										●	
Compliance: eDiary			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
End of treatment																	●		
End of trial																	●		●

Footer	Description
a	There is staggered recruitment for the 4 first patients in the trial on the concizumab arm.
b	Concizumab administration is performed at home except for visit 2 and visit 3 for patients randomised to concizumab and visit 9 and 9.1 for patients randomised to eptacog alfa. Sampling for Free TFPI, Anti-concizumab antibodies, Concizumab ELISA and Total TFPI are done prior to concizumab administration.
c	The duration of the visits will last according to patient's individual training need on concizumab administration, NovoPen®4, eDiary training etc. Visit 3 and visit 9.1 have a PK session of 24 hours and a safety follow up visit the following day.
d	Visit and procedures only performed for patients randomised to eptacog alfa and switching to concizumab treatment.Visit 9.1 should be performed 7 days (+ 1 day) after visit 9.
e	For patients being dose escalated on concizumab a phone call is recommended 1 week after first dose of concizumab.
f	Daily dosing preferably at the same time in the morning.
g	Evaluation of the laboratory results obtained from samples taken at screening.
h	Bleeding episodes occurring between visit 1 and visit 2 or at site should be registered in the eCRF. All bleeding episodes except for severe occurring after visit 2 at home should be registered in the eDiary. Severe bleeding episodes must be registered in the eCRF.
i	Eptacog alfa will be given to treat breakthrough bleeding episodes.
j	Sampling time schedule for thrombin generation, haematology, coagulation parameters, concizumab ELISA and FVII ELISA: pre-dose (-1 hour), post-dose: 10 min (±2 min), 1h (± 10 min), 3h (± 10 min), 6h (± 10 min), 9h (± 10 min), 12h (± 20 min) and 24h (± 20 min). All time points, except pre-dose, occur after eptacog alfa administration.
k	ONLY for patients randomised to concizumab arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
l	At visit 2, visit 3, visit 9 and 16 blood samples should be collected pre-dose. Patients must not treat themselves with concizumab until sampling has been performed.
m	Only body weight should be measured.

n	Vital signs should be evaluated before and after trial drug administration at visit 2 and visit 3 for concizumab arm and at visit 9 and visit 9.1 for patients in eptacog alfa arm switching to concizumab treatment.
o	In case clinical signs of e.g. hypersensitivity reactions or immune related events are seen, additional samples for ADAs may be taken. All antibody samples from the affected patient will be analysed on an ongoing basis. If antibodies are detected, additional blood samples will be taken and stored for characterisation of the antibodies.
p	Blood sampling for anti-concizumab antibodies and concizumab ELISA testing should only be collected for patients on concizumab.
q	If needed dispensing of eptacog alfa, histidine, trial injection kits and Direction For Use (DFU).
r	First treatment dose of concizumab is a loading dose and will be administered at visit 2 for the concizumab arm and visit 9 for the eptacog arm.
s	The patient must be in a non-bleeding state at the time of the first concizumab administration and should not have received any bypassing agent drugs,(e.g., eptacog alfa, FEIBA®) for treatment of a bleeding episode within a period of 24h (for eptacog alfa) or 48h (for FEIBA®) prior to first concizumab. Only eptacog alfa is allowed after visit 2.
t	Eptacog alfa administered in a non-bleeding state at site at visit 3 for the concizumab arm and at visit 9.1 for the eptacog alfa arm. The concizumab dose should be administered first followed by eptacog alfa dose. The interval between the concizumab and eptacog alfa should not exceed more than 30 min.
u	Patient treated with concizumab should be dose escalated at next scheduled visit if he experiences ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab. If the investigator judges that next scheduled visit is too late an unscheduled visit should be performed for dose escalation.
v	Home treatment training must take place at visit 2 at the latest and whenever needed afterwards. Patients randomised to eptacog alfa will be re-trained in NovoPen®4 and s.c. administration at visit 9 and 9.1. If necessary training can be performed as needed at other visits. The eDiary will be provided to the patients at visit 2 if the patient feels capable in s.c. administration and using the eDiary. Further the patients will be trained in recognition of signs/symptoms of thrombosis.
w	Only for patients randomised to on-demand arm.
x	*Visit repeated every 8 week until patient either discontinues, completes extension or is enrolled into phase 3 programme*
y	*For patients continuing in a subsequent trial End of Trial must be completed at visit 16. For patients declining participation in the prolongation, End of Trial must be completed at visit 17, 8 weeks after End of Treatment.*
z	*PRO questionnaires should only be completed at 15.1 for patients continuing in the prolongation of the trial.*
aa	*PRO questionnaires should only be completed at visit 16 for patients not continuing in the prolongation of the trial*

Section 4.2.2.1 Supportive secondary efficacy endpoints

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

Supportive secondary safety endpoints

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

Supportive secondary pharmacokinetic endpoints

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

Supportive secondary pharmacodynamic endpoints

- Free TFPI concentration
  - Value prior to the last dose administration at 24 weeks
  - Value prior to the last dose administration *after* at *least* 76 weeks
- Thrombin generation
  - Peak thrombin generation (nM) prior to the last dose administration at 24 weeks

- Peak thrombin generation (nM) prior to the last dose administration *after* at *least* 76 weeks
- Endogenous thrombin potential (nM^xmin) prior to the last dose administration at 24 weeks
- Endogenous thrombin potential (nM^xmin) prior to the last dose administration *after* at *least* 76 weeks
- Velocity index (nM/min) prior to the last dose administration at 24 weeks
- Velocity index (nM/min) prior to the last dose administration *after* at *least* 76 weeks

