Protocol

VOYAGER2

Protocol Title:
Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Peroral Doses of Inno8 in People with Haemophilia A.

Short Title:
A research study looking at how different doses of study medicine (Inno8) work in the body of people with haemophilia A

Substance Name: Inno8

Protocol Number: NN7442-8454

Protocol Version Number: Version 2.0

Protocol Version Applicability: Global

Universal Trial Number: U1111-1317-4366

EU CT Number: 2025-520490-38

Pre-IND Number: 157526

Study Phase: 1

Sponsor Name: Novo Nordisk A/S

Sponsor Legal Address: Novo Allé, 2880 Bagsvaerd, Denmark

In the following, Novo Nordisk A/S and its affiliates will be stated as “Novo Nordisk”.
This confidential document is the property of Novo Nordisk. No unpublished information contained herein may be disclosed without prior written approval from Novo Nordisk. Access to this document must be restricted to relevant parties.

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 2.0	07 May 2025	Global
Original protocol version 1.0	09 April 2025	Global

Protocol version 2.0 (07 May 2025)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014;[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 2.0:

This version of the protocol is prepared to correct a few inconsistencies in protocol version 1.0. Details of these corrections are listed below. In addition, formatting errors are corrected.

Section # and name	Description of change	Brief rationale
Section 4.1 Overall design	The sentence in the end of 3rd paragraph of this section stating that "The participants must bring this container/duma to the site for dosing day 10 (visit 11), where they will be dosed on-site" has been corrected to "The participants must bring this container/duma to the site for dosing day 10 (visit 11), where the participants will self-administer the trial product on-site"	To avoid confusion and align with text in Section 6.4.
Section 11 References	The reference list is updated	Due to a technical error, the previous protocol version (1.0) had reference list not matching with the references in the document. This has been now corrected.

Table of contents

Page

Protocol amendment summary of changes table **2**

Table of contents **3**

1 Protocol summary **7**
1.1 Synopsis 7
1.2 Schedule of activities 9
1.3 Schedule of PK, PD and safety assessments 13

2 Introduction **15**
2.1 Study rationale 15
2.2 Background 16
2.2.1 Inno8 16
2.2.2 Study population 16
2.3 Benefit-risk assessment 17
2.3.1 Risk assessment 17
2.3.2 Benefit assessment 18
2.3.3 Overall benefit-risk conclusion 18

3 Objectives and endpoints **19**

4 Study design **20**
4.1 Overall design 20
4.2 Scientific rationale for study design 21
4.2.1 Rationale for study design 21
4.2.2 Rationale for study population 22
4.3 Justification for dose 23
4.3.1 Selected doses 23
4.3.2 Exposure limit 24
4.4 End of study definition 25

5 Study population **26**
5.1 Inclusion criteria 26
5.2 Exclusion criteria 26
5.3 Lifestyle considerations 27
5.3.1 Meals and dietary restrictions 28
5.3.2 Physical activity 28
5.3.3 Other restrictions 28
5.4 Screen failures 28
5.4.1 Rescreening 29
5.5 Rescheduling criteria 29
5.5.1 Participants screened but not dosed 30

6 Study intervention(s) and concomitant therapy **31**
6.1 Study intervention(s) administered 31
6.2 Preparation, handling, storage and accountability 32
6.3 Measures to minimise bias: Randomisation and blinding 33
6.4 Study intervention compliance 33
6.5 Dose modification 33
6.5.1 Dose escalation studies 33
6.5.1.1 Sentinels 33
6.5.1.2 Dose escalation 34
6.6 Continued access to study intervention after end of study 34
6.7 Treatment of overdose 34
6.8 Concomitant therapy 35

6.9 Bleeding episodes 35
6.9.1 Treatment of bleeding episodes 35
6.9.2 Recording of bleeding episodes 37
6.9.3 Severity rating of bleeding episodes 38
6.9.4 Treatment of bleeds in connection with a surgery 38

7 Discontinuation of study intervention and participant discontinuation/withdrawal 40
7.1 Discontinuation of study intervention 40
7.1.1 Stopping criteria 40
7.1.1.1 Participant level 40
7.1.1.2 Cohort level 41
7.2 Participant discontinuation/withdrawal from the study 41
7.2.1 Replacement of participants 42
7.3 Lost to follow-up 42

8 Study assessments and procedures 44
8.1 Screening/baseline assessments and procedures 44
8.2 Efficacy assessments 45
8.3 Safety assessments 46
8.3.1 Physical examinations 46
8.3.2 Vital signs 46
8.3.3 Electrocardiograms 47
8.3.4 Clinical safety laboratory assessments 47
8.4 Adverse events and other safety reporting 47
8.4.1 Time period and frequency for collecting AE information 48
8.4.2 Method of detecting AEs 48
8.4.3 Follow-up of AEs 49
8.4.4 Regulatory reporting requirements for SAEs 49
8.4.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs 49
8.4.6 Adverse event of special interest 49
8.4.7 Technical complaints 50
8.5 Pharmacokinetics 50
8.6 Pharmacodynamics 50
8.7 Genetics 52
8.8 Biomarkers 52
8.9 Immunogenicity assessments 52
8.10 Human biosamples for future research 54

9 Statistical considerations 55
9.1 Statistical hypotheses 55
9.1.1 Multiplicity adjustment 55
9.2 Analysis sets 55
9.3 Statistical analyses 55
9.3.1 General considerations 55
9.3.2 Primary endpoint analysis 55
9.3.2.1 Definition of endpoints 55
9.3.2.2 Main analytical approach 55
9.3.2.3 Sensitivity analysis 56
9.3.2.4 Supplementary analysis 56
9.3.3 Secondary endpoint analysis 56
9.3.3.1 Pharmacokinetic analysis 56
9.3.3.2 Pharmacodynamic analysis 57
9.3.3.3 Safety analysis 57
9.3.4 Exploratory endpoint analysis 57
9.3.5 Other safety analyses 57