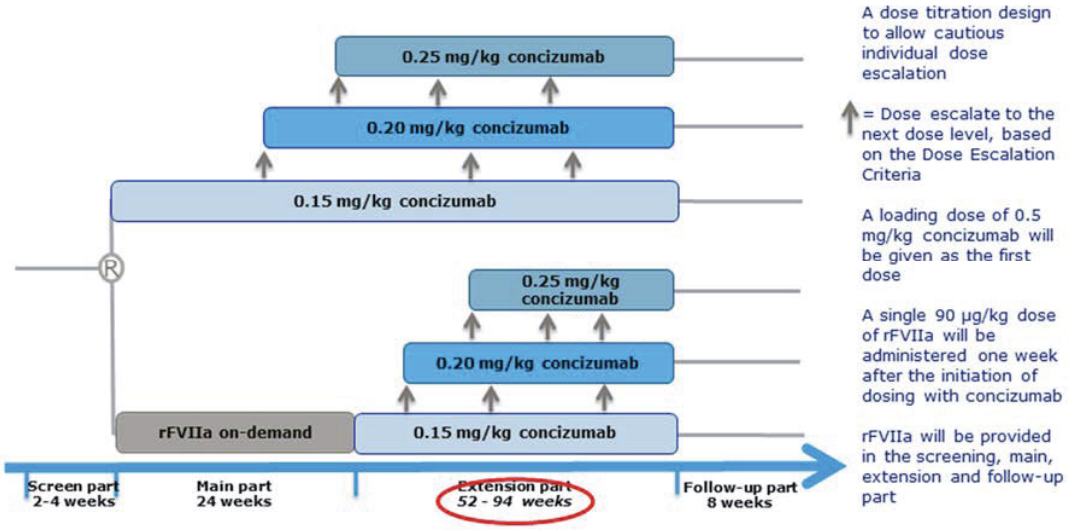
Section 4.2.3.2 Exploratory patient reported outcome endpoints

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

All endpoints referring to a time frame of either 24 weeks, or of at least 24 weeks, will be evaluated in the main part of the trial.

All endpoints referring to a time frame of *at least* 76 weeks will be evaluated in the extension part of the trial.

Section 5.1 Type of trial (Figure 5-1)



Section 5.1 Type of trial

The total trial duration for the individual patient will be approximately 86-~~88~~-*130* weeks, including a 2-4 week screening period, a 76-*118* week treatment period, and a follow-up period of 8 weeks, see Figure 5-1

The trial is split into a main part which lasts *at least* 24 weeks for all patients in the trial and an extension part which lasts up to ~~52~~ *94* weeks. In the main part, the primary and selected secondary endpoints will be analysed when 16 patients have completed a minimum of 24 weeks of concizumab prophylaxis and 8 patients have completed a minimum of 24 weeks of eptacog alfa (rFVIIa) on-demand or have withdrawn.

Section 5.2 Rationale for trial design

The duration of *at least* 24 weeks for the main part of the trial is deemed necessary in order to obtain information on the annualised bleeding rate on concizumab prophylaxis. The duration of the extension part of the trial will be *up to 94* ~~52~~ weeks and provide further information on efficacy, i.e. annualised bleeding rate, and also provide additional safety data upon 76-*118* week~~s~~ treatment with concizumab.

Patients participating in NN7415-4310 will be offered screening for eligibility to participate in the subsequent clinical trials for concizumab, following their participation in NN7415-4310 and provided that either the site participates in the subsequent trial with concizumab or if possible the patient can be transferred to a participating site. It is expected that the majority of the participating patients will join subsequent trial and thus may continue prophylactic treatment with concizumab.

Section 5.3 Treatment of patients (Table 5-1)

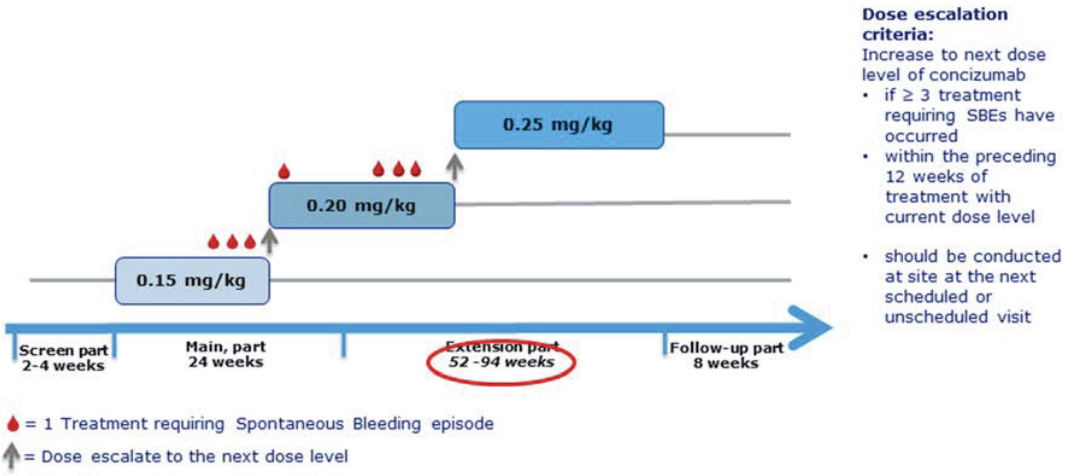
Compound Name	Strength	Dosage form	Route of administration	Treatment period
concizumab B [a]	100 mg/mL	solution for s.c. injection in a 3 mL cartridge [b]	Subcutaneous administration using NovoPen®4	For prophylactic treatment ~~in~~ *for at least* 76 weeks (for concizumab arm in the main part and extension part). For prophylactic treatment ~~in~~ *for at least* 52 weeks (for comparator arm in the extension part).
eptacog alfa (rFVIIa) [a, c]	5 mg/vial	Powder for solution for i.v. injection	Intravenous administration	For treatment of breakthrough bleeding episodes at the discretion of the investigator (screening, main, extension and follow up part). [c] Administration of doses higher than 90µg/kg to patients exposed to concizumab is not allowed. For on-demand treatment at the discretion of the investigator in 24 weeks for comparator arm in the main part. In the concizumab arm and comparator arm after switching to concizumab in the

				extension part of the study a single 90µg/kg dose for initial safety assessments in a non-bleeding state.[a] Will be provided for as long as patients participate in the trial (screening, main, extension and follow up part)

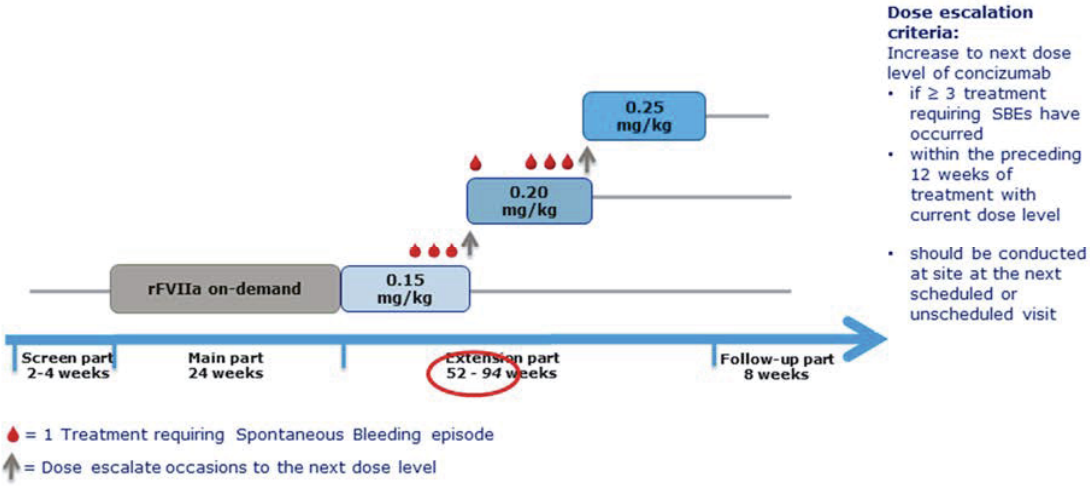
Section 5.3.3 Dose escalation

All spontaneous bleeding episodes (sBEs) are counted from 2 weeks after visit 2 (or visit 9 when switching from eptacog alfa (rFVIIa) to concizumab) (first treatment visit) until visit 16 (end of treatment visit), i.e. a total ~~of 74~~ *of up to 116* weeks. Dose escalation will be based on the number of spontaneous treated bleeding episodes in patients within preceding 12 weeks. However, before dose escalation can occur, to ensure the safety of the patients, the investigator must take into account the full clinical picture the patient is presenting with and all available laboratory results, including coagulation parameters.

Section 5.3.3 Dose escalation (Figure 5-3)



Section 5.3.3 Dose escalation (Figure 5-4)



Section 5.3.4 Co-administration of eptacog alfa (rFVIIa)

The patients will receive prophylactic doses of concizumab 0.15 mg/kg daily throughout the main part (*at least* 24 weeks) and the extension part (~~52~~ *up to 94* weeks), unless dose escalation criteria are fulfilled, see Section 5.3.3.

Section 5.5 Rationale for treatment

The treatment period during at least 24 weeks (the main part of the trial) is considered necessary for providing robust data that allow demonstration of clinical proof of concept and to support decision

making regarding a phase 3 confirmatory trial. Dosing for *up to 94* additional ~~52~~ weeks will provide valuable long term efficacy and safety data.

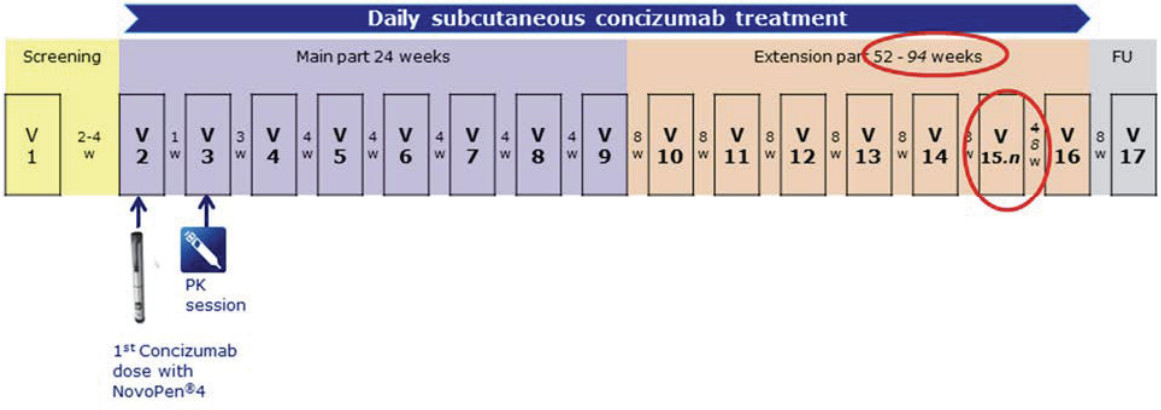
Section 7 Milestones

~~Planned~~ FPFV:	10-Aug-2017
~~Planned~~ FPFT:	30-Aug-2017
~~Planned~~ LPFV:	09-Mar-2018
Planned LPLV:	~~23-Oct-2019~~ *31-Jan-2020*

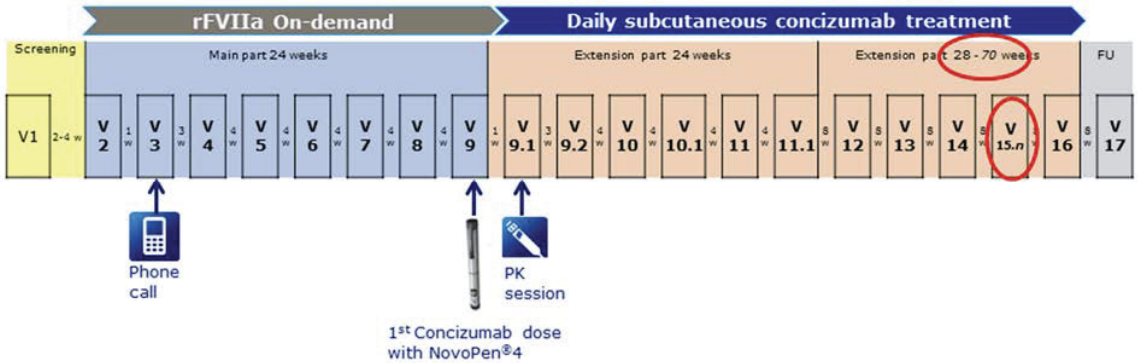
The total duration of concizumab treatment in this trial is *at least* 76 weeks for an individual patient randomised to concizumab prophylaxis treatment at visit 2.