9.3.6 Other analyses 57
9.4 Interim analysis 58
9.5 Sample size determination 58

10 Supporting documentation and operational considerations 59
10.1 Appendix 1: Regulatory, ethical and study oversight considerations 59
10.1.1 Regulatory and ethical considerations 59
10.1.2 Financial disclosure 60
10.1.3 Informed consent process 60
10.1.4 Recruitment and information to participants during the study 60
10.1.5 Data protection 61
10.1.6 Committees structure 62
10.1.6.1 Novo Nordisk safety committee 62
10.1.7 Dissemination of clinical study data 62
10.1.8 Data quality assurance 62
10.1.8.1 Case report forms (CRF) 62
10.1.8.2 Monitoring 63
10.1.8.3 Protocol compliance 63
10.1.9 Source documents and source data 64
10.1.10 Retention of clinical study documentation 64
10.1.11 Study and site start and closure 65
10.1.12 Responsibilities 65
10.1.13 Indemnity statement 66
10.1.14 Publication policy 67
10.1.14.1 Communication of results 67
10.1.14.2 Authorship 67
10.1.14.3 Site-specific publications by investigators 68
10.1.14.4 Investigator access to data and review of results 68
10.2 Appendix 2: Clinical laboratory tests 69
10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up and reporting 72
10.3.1 Definition of AE 72
10.3.2 Definition of an SAE 72
10.3.3 Description of AESIs, AEs requiring additional data collection and other events requiring collection of additional information 73
10.3.4 Recording and follow-up of AEs and/or SAEs 78
10.3.4.1 AE and SAE recording 78
10.3.4.2 Assessment of severity 79
10.3.4.3 Assessment of causality 79
10.3.4.4 Outcome of AEs 80
10.3.4.5 Follow-up of AE and SAE 80
10.3.5 Reporting of SAEs and AESIs 81
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information 83
10.5 Appendix 5: Genetics 84
10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting 85
10.6.1 Definition of technical complaint 85
10.6.2 Recording and follow-up of technical complaints 85
10.7 Appendix 7: Country-specific requirements 87
10.8 Appendix 8: Abbreviations 88

11 References 90

Protocol attachment I Global list of key staff and relevant departments and key suppliers of clinical relevance

Protocol attachment II Country list of key staff and relevant departments and key suppliers of clinical relevance

1 Protocol summary

1.1 Synopsis

This is an interventional, multi-national, multi-centre, open-label, multiple ascending dose (MAD), phase 1 study.

Rationale:

The purpose of this study is to provide safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) data of multiple peroral doses of Inno8 during 10-days treatment in people with haemophilia A, thereby supporting further clinical development of peroral Inno8 for prophylaxis in people with haemophilia A with or without FVIII inhibitors.

Objectives and endpoints:

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To investigate the safety and tolerability of multiple peroral doses of Inno8 in people with haemophilia A	Primary:		
	Number of treatment emergent adverse events	From time of dosing (Day 1) to end of follow-up (Day 46)	Count
Key Secondary	Title	Time frame	Unit
To investigate the pharmacokinetics of multiple peroral doses of Inno8 in people with haemophilia A	Supportive secondary:		
	C_{max}: the maximum concentration of Inno8 after multiple doses	From Day 10 to Day 11	ng/mL
	$AUC_{0\text{-}24h}$: the area under the Inno8 concentration-time curve in the dosing interval after multiple doses	From Day 10 to Day 11	ng*day/mL

Overall design:

The study consists of:

- a 28-days screening period,
- a 10-days intervention period,
- a 35-days follow-up period.

During the 10-day intervention period, the study participants will be attended by site staff daily either at on-site or at-home visits or through phone/video calls for collection of information and/or blood samples for laboratory assessments. The safety, PK and PD data will be collected at regular intervals throughout the study period.

Study intervention groups and duration:

This study consists of 2 cohorts, of which:

- the participants in cohort 1 will receive the highest dose of peroral Inno8 administered in the MAD cohort of NN7442-7582 study and

- the participants in cohort 2 will receive a higher dose that is up to two-fold higher than cohort 1, assessed by dose or exposure, as appropriate, depending on dose proportionality and bioavailability determined in NN7442-7582 study.

All the study participants will receive daily doses of Inno8 for 10 days, administered perorally. Each Inno8 dose may include 1-2 tablets with a dose range between 10 mg to 200 mg. The trial product is provided in a 40 mL HDPE bottle (10 tablets per bottle).

Total study duration for the individual participant will be up to 11 weeks (from screening to end of study visit).

Number of participants:

An adequate number of participants will be screened to achieve a planned total of 20 male participants with haemophilia A with or without FVIII inhibitors (10 in cohort 1 and 10 in cohort 2). In case replacement is needed, additional participants may be exposed to the study intervention.

Participant characteristics:

The participants will at inclusion meet the following key inclusion criteria and none of the following key exclusion criteria:

Key inclusion criteria:

- Male
- Age 18-64 years (both inclusive) at the time of signing the informed consent.
- Body weight ≥45 kgs
- Diagnosis of congenital haemophilia A with FVIII activity ≤ 15% with or without FVIII inhibitors, based on medical records.

Key exclusion criteria:

- Current or prior exposure to any prophylactic treatment for haemophilia A within 5 half-lives of the medicinal product by the time of screening
- Body mass index ≥30.0 kg/m^2
- Increased risk of thrombosis, e.g. known history of personal or first-degree relative(s) with unprovoked deep vein thrombosis
- Any clinical signs or established diagnosis of venous or arterial thromboembolic disease
- Any known coagulation disorders other than haemophilia A
- Ongoing or planned immune tolerance induction therapy
- Presence of clinically significant gastrointestinal disorders potentially affecting absorption of drugs and/or nutrients, as judged by the investigator.

Data monitoring committee:

No data monitoring committee is used for this study.