The total duration of concizumab treatment in the trial is *at least* 52 weeks for an individual patient randomised to eptacog alfa (rFVIIa) on-demand treatment at visit 2.

Section 8 Methods and assessments (Figure 8-1)



Section 8 Methods and assessments (Figure 8-2)



Section 8.1 Visit procedures

Extension Part:

- Visit 9.1 (treatment and PK-visit with concizumab and eptacog alfa (rFVIIa) at site ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 9.2 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 10 (Assessment visit, patients treat themselves at home)
- Visit 10.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on-demand arm)
- Visit 11 (Assessment visit, patients treat themselves at home)
- Visit 11.1 (Assessment visit, patients treat themselves at home - ONLY for patients randomised to the eptacog alfa (rFVIIa) on demand-arm)
- Visit 12 (Assessment visit, patients treat themselves at home)
- Visit 13 (Assessment visit, patients treat themselves at home)
- Visit 14 (Assessment visit, patients treat themselves at home)
- Visit 15-*15.n* (Assessment visit, patients treat themselves at home)
- Visit 16 (Assessment visit and End of treatment)

Follow-up part

- Visit 17 (Assessment visit and End of trial)

Section 8.1.4 Premature discontinuation of trial product

The patients who permanently prematurely discontinue trial product at Investigator's discretion due to a safety concern after completion of the main part of the trial may have visit 17 scheduled 8 weeks after visit 16. Furthermore additional unscheduled visits will be conducted at least every 8 weeks for safety assessments (see Section 8.4 and 8.5.2), PK and PD markers. The patients who permanently prematurely discontinue trial product due to safety concerns may have the safety follow up period extended at Investigator's discretion until the safety concern have been resolved, but no later than Last Patient Last Visit as defined in Milestones (Section 7 of the protocol).

Section 8.1.12.7 Visit 12, 13, 14 and 15, *15.1, 15.2, 15.n*

Visits 12~~,~~ *to15.n* ~~13, 14 and 15~~ are to be scheduled *with an interval of 8 weeks* ~~on trial day 337 (48 weeks), 393(56 weeks), day 449 (64 weeks) and day 505 (72 weeks) respectively~~ with a visit window of ±7 days *until the patient either discontinues treatment or completes visit 16.*

If patient declines participation in the prolongation of the extension, visit 16 should be conducted 4 weeks after visit 15 (see Section 8.1.12.8)

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs, body measurement (weight only) and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary. Based on the assessment of any spontaneous bleeding episodes the investigator must evaluate if an escalation of the concizumab doses is needed according to the escalation rules described in section 5.3.3. All decisions to escalate the concizumab dose must be recorded in the eCRF.

A dispensing call must be performed in the IWRS.

In order to determine the correct amount of the patient's daily dose of concizumab, until next scheduled visit, investigator will consult the dosing table in the TMM on basis of the patient's current body weight. Investigator will communicate the daily dose of concizumab to the patient and record the dose for the coming home treatment period in the eCRF.

At the visit the patient will be provided with concizumab and/or eptacog alfa (rFVIIa) and trial injection kits, if necessary, to be able to conduct home treatment until next scheduled visit.

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes or any sign of thrombosis) arise after he has left the site.

At visit 15.1 only patients in the prolongation will be asked to complete the ePRO questionnaires before any other trial related activities are performed according to section 8.6.1~~;~~

- *Hemo-TEM*
- *SF-36v2*
- *SDS*
- *TSQM*
- *SIAQ-ISRQ*

At *the last visit (visit 15 or 15.n) before visit 16 (End of treatment)* ~~(visit 15)~~ patients should be reminded that treatment with concizumab must take place after the blood sampling at visit 16.

Section 8.1.12.8 Visit 16
Visit 16 is to be scheduled:

- on trial day 533 *(for patients declining participation in the prolongation of the trial)*
- *or later (for patients continuing in the extension or enrolled in a subsequent trial)* ~~(76 weeks)~~

with a visit window of ± 7days. Further visit 16 should be scheduled to be conducted at the last day of treatment with concizumab.

Patients ***not*** *continuing in the prolongation* will be asked to complete the PRO questionnaires before any other trial related activities are performed according to section 8.6.1

- Hemo-TEM
- SF-36v2
- SDS
- TSQM
- SIAQ-ISRQ

All assessments are listed in Section 2, and the assessment results from concomitant medication, vital signs and details of adverse events must be entered into the eCRF. Treatment with concizumab must take place after the blood sampling at this visit.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data from the eDiary.

For patients not continuing in the prolongation of the trial a completion session must be made at Visit 16 in the IWRS. In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat any bleeding episodes. Eptacog alfa (rFVIIa) may be requested via IWRS. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period. If necessary, the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

For patients continuing in the prolongation of the trial and are enrolled in a subsequent trial as completion session must be made at visit 16 in the IWRS, but no additional trial product (eptacog alfa) will be provided to the patient

For patients continuing in the prolongation of the trial but not enrolled in a subsequent trial a completion session must be made at Visit 16 in the IWRS. In the period from visit 16 to visit 17 the patient can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat any bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period. If necessary, the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.

~~In the period from visit 16 to visit 17 patients can be treated with eptacog alfa (rFVIIa) or other products at the discretion of the investigator to treat eventual bleeding episodes. Only eptacog alfa (rFVIIa) will be provided by Novo Nordisk during this period.~~

~~If necessary, a dispensing call must be performed in the IWRS. At the visit the patient will be provided with eptacog alfa (rFVIIa) and trial injection kits to be able to conduct home treatment until next scheduled visit.~~

The patient will be asked to return all used, partly used and unused concizumab cartridges and eptacog alfa (rFVIIa) during the trial as instructed by the investigator. NovoPen®4 must be returned. Drug accountability must be performed for concizumab and eptacog alfa (rFVIIa). Unused histidine syringes should be returned at every visit and new histidine syringes should be dispensed to the patient.

The patient must be instructed to call the site if any questions or issues (e.g. bleeding episodes) arise after he has left the site.

The End-of-Trial information must be entered in the End-of-Trial form in the eCRF at visit 16 for all patients continuing in a subsequent trial with concizumab.

Section 8.1.13 Visit 17 (End of trial) – Follow-up part

~~Visit~~ *For patients not enrolled into a subsequent trial with concizumab visit* 17 is to be scheduled *8 weeks after visit 16* ~~on trial day 589 (84 weeks)~~ with a visit window of minus 7 days.

All assessments are listed in Section 2, and the assessment results from concomitant medication, physical examination, body measurements (weight only), vital signs and details of adverse events must be entered into the eCRF.

Investigator must perform compliance check of treatment and reporting of bleeding episodes through reviewing collected data. Patients should be asked if their female partner has become pregnant, see Section 12.5.1.

The patient will be asked to return all used, partly used and unused eptacog alfa (rFVIIa), unused histidine syringes, eDiary device and Trial card. Drug accountability must be performed for eptacog alfa (rFVIIa).

End-of-Trial information must be entered in the End-of-Trial form in the eCRF *at visit 17 for all patients **not** continuing in a subsequent trial with concizumab. .*

~~Completion or treatment discontinuation (if the trial is not completed) session should be performed in IWRS~~ *If eptacog alfa (rFVIIa) was requested at visit 16 drug accountability should be performed in IWRS*, see Section 10.

Section 8.1.14 Unscheduled Visit

Unscheduled visits can be performed at any time during the trial as listed in Section 2. *Unscheduled visits may be performed after visit 17 at the discretion of the investigator for patients who has*

permanently prematurely discontinue trial product due to a safety concern (see Section 8.1.4). The purpose of the unscheduled visit must be documented in the eCRF.

During unscheduled visits assessments and blood sampling must be performed according to Section 2. Assessment results must be recorded in the eCRF. Assessments and blood sampling can be omitted if the only reason for the unscheduled visit is dispensing of trial product *or replacement of eDiary or NovoPen® 4* .

Section 8.5 Laboratory assessments
An approximate total blood volume of *768* ~~625~~ mL will be taken from each patient on the concizumab arm and *868* ~~725~~ mL from each patient on the eptacog alfa (rFVIIa) arm.

Section 8.5.2.7 Anti-concizumab antibodies
The *binding ADA* samples will be analysed in batches during the trial and results will be available to the data monitoring committee approximately every third month after the first patient has been dosed. Neutralising antibodies will be analysed and reported at the EOT. A detailed description of the assay methods will be included in the antibody analysis report at the end of the trial.

Investigators will be notified in case their patient is shown to have developed *binding and/or* neutralising antibodies against concizumab.

In the event that a trial patient develops binding ADAs towards concizumab during the course of the trial and has measurable binding ADAs at his End-of-Trial visit, the patient may attend an ADA follow-up visit. The ADA positive patients will be called for additional visits, e.g. every 4 to 6 weeks, for safety assessment and blood sampling for *binding* ADA*s* and PD markers (free TFPI and Thrombin generation). The ADA positive patients will be followed no longer than one year after End-of-Trial.

Section 8.6.1 Patient reported outcome
The PROs should be assessed at the scheduled visits following the order listed below:

- visit 1 (Hemo-TEM, VERITAS-Pro® or VERITAS-PRN®)
- visit 2 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 3 (PGI-C, Hemo-TEM)
- visit 4 (PGI-C, Hemo-TEM)[a]
- visit 5 (PGI-C, Hemo-TEM)
- visit 6 (PGI-C, Hemo-TEM)
- visit 7 (PGI-C, Hemo-TEM)
- visit 8 (PGI-C, Hemo-TEM)
- visit 9 (PGI-C, Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit 10 (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)
- visit ~~16~~*15.1 or 16* (Hemo-TEM, SF-36v2, SDS, TSQM, SIAQ-ISRQ)

Section 8.6.1 Patient reported outcome
At visit 3-8: before any visit-related activities the patient should complete the PGI-C before the Hemo-Tem. These are the rules that apply:

- If the patient responds "1" to question 1 in the PGI-C, the patient should also complete the Hemo-TEM. In this case the patient should not fill in the PGI-C any more in the trial and the Hemo-TEM only again at visits 9, 10 and *15.1or* 16.

- If the patient responds "0" or "2" to question 1 in the PGI-C, the patient should not complete any other questionnaires at this visit, but should repeat the procedure at next visit.

At visit 10 and *15.1or* 16 all patients should complete Hemo-TEM, SF-36v2, SDS, TSQM and SIAQ-ISRQ.

Section 8.6.1 Patient reported outcome
The investigator must check the ePROs for completeness. ~~potential AEs and SAEs.~~ The completed ePROs should be transmitted at each visit to the PRO database by the Investigator.

Section 12.1.1 Adverse event
Bleeding episodes and other symptoms (e.g. pain, swelling, synovitis, arthralgia, ~~injection site haematoma~~) in connection with bleeding episodes should not be reported as AEs/SAEs unless the event is fatal, life-threatening or evaluated by the investigator as related to trial product or trial procedure. All bleeding episodes and other findings related to underlying disease will be captured in the eCRF/eDiary

Section 12.2 Reporting of adverse events
All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the patient has signed the informed consent until *visit 16 (end of treatment) for patients enrolling into a subsequent trial with concizumab and at* the end of the post-treatment follow-up period (visit 17) *for patient not enrolling into a new trial*. The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12-1

Section 12.2 Reporting of adverse events
When eptacog alfa (rFVIIa), NovoSeven® is used as IMP, expectedness ~~should be performed according to the Company Core Data Sheet (CCDS)~~ *is performed according to the following reference documents: Investigator's Brochure; current version and any updates thereto*.