1.2 Schedule of activities

Table 1-1 Schedule of activities (SoA)

Procedure	Protocol section	Screening	Intervention Period									End of Treatment	Follow-up Period					End of Study
Visit		V1	V2[a]	V3	P4	V5	P6	P7	V8	V/H9[b]	V/H10[b]	V11[a]	V12	V13	V14	V15	V16	V17[c]
Timing of Visit (Days)		-28	1	2	3	4	5	6	7	8	9	10	11	17	23	29	36	46
Visit Window (Days)		1/13	0	0	0	0	0	0	0	0	0	0	0	±1	±2	±2	±2	+3
Informed Consent[d]	10.1.3	X																
Demography[e]	8.1	X																
Eligibility Criteria	5.1, 5.2	X	X															
Treatment allocation	5.5		X															
Treatment Discontinuation Criteria	7.1		X	X	X	X	X	X	X	X	X	X						
Concomitant Medication	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body measurements	8.3.1	X																
Vital Signs[f]	8.3.2	X	X	X		X			X	X	X	X	X				X	X
Physical Examination[f]	8.3.1	X	X	X					X	X			X				X	X
ECG[f]	8.3.3	X	X	X									X				X	X
Medical History/Concomitant Illness[g]	8	X	X															

Procedure	Protocol section	Screening	Intervention Period									End of Treatment	Follow-up Period					End of Study
Visit		V1	V2[a]	V3	P4	V5	P6	P7	V8	V/H9[b]	V/H10[b]	V11[a]	V12	V13	V14	V15	V16	V17[c]
Timing of Visit (Days)		-28	1	2	3	4	5	6	7	8	9	10	11	17	23	29	36	46
Visit Window (Days)		1/13	0	0	0	0	0	0	0	0	0	0	0	±1	±2	±2	±2	+3
Adverse event[g]	8.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[f]	10.2	X	X	X		X			X	X	X	X	X	X	X		X	X
Anti-Inno8 antibodies			X														X	X
Coagulation parameters		X	X	X		X			X	(X)	(X)	X	X	X	X		X	X
Biochemistry		X	X	X		X			X	(X)	(X)	X	X	X	X		X	X
Haematology		X	X	X		X			X	X	X	X	X	X	X		X	X
Urinalysis		X	X			X						X	X					X
Lipids		X																
eGFR		X	X	X		X			X	(X)	(X)	X	X	X	X		X	X
PK Inno8[f]	8.5		X	X		X			X	(X)	(X)	X	X	X	X	X	X	X
Inno8 activity	8.6		X	X		X			X	(X)	(X)	X	X	X	X	X	X	X
Thrombin Generation[f]	8.6		X	X		X			X	(X)	(X)	X	X	X	X	X	X	X
aPTT[f]	8.6		X	X		X			X	(X)	(X)	X	X	X	X	X	X	X
Administration of Trial Product[h]	6.1		X	X	X	X	X	X	X	X	X	X						

Procedure	Protocol section	Screening	Intervention Period									End of Treatment	Follow-up Period					End of Study
Visit		V1	V2[a]	V3	P4	V5	P6	P7	V8	V/H9[b]	V/H10[b]	V11[a]	V12	V13	V14	V15	V16	V17[c]
Timing of Visit (Days)		-28	1	2	3	4	5	6	7	8	9	10	11	17	23	29	36	46
Visit Window (Days)		1/13	0	0	0	0	0	0	0	0	0	0	0	±1	±2	±2	±2	+3
Drug dispensing[i]	6.2		X															
Drug accountability	6.2											X						
Treatment compliance contact	6.4				X	X	X	X	X	X	X							
Reminders																		
Hand Out ID Card			X															
End of Study form																		X
Attend Visit Fasting for on-site dosing	5.3.1		X	X								X						

Abbreviations: AE = Adverse event; aPTT = activated partial prothromboplastin time; ECG = electocardiogram; eGFR = estimated glomerular filtration rate; P = phone/video call visit; PD = pharmacodynamics; PK = pharmacokinetics; V = on-site visit, V/H = On-site visit or home visit.

[a] Site visits with 24-hour PK profile, which means PK samples at these visits are collected pre-dose, 30 min, 1h, 2h, 4h and 8h after dosing, and also 24h after dosing on the next day.

[b] Visits 9 and 10 can either be home visits or on-site visits. In case of a home visit, blood samples collected will be used only to assess haematology, i.e., all the assessments marked as "(X)" in these visits will be performed only if visit 9 or 10 is an on-site visit.

[c] In case of early discontinuation or withdrawal, participants should attend an end of study visit (V17) at least 35 days after last administration of study intervention.

[d] The informed consent must be obtained before any study related procedures. Date of the informed consent must be recorded in the case report form (CRF) at the screening visit (visit 1).

[e] Demography consists of age, year of birth, sex, ethnicity and race (according to local regulation). Ethnicity and race must be self-reported by the participant.

[f] PK, PD and safety assessments will be performed according to Table 1-2.

[g] Report conditions identified before first administration of study intervention as medical history/concomitant illness in accordance with Section 8.1. Report conditions identified after first administration of study intervention as AEs in accordance with Section 8.4.

[h] Administration of trial product must take place in the morning after an overnight fast as mentioned in Section 5.3.1.

[i] The trial product will be allocated to the participant at visit 2 and the dose will be administered on-site. The bottle with remaining trial product will be kept at the site until visit 3 where it will be handed over to the participant, see Section 4.1 for details.

1.3 Schedule of PK, PD and safety assessments

Table 1-2 Schedule of PK, PD and safety assessments

Visit	Day no.	Nominal time (from dosing)	Sampling window	Note	PK sampling	TGT	aPTT	Inno8 activity	Safety assessments[a]
V2	1	-1 hour	±30 min	Pre-dose sample	X	X	X	X	Physical examination, ECG, Vital signs, Anti-Inno8 antibodies, Urinalysis, Safety laboratory assessment[b]
		0 hours	N/A	On-site dosing					
		30 min	±10 min		X	X	X	X	
		1 hour	±15 min		X	X	X	X	ECG, Vital signs
		2 hours	±15 min		X				
		4 hours	±15 min		X	X	X	X	Physical examination, ECG, Vital signs
		8 hours	±30 min		X	X	X	X	
V3	2	24hours	±1 hour	Pre-dose sample	X	X	X	X	Physical examination, ECG, Vital signs, Safety laboratory assessment[b]
		0 hours	N/A	On-site dosing					
P4	3	N/A	N/A	Home dosing					
V5	4	N/A	N/A	Home dosing	X	X	X	X	Vital signs, Urinalysis, Safety laboratory assessment[b]
P6	5	N/A	N/A	Home dosing					
P7	6	N/A	N/A	Home dosing					
V8	7	N/A	N/A	Home dosing	X	X	X	X	Physical examination, Vital signs, Safety laboratory assessment[b]
V/H9[c]	8	N/A	N/A	Home dosing	(X)[c]	(X)[c]	(X)[c]	(X)[c]	Physical examination, Vital signs, Safety laboratory assessment[b, c]
V/H10[c]	9	N/A	N/A	Home dosing	(X)[c]	(X)[c]	(X)[c]	(X)[c]	Vital signs, Safety laboratory assessment[b, c]
V11	10	-1 hour	±30 min	Pre-dose sample	X	X	X	X	Vital signs, Urinalysis, Safety laboratory assessment[b]
		0 hours	N/A	On-site dosing					
		1 hour	±15 min		X	X	X	X	
		2 hours	±15 min		X				
		4 hours	±15 min		X	X	X	X	
		8 hours	±15 min		X	X	X	X	

Visit	Day no.	Nominal time (from dosing)	Sampling window	Note	PK sampling	TGT	aPTT	Inno8 activity	Safety assessments[a]
V12	11	24 hours	±2 hours		X	X	X	X	Physical examination, ECG, Vital signs, Urinalysis, Safety laboratory assessment[b]
V13	17	168 hours	±24 hours		X	X	X	X	Safety laboratory assessment[b]
V14	23	312 hours	±48 hours		X	X	X	X	Safety laboratory assessment[b]
V15	29	456 hours	±48 hours		X	X	X	X	
V16	36	624 hours	±48 hours		X	X	X	X	Physical examination, ECG, Vital signs, Safety laboratory assessment[b], Anti-Inno8 antibodies
V17	46	864 hours	±72 hours		X	X	X	X	Physical examination, ECG, Vital signs, Urinalysis, Safety laboratory assessment[b], Anti-Inno8 antibodies

Abbreviations: aPTT = activated partial prothromboplastin time; ECG = electrocardiogram; H = Home visit; P = Phone/video call visit; PD = pharmacodynamics; PK = pharmacokinetics; TGT = thrombin generation test; V = On-site visit.

Footnotes:

[a] When multiple assessments occur at the same time, blood samples should be collected after ECG and vital signs

[b] In this table, safety laboratory assessments include only biochemistry, haematology, coagulation parameters and eGFR. Though urinalysis is generally considered a safety laboratory assessment in this protocol; it is included separately in the table to clearly indicate a separate schedule for it. See Appendix 2 (Section 10.2) for full list of protocol-defined laboratory assessments.

[c] Visits 9 and 10 can either be home visits or on-site visits. In case of a home visit, blood samples will be collected only to assess haematology. All the laboratory assessments including PK, Inno8 activity, TGT, aPTT, biochemistry, coagulation parameters and eGFR will be done only if visit 9 or 10 is an onsite visit.

2 Introduction

Haemophilia A is a rare recessive X-linked congenital bleeding disorder caused by mutations in the F8 gene encoding coagulation factor VIII (FVIII), on the long arm of the X-chromosome. FVIII is essential for blood coagulation, and people with haemophilia A lack or have a reduced production of FVIII or produce functionally defective FVIII molecules. Approximately 1 in 5,000 males are born with haemophilia A.[2] Globally, over 257,146 people with haemophilia are identified, of which around 208,957 are diagnosed with haemophilia A.[3] People with haemophilia A may also develop antibodies against FVIII (also known as inhibitors), inactivating the procoagulant activity of FVIII, significantly complicating haemophilia A care.

Novo Nordisk has developed a subcutaneous FVIII mimetic bispecific antibody (Mim8) for routine prophylaxis in people with haemophilia A with and without inhibitors. Currently, two phase 3 studies are ongoing with Mim8: one paediatric study (NN7769-4516) and the pivotal phase 3 study in adults and adolescents (NN7769-4514), both in haemophilia A with and without inhibitors to FVIII. There are currently no orally administered prophylactic treatment options for haemophilia patients. An oral treatment is expected to be an attractive extension to the current treatment options.

In the current programme, Novo Nordisk is developing a perorally administered Factor VIIIa mimetic tablet (Inno8, NNC0442-0344) for prevention of bleeding, and long-term prophylaxis, in people with haemophilia A, irrespective of inhibitor status or severity.

Inno8 is currently being investigated in a first human dose (FHD) study (NN7442-7582), which aims to provide safety, tolerability, PK and PD data in healthy male participants.

2.1 Study rationale

The purpose of this study is to provide safety, tolerability, PK and PD data of multiple peroral doses of Inno8 during 10 days of treatment in people with haemophilia A, thereby supporting further clinical development of peroral Inno8 for prophylaxis in people with haemophilia A with or without FVIII inhibitors.

The FHD study that is currently investigating safety, tolerability, PK and PD of Inno8 in healthy male participants (NN7442-7582), consists of a single ascending dose (SAD) part in which Inno8 is administered intravenously (i.v.) and a multiple ascending dose (MAD) part in which Inno8 is administered perorally. Therapeutically relevant exposures of Inno8 are not being tested in NN7442-7582 study to avoid the potential risk of administering a procoagulant agent to people with normal FVIII levels leading to possible thromboembolic events.

Similar to the MAD part of NN7442-7582 study, multiple peroral doses of Inno8 will be administered in the current study. However, this is the first clinical study to be conducted in people with haemophilia A. This study will have 2 MAD cohorts (see Figure 4-1), with a dose escalation from cohort 1 to cohort 2 (see Section 6.5.1.2). In cohort 2, doses of Inno8 at potentially therapeutic exposure levels are tested and thus enable the collection of safety, PK and PD data from the target population (people with haemophilia A) after administration of Inno8 at therapeutic levels. The population selected for this study is suitable for this purpose as people with haemophilia A with a low FVIII activity of <15% are not considered to be in need of prophylactic treatment and the

exposure to potentially therapeutic levels of Inno8 is considered to be safe in them (see Section 4.2.2 for details).