Section 12.7 Rules for putting enrolment on hold
*~~Superficial thrombophlebitis or venous thrombosis associated with indwelling catheters is not considered a significant thromboembolic event unless evaluated as such by the investigator~~

Section 17 Statistical considerations

Endpoints comprising number of bleeding episodes will be evaluated based on treated bleeding episodes only. Multiple bleeding locations occurring from the same event (e.g., due to a bicycle accident) or at the same time point will be counted as one bleeding episode. Further, the endpoints will not include re-bleed. A re-bleed is defined as a bleeding episode (worsening of bleeding site conditions e.g. swelling, pain) within 72 hours after stopping *treatment* of a previous bleeding episode at the same (or subset of the same) anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping *treatment*, the ~~treatment~~ *bleed* is defined as a new bleeding episode.

Data collected among permanently prematurely discontinued from trial product due to a safety concern patients after visit 17, in the possible extended safety follow-up period (ref section 8.1.4) will be listed only.

Section 17.3.1 Estimand and primary statistical analysis

The estimand for the primary endpoint will be estimated using negative binomial regression with log of exposure time ~~in~~ (*the included observational period of the* main part*)* as offset and regimen as factor. *The offset for first CPoC criterion of patients in concizumab arm is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for subjects on 0.15 mg/kg. The offset for the second criterion of patients in concizumab arm is the log of the individual exposure time in the main part. For both criteria and patients in the on-demand arm, the offset is the log of the exposure time in the main part. The analysis provides*, ~~providing~~ an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis has the underlying assumption that the missing data mechanism is "missing at random", i.e. MAR. Under this assumption, the statistical behaviour of the missing data (given the observed responses and the mean value structure) is assumed to be the same as for the observed data. The estimand will be estimated based on the FAS and only data collected prior to discontinuation of trial product or initiation of alternative treatment options will be used to draw inference.

Section 17.3.3 Additional analysis

An additional evaluation of the primary endpoint will be made, including *the* actual concizumab dose level *(interpreted as the patients last dose level)* as additional factor in the primary analysis model specified above. Point estimates and 95% confidence interval will be provided for the ABR at the different dose levels of concizumab (0.15, 0.20 and 0.25 mg/kg). Furthermore, a~~n~~ *series of* ~~analyseis~~ *analyses* with individual steady state PK/PD assessments included as covariates in the negative binomial regression model as specified for the primary analysis of number of bleeding episodes will be performed in order to evaluate possible associations between PK/PD and ABR that potentially could guide dose-selection. The referred steady-state PK/PD assessments comprise the

concizumab trough level, TFPI value prior to the last s.c. dose administration, peak thrombin generation (nM), Endogenous thrombin potential (nMxmin) and velocity index (nM/min).

17.4.1 Supportive secondary efficacy endpoints

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

Section 17.4.1 Supportive secondary efficacy endpoints

The remaining supportive secondary efficacy endpoints will be summarised descriptively by treatment regimen. In addition, number of bleeding episodes during *at least* 76 weeks of treatment with prophylactic concizumab will be analysed using a negative binomial model with log of trial duration as offset, providing estimates of the ABR with confidence interval for that particular regimen.

Section 17.4.2 Supportive secondary safety endpoints

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

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

TEAE is defined as an event that has onset ~~from the first exposure~~ ~~to treatment~~ *after randomisation* until the last visit in the trial. *Adverse events collected among permanently prematurely discontinued from trial product due to a safety concern patients after visit 17 in the possible extended safety follow-up period (ref section 8.1.4) are not considered treatment emergent.* Treatment-emergent adverse event endpoints will be summarised by system organ class, preferred term, seriousness, severity and relation to trial product. All adverse events will further be listed. *Relations to Novo Nordisk marketed products used by patients in the trial, such as eptacog alpha, is reported as described in section 12.2 of the protocol and not reported in the report of the trial*

Section 17.4.3 Supportive secondary pharmacokinetic endpoints

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

Section 17.4.4 Supportive secondary pharmacodynamic endpoints

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

Section 17.4.5.2 Exploratory patient reported outcome endpoints

- Change in Hemo-TEM after 24 weeks from treatment onset
- Change in Hemo-TEM after *at least* 76 weeks from treatment onset
- Change in SF-36v2 after 24 weeks from treatment onset
- Change in SF-36v2 after *at least* 76 weeks from treatment onset
- Change in SDS after 24 weeks from treatment onset
- Change in SDS after *at least* 76 weeks from treatment onset
- Change in TSQM after 24 weeks from treatment onset
- Change in TSQM after *at least* 76 weeks from treatment onset
- Change in SIAQ-ISRQ after 24 weeks from treatment onset
- Change in SIAQ-ISRQ after *at least* 76 weeks from treatment onset

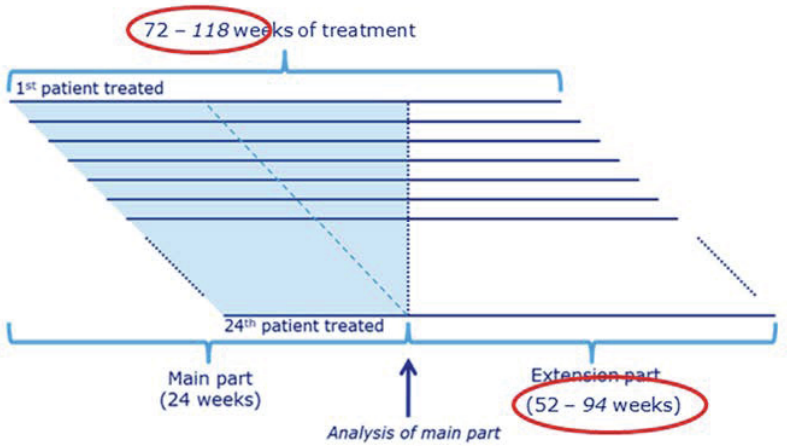
- Status of PGI-C after 24 weeks from treatment onset

VERITAS-PRN®, SF-36v2, SDS and TSQM will be scored according to their respective scoring algorithms. Change *after 24 weeks of treatment onset for SF-36v2, SDS and TSQM* from visit 2 to visit 9 will be analysed with an ANCOVA model including regimen as a factor and baseline score as covariate.

Section 17.5 Interim analysis

The trial does not include a formal interim analysis. However, the split of the trial into a main and extension part offers the opportunity of reporting results before the end of the trial. *For patients in the concizumab s.c. prophylaxis arm,* main ~~Main~~ part is defined to end when the last patient has completed a minimum of 24 weeks of treatment or at LPFT (visit 2) + 24 weeks if the last patient has withdrawn before visit 9. *For patients in the on-demand arm, the main part consists of observations from randomisation until transfer to concizumab s.c. prophylaxis treatment or withdrawal from trial, whichever comes first.* All observations for these patients after transfer to concizumab treatment are regarded as extension part of the trial. Other reporting of the trial might be done during the extension part once the data collection and review of the main part data has been finalised and individual CTRs might in such case be issued. A CTR describing results from the main and the extension part will be written when the last patient has either completed or withdrawn from the trial. All main conclusions regarding clinical proof of concept and dose guidance for phase 3 will be based on the reporting after the main part, see Figure 17-1.

Section 17.5 Interim analysis (Figure 17-1)



2.2 Informed Consent

2.2.1 Master Informed Consent

What kind of trial products will you receive?

If you agree to participate in the trial you will either inject one dose of concizumab daily for up to ~~76~~ *118* weeks (concizumab treatment), or receive on-demand treatment with eptacog alfa for bleeding episodes in the first 24 weeks of the trial (on-demand treatment), before switching to daily concizumab treatment for the remaining period (~~52~~ *56 - 94* weeks). If you experience a bleeding episode during treatment with concizumab, you will treat this with eptacog alfa. If you experience 3 or more bleeding episodes within a 12 week period of concizumab treatment, your trial doctor will discuss with you the possibility of increasing your concizumab dose. Bleeding episodes that occur within the first 2 weeks of concizumab treatment will not be included in the total number of bleeding episodes required for dose escalation. You will start treatment with the lowest dose of concizumab, 0.15 mg/kg. It will be possible to increase your dose twice during the trial: from 0.15 to 0.20 mg/kg and from 0.20 to 0.25 mg/kg if the bleeding episodes occur within a second 12 week period after dose escalation has taken place. If you are receiving on-demand treatment, you will receive eptacog alfa for on-demand treatment of your bleeding episodes during the first 24 weeks of the trial.

~~After 52 or 76 weeks of treatment with concizumab~~ *Once you have treated yourself daily with concizumab for a period of 56-118 weeks you and your doctor will decide if you can continue being treated with concizumab in a new trial as long as your site participates in the trial or if you can be transferred to a site nearby. If you choose to say yes your last visit will be visit 16 and you will continue in the new trial. If you choose to say no you will* discontinue treatment *with concizumab at*

visit 16 and be followed for an additional 8 weeks before completing the trial. During this period you will be provided with eptacog alfa for the treatment of bleeding episodes.

What will happen at the different visits in the trial?
If you meet all criteria, your involvement in the trial will last *from* ~~approximately 88~~ *90 up to 130* weeks *depending on when you started in the trial*. During this time you will have ~~17 or 21~~*between 16 to 26* planned visits to your trial site. The duration of each visit at the site may vary depending upon the different assessments to be performed and the routines at the site. Please feel free to ask the trial doctor how much time you should expect to spend on each specific visit.

Treatment at Home (Visits 4 to 16):

Concizumab Treatment
Visit 4 occurs approximately 3 weeks after visit 3. Visits 5 to 9 are scheduled approximately 4 weeks apart and visits 10 to 16 are scheduled approximately 8 weeks apart. *If you choose to continue in the trial the extra visits will be placed between visit 15 and visit 16 with following numbers 15.1, 15.2 and so on. The number of planned extra visits will be up to 5 depending on when you started in the trial.* You will receive concizumab to take home at each visit and eptacog alfa at visits 3, 6, 9, 10, 11 and 12 to 16, or at an unscheduled visit if needed.

At each visit your trial doctor will ask you if you have had any change in your health or medications since the last visit and evaluate if the trial is suitable for you to continue. Blood will be drawn for analysis, vital signs measured, and weight recorded. Your trial doctor or nurse will review your electronic diary and any information that you entered about bleeding episodes that may have occurred between visits. You will be asked to complete up to 6 questionnaires related to your quality of life, well-being and treatment at visits 4 to 10 and 5 questionnaires at visit ~~16~~*15.1*.

On-demand Treatment
Visit 9.2 occurs approximately 3 weeks after visit 9.1. Visits 10 to 12 are scheduled approximately 4 weeks apart and visits 12 to 16 are scheduled approximately 8 weeks apart. *If you choose to continue in the trial the extra visits will be placed between visit 15 and visit 16 with following numbers 15.1, 15.2 and so on. The number of extra planned visits will be up to 5 depending on when you started in the trial.*

At each visit your trial doctor will ask you if you have had any change in your health or medications since the last visit and evaluate if the trial is suitable for you to continue. Blood will be drawn for analysis, vital signs measured and weight recorded. Your trial doctor or nurse will review your electronic diary and any information that you entered about bleeding episodes that may have occurred between visits. You will be asked to complete 2 questionnaires related to your quality of life, well-being and treatment at visits 4 to 8 and 5 questionnaires at visit 10 and ~~16~~*15.1*.

Follow-up visit (Visit 17):

This visit will only happen if you do not continue in a new trial.