See Section 4.1 for further details on study design, Section 4.2 for details on the scientific rationale for the study design, and Section 6.1 for details on dose and trial product strength.

As a pharmaceutical company, Novo Nordisk has a legitimate interest in conducting research to learn how the medicines we develop work and learn more about how to prevent and/or treat serious chronic diseases and related conditions. As part of conducting research, Novo Nordisk also has a legitimate interest to communicate the results of our research and interact with competent authorities.

Novo Nordisk may also share data with external researchers who are not part of this study for research purposes, to find out more about Inno8, haemophilia A or related conditions and to help improve medical care and scientific understanding.

2.2 Background

2.2.1 Inno8

The Inno8 molecule consists of a single-chain, bispecific V_HH binding zymogen and activated coagulation factor IX (FIX and FIXa) and zymogen factor X (FX) with unique epitopes. It promotes coagulation by enhancing FX-activation in the absence of FVIII. To allow for peroral administration and absorption, the Inno8 tablet contains the absorption enhancer salcaprozate sodium, SNAC (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate caprylate)).

The effect of Inno8 has been evaluated in several *in vitro* and *in vivo* pharmacology studies together with Mim8 and emicizumab sequence identical analogue (SIA). Inno8 was found to increase in vitro coagulation (thrombin generation and clot formation) in a concentration dependent manner, and is demonstrated to be more potent, i.e. increase coagulation at lower concentrations compared to both emiciziumab SIA and Mim8 in several different assays, including a dose-dependent procoagulant effect in TG assay.

Inno8 does not cross-react with any relevant nonclinical toxicology species due to the human specific binding epitope on FIX. According to ICH S6(R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals[4], the use of transgenic animals or homologous protein is suggested when no relevant toxicology species exist. However, development of a transgenic mouse expressing human factor IX and X failed to adequately reflect human pharmacology. Further, an identified homologous protein (Inno8-surrogate) did not display similar potency and efficacy as Inno8, nor did it mirror the mechanism of action of Inno8.

Please refer to the IB for further details on Inno8 and nonclinical safety assessments.

2.2.2 Study population

To support the clinical development of Inno8, safety, tolerability as well as PK and PD properties of Inno8 peroral doses are assessed in people with haemophilia A with ≤ 15% FVIII activity, with or without FVIII inhibitors in this study. The study participants are male, 18-64 years in age with a body weight of ≥ 45 kg.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Inno8 may be found in the investigator's brochure.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Study intervention (Inno8)		
Hypersensitivity	As with any protein-based compound there is a risk of hypersensitivity to Inno8.	Participants with known or suspected hypersensitivity to similar products are excluded from the study. Sentinel approach is implemented in cohorts with exposures predicted to exceed previously safety cleared exposures. Participants are kept in the site for observation for at least 8 hours post-dose (covering expected C_{max}) after first dosing. Hereafter there will be daily contact with participants, either as site visits, home visits or phone/video calls.
Thromboembolic events	As for other pro-coagulant compounds, Inno8 carries a potential risk of exaggerated pharmacology and thrombus formation.	Participants with increased risk of thromboembolic events are excluded from the study. Safety laboratory measurements include markers for exaggerated pharmacology
Thrombotic microangiopathy	Thrombotic microangiopathy has been observed in clinical studies with other FVIII mimetics, when combined with aPCC treatment.	Guidance on treatment of bleeds during treatment with Inno8 is provided.
Study procedures		
Discomfort related to invasive study procedures	Discomfort may occur around the site of blood sampling.	Experienced and trained site personnel will ensure minimization of discomfort caused by study procedures.
Incorrect dosing or non-compliance with dosing conditions	Since the participants are allowed for home-dosing from visits 4 to visit 10 and are not monitored while they are dosing, there is a chance that the participant could overdose (take 3 instead of 2 tablets), or underdose (take 1 instead of 2 tablets), or not follow the pre- and post-dose fasting times precisely.	Site staff will remain in contact during the dosing period either through on-site visits or at-home visits or phone/video calls for collection of information as well as remind participants about compliance with dosing conditions.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Communication between sponsor and sites regarding sentinel evaluation and stopping criteria	This study will be enrolling participants across multiple sites. Information on the safety of participants and occurrence of AEs will therefore be with investigators at each site. This induces a risk of missing an overview of sentinel evaluation and potential fulfilling of stopping criteria.	This is mitigated by a centralised evaluation of sentinels done by the Novo Nordisk medical specialist based on the recommendations by the investigators and safety data from the sites with sentinel participants. Information on events potentially triggering cohort level stopping criteria (see Section 7.1.1.2) will be distributed from the site at which the event triggering stopping criteria occurred to all the other sites and the sponsor, through an immediate email.
Other		
No other potential risk of clinical significance identified in this study		

Abbreviations: AE = adverse events; aPCC = activated prothrombin complex concentrate; FVIII = factor VIII.

Study-specific risk assessment related to data processing is described in Table 2-2 below. For a general description of measures taken to mitigate potential risks to data privacy and protect participants' personal data, please see Appendix 1 (Section 10.1.5).

Table 2-2 Assessments of study-specific risks related to data processing

Potential risk related to data processing	Summary of data/rationale for risk	Mitigation and monitoring strategy
Home nursing	Risk that participants' names or addresses are breached, i.e, this information could potentially be shared with people not directly involved in the actual study conduct (e.g.: third party agents not covered under confidentiality agreements) and could potentially be misused.	Clear procedures will be established for handling of data, e.g., password protection of PCs containing access to participant names. Relevant staff will receive training on handling personal data with due care.

2.3.2 Benefit assessment

Participants in this study are not expected to benefit from receiving Inno8. Participants will have their health condition evaluated as part of the study procedures (e.g., physical examination, ECG and laboratory safety parameters). Participants will contribute to the process of developing the first orally administered FVIII product. This could have a positive impact on people with haemophilia A who have a potential barrier to injectable dosing and/or have a preference for oral dosing.