Concizumab & On-demand Treatment
There will be a period of approximately 8 weeks between visit 16 and 17 (follow-up and end of trial visit). Blood will be drawn for analysis, vital signs measured, details of any other medications you may be taking recorded and a physical examination performed. You will return the electronic diary and any remaining eptacog alfa. At the final visit, you and your trial doctor will discuss the best alternatives for your future treatment. Novo Nordisk will not offer any free medication, additional care or continued treatment with the trial products after the completion of the trial.

Between Visits:
During the trial blood samples will be taken for different tests. The total amount of blood drawn in the course of the trial is ~~approximately 625~~ *up to 768* mL for patients receiving concizumab treatment and ~~725~~ *up to 868* mL for patients receiving on-demand treatment *depending on how many planned visits you will have before completing the trial*. For comparison purposes the blood taken at a blood donation is approximately 500 mL.

Who can you contact during and after the trial?
<EU countries only: If you have any questions, concerns or complaints as to how Novo Nordisk is using your personal information, you can contact your study doctor. Your study doctor will then contact Novo Nordisk's Data Protection Officer. The [Country] Data Protection Authority is responsible for making sure that laws about personal information are followed in [Country]. For more information about your rights, or if you wish to make a complaint, you can contact [Data Protection Authorities contact information].>

2.2.2 Genotyping and Long-term Storage of Human Samples Informed Consent

<EU countries only: If you have any questions, concerns or complaints as to how Novo Nordisk is using your personal information, you can contact your study doctor. Your study doctor will then contact Novo Nordisk's Data Protection Officer. The [Country] Data Protection Authority is responsible for making sure that laws about personal information are followed in [Country]. For more information about your rights, or if you wish to make a complaint, you can contact [Data Protection Authorities contact information].>

2.2.3 Female partner of a Male Subject in Case of an Abnormal Pregnancy Informed Consent

<EU countries only: If you have any questions, concerns or complaints as to how Novo Nordisk is using your personal information, you can contact your study doctor. Your study doctor will then contact Novo Nordisk's Data Protection Officer. The [Country] Data Protection Authority is responsible for making sure that laws about personal information are followed in [Country]. For

more information about your rights, or if you wish to make a complaint, you can contact [Data Protection Authorities contact information].>

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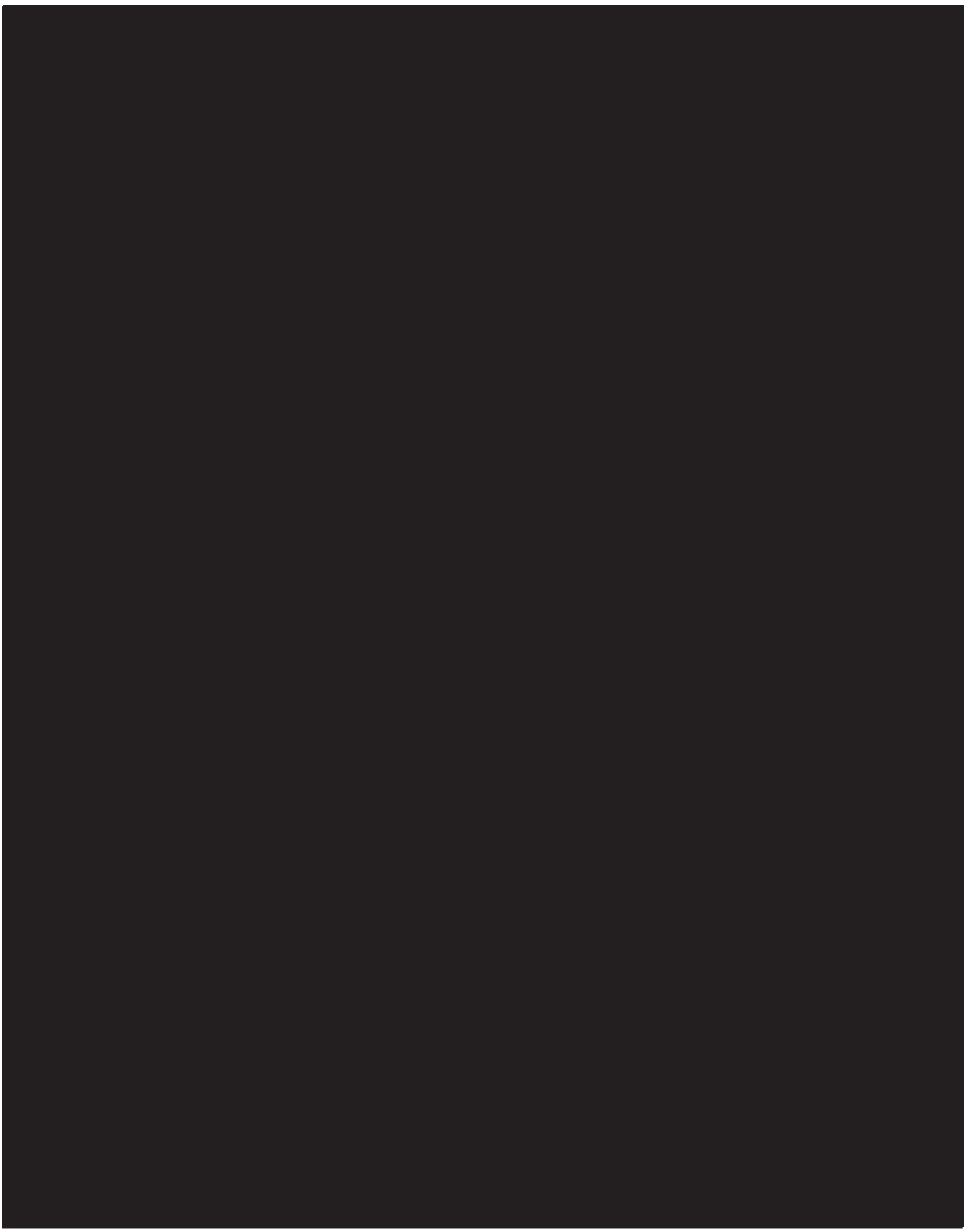

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