2.3.3 Overall benefit-risk conclusion

All participants in this study will have a thorough medical check before entering the study. During the study, they will be followed closely and carefully by qualified medical staff. In addition, precautions have been implemented to minimise the risks related to participation in the study. Therefore, it is concluded that the potential risks identified in association with Inno8 are justified by the anticipated benefits that may be afforded to people with haemophilia A with or without FVIII inhibitors.

3 Objectives and endpoints

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
To investigate the safety and tolerability of multiple peroral doses of Inno8 in people with haemophilia A	Primary:		
	Number of treatment emergent adverse events	From time of dosing (Day 1) to end of follow-up (Day 46)	Count
	Supportive secondary:		
	Change in D-dimer	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
	Change in prothrombin fragment 1 and 2	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
	Change in fibrinogen	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
	Change in platelets	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
	Occurrence of anti-Inno8 antibodies	From time of dosing (Day 1) to end of follow-up (Day 46)	Count
	Exploratory secondary:		
	Change in FIX	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
	Change in FX	From time of dosing (Day 1) to end of follow-up (Day 46)	Absolute and %
Secondary	Title	Time frame	Unit
To investigate the pharmacokinetics of multiple peroral doses of Inno8 in people with haemophilia A	Supportive secondary:		
	C_{max}: the maximum concentration of Inno8 after multiple doses	From Day 10 to Day 11	ng/mL
	T_{max}: the time to C_{max} after last multiple dose	From day 10 to Day 11	Hours
	T_{max}: the time to C_{max} after first dose	From Day 1 to Day 2	Hours
	AUC_{0-24h}: the area under the Inno8 concentration-time curve in the dosing interval after multiple doses	From Day 10 to Day 11	ng*day/mL
To investigate the pharmacodynamics of multiple peroral doses of Inno8 in people with haemophilia A	Supportive secondary:		
	Maximum thrombin generation (peak height)	From Day 10 to Day 11	nM
	Exploratory secondary:		
	Maximum change in activated partial thromboplastin time (aPTT)	From baseline (Day 1) to Day 11	Seconds

Abbreviations: aPTT = activated partial thromboplastin time

4 Study design

4.1 Overall design

This is an interventional, multi-national, multi-centre, open-label, MAD phase 1 study, investigating safety, tolerability, PK and PD properties of peroral Inno8.

A total of 20 male participants with haemophilia A with or without FVIII inhibitors are planned to be dosed. The study consists of:

- a 28-days screening period,
- a 10-days intervention period,
- a 35-days follow-up period.

Participants will sign the informed consent, at the screening visit (visit 1). Screening period will be up to 4 weeks (28 days). If a participant is found eligible at screening, he will be invited to an on-site treatment visit (visit 2), at least 15 days after the screening. At visit 2, the trial product will be dispensed, and the participant will receive the first per-oral dose of Inno8 on-site. The trial product will be kept at the site until visit 3 where the participant will receive the second per-oral dose of Inno8 on-site and hereafter the bottle(s) containing the remaining trial product will be handed over to the participant. The participant will self-administer the dose at home from dosing day 3 (phone/video call visit 4) till dosing day 9 (visit 10) as per the dosing conditions mentioned in Section 5.3.1. The participants must bring this container/duma to the site for dosing day 10 (visit 11), where the participants will self-administer the trial product on-site.

Following the first dose at visit 2, the participant should stay at or near the site for approximately 9 hours to allow for monitoring of potential AEs, safety assessments and collection of blood samples for PK and PD assessments. The 9-hour period is also expected to cover the time required to reach maximum plasma concentration (C_{max}) of the first dose. The following morning, the participant must be present on-site for visit 3 before dosing, for pre-dose assessments. During the entire 10-day dosing period, the study participants will be attended by site staff daily either at on-site or at-home visits or through phone/video calls for collection of information and/or blood samples for safety, PK and PD assessments, as per the schedule of activities (SoA) (Table 1-1) and schedule of PK, PD and safety assessments (Table 1-2). Last day of dosing will include an on-site visit of approximately 9 hours, which is expected to cover the time required to reach C_{max} of the last dose. Participants must return to the site, the following morning for pre-dose assessments. After the last dose, participants will be asked to attend the site for regular out-patient visits where safety and PK are monitored, until the follow-up visit at the end of study (i.e., from visit 12 to visit 17). The follow-up period after the last dose is 35 days, corresponding to approximately 5 half-lives of the drug. Total study duration for the individual participant will be up to 11 weeks (from screening to end of study visit).

The study design is shown in Figure 4-1 and the visit schedule is shown in Figure 4-2. For a complete overview of the visit structure and assessments on individual visits, please see the SoA (Table 1-1) and the schedule of PK, PD and safety assessments (Table 1-2).

In the FHD-study (NN7442-7582), healthy participants are being dosed with Inno8 in 5 SAD cohorts (i.v. formulation) and 4 MAD cohorts (peroral doses). In the current study (NN7442-8454),

participants with haemophilia A will be dosed perorally in 2 MAD cohorts with a single dose escalation from cohort 1 to cohort 2, where the dose in cohort 1 is same as that of the highest dose tested in the MAD part of NN7442-7582 study.

A total of 10 participants are planned to be included in each cohort. Dosing of cohort 2 can be initiated after at least 8 participants in cohort 1 have completed their 10 days of treatment (see Section 4.3.1 for details). Sentinel dosing will be applied for cohort 2, as the doses used in this cohort are not previously tested in humans and this approach will minimise the risk of unexpected safety concerns. Two sentinel participants will be dosed ahead of the rest of the cohort. The sentinel observational period is 72 hours. See Section 6.1 for details on dose levels, Section 6.5.1.1 for details on sentinels and Section 6.5.1.2 on dose escalation.

Figure 4-1 Study design

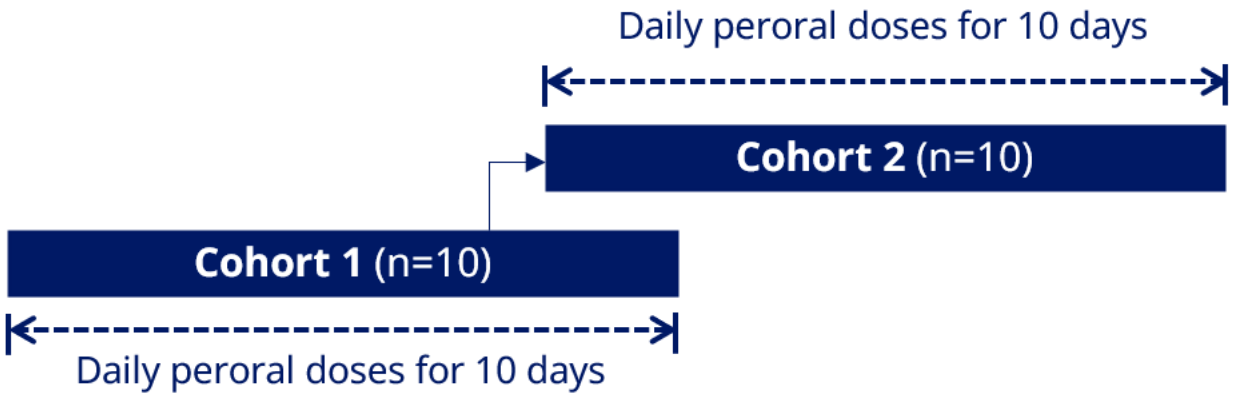
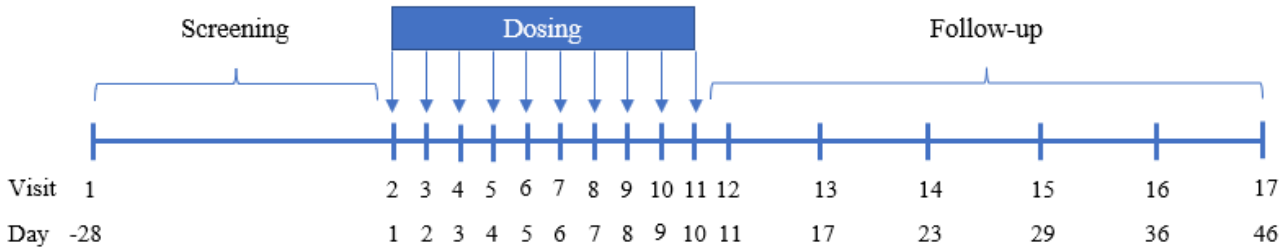


Figure 4-2 Visit schedule



4.2 Scientific rationale for study design

4.2.1 Rationale for study design

The study design and study population are chosen to effectively assess safety, tolerability as well as PK and PD of Inno8 in a multiple-dose setting in people with haemophilia A, with or without FVIII inhibitors, with a FVIII activity ≤15% and not in need of prophylactic treatment.

This is the first study in which people with haemophilia A receive Inno8. It is considered a continued dose escalation study from the NN7442-7582 study. Given that the primary objective of this study is to investigate safety and tolerability of Inno8 in people with haemophilia A, all participants will receive Inno8 in an open-label and uncontrolled study design.

A cautious approach in dosing participants with haemophilia A will be followed in this study by dosing a total of 8 participants for 10 days in cohort 1 with the dose safety cleared in NN7442-7582 prior to the initiation of cohort 2.

The first treatment visit (visit 2) of the first study participant in cohort 1 of this study is scheduled after the data from NN7442-7582 MAD cohort with the same Inno8 dose is safety cleared. This is to ensure that safety of the cohort 1 dose has been investigated in healthy participants prior to administration in participants with haemophilia, as well as to ensure that the PK and PD data from healthy participants is available for comparison with that collected from participants with haemophilia.

Timing of visits is based on PK modelling of plasma concentration data from dogs scaled to humans as well as data from NN7442-7582 study, and follow-up corresponds to the estimated time to cover 95% of the predicted area under the concentration-time curve.

The dosing duration of 10 days is chosen to match the dosing period used in the MAD part of NN7442-7582 study, and to capture the expected accumulation of exposure and within-subject variability.

The number of participants receiving the active trial product in each cohort (10 participants) is selected to account for the expected between subject variability following peroral dosing, and to enable an estimate on variability of exposure. Peroral dosing will be initiated after an overnight fast and with 30-35 min post dosing fasting as absorption of peroral Inno8 is significantly affected by food and fluid in the stomach. Please refer to Section 5.3.1 for meals and dietary restrictions and the IB for further details about dosing conditions for Inno8. All participants will be in contact with the site staff during the dosing period either through on-site visits or at-home visits or phone/video calls for safety precautions and collection of information about compliance with dosing conditions.

4.2.2 Rationale for study population

The study population includes male participants with haemophilia A (FVIII activity ≤ 15%) with or without FVIII inhibitors. The participants are 18–64 years of age, with a body weight ≥45 kgs and with a body mass index (BMI) ≤30.0 kg/m^2. Though Inno8 is still in an early stage of clinical development, testing it in the population with haemophilia A allows us to explore safety, PK and PD of Inno8 at higher exposures than those previously tested in healthy participants in NN7442-7582.

People with FVIII activity below normal level are chosen to be included as study participants. This is to decrease the potential risk of thromboembolic events when potentially therapeutic levels of Inno8 are tested in cohort 2 of the study. Similarly, it is also considered important to choose participants who are not in need of prophylactic treatment, as lower Inno8 exposures will not provide optimal prophylaxis against bleeds in participants. In general clinical practice, people with haemophilia A with a FVIII activity 15% and above are known to be at a very low risk of bleeding, while FVIII activity levels below 15% covers a broad range of the population with haemophilia A in terms of severity.[5-7]

As the participants not in need of prophylactic treatment are selected for this study, they will not need a wash-out period to switch to Inno8.

4.3 Justification for dose

Inno8 will be administered perorally, once daily for 10 days. Participants in cohort 1 of this study will receive the same dose as of the highest peroral dose administered in NN7442-7582 MAD part in healthy participants for 10 days. The aim is to investigate PK and PD properties along with inter- and intra-subject variability in Inno8 exposure with peroral dosing in people with haemophilia A compared to healthy participants.

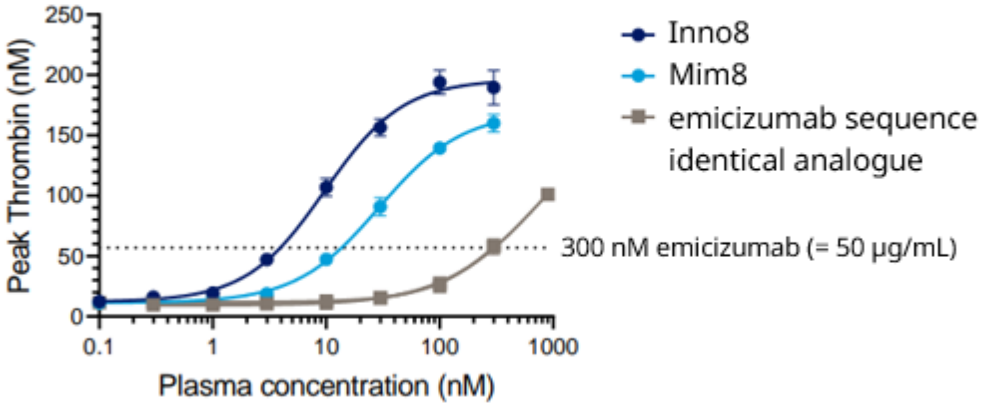
The time to maximum plasma concentration after a single dose of Inno8 is predicted to be about 4 hours, and the terminal half-life of Inno8 is predicted to be about 175 hours. This supports a once daily peroral dosing scheme.

4.3.1 Selected doses

The doses in NN7442-7582 are determined from the PK model on predicted human PK. The human PK model of Inno8 is based on the nonclinical data from dog using standard single species allometric scaling methods. Due to the lack of cross-species reactivity, the dose setting, in relation to PD effects, has been based on in vitro potency of Inno8, measured by aPTT clot time and TG, and compared to Mim8 and emicizumab (two other FVIIIa mimetic compounds), see Figure 4-3. The therapeutic plasma concentration following emicizumab treatment and the data collected in study NN7769-4513 (FHD study of Mim8), has been taken into consideration.

Up to 4 cohorts are planned in the MAD part of NN7442-7582, with 13 randomised participants in each; 10 participants on active treatment and 3 on placebo (a total of 52 men enrolled, of which 40 participants will receive Inno8 and 12 will receive placebo). The target plasma concentration in the highest MAD dose corresponds to 60% of the emicizumab equivalent therapeutic concentration (50 µg/mL) based upon the thrombin generation test (TGT) response. At this concentration no signs of exaggerated pharmacology are expected in the healthy participants.

Figure 4-3 In vitro potency of Inno8 vs emicizumab and Mim8

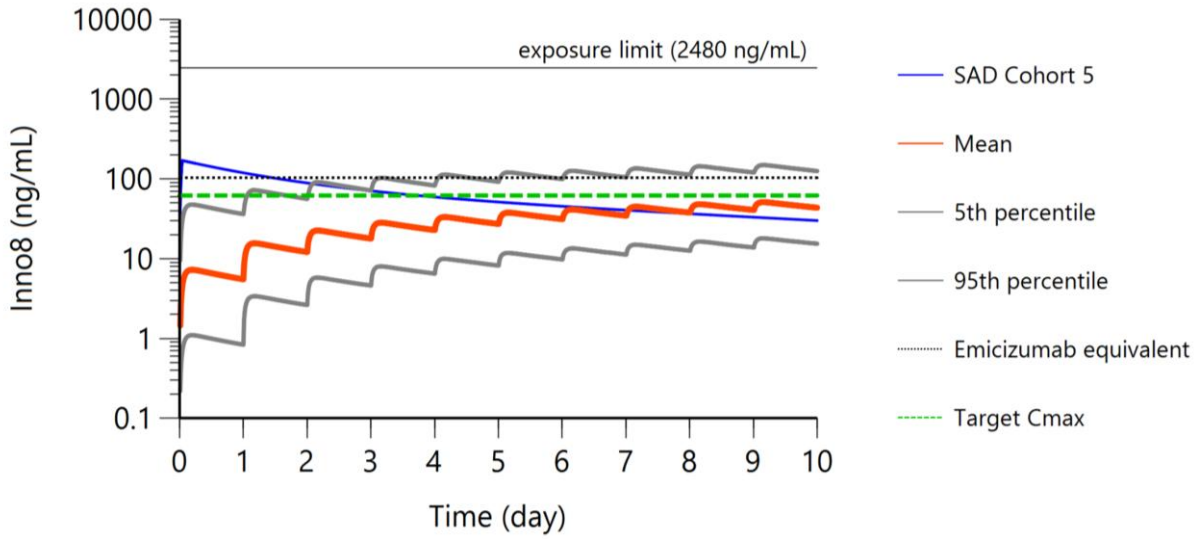


Footnote: Head-to-head comparison of in vitro potency in thrombin generation assay.

This study in participants with haemophilia A (NN7442-8454) will be initiated when safety of the Inno8 target exposures in the MAD cohort have been evaluated in NN7442-7582.

Two dose levels are planned in the current study. The lower dose (cohort 1) will be the same as the highest dose administered in NN7442-7582 MAD part, in healthy volunteers for 10 days (see Figure 4-4). The higher dose (cohort 2) will be up to two-fold higher, assessed by dose or exposure, as appropriate, depending on dose proportionality and bioavailability determined in NN7442-7582. At least 8 participants in cohort 1 of the current study (NN7442-8454) will be dosed for 10 days with a dose that is safety cleared in NN7442-7582, prior to the initiation of cohort 2.

Figure 4-4 Predicted Inno8 Exposure at low dose level in NN7442-8454



Footnote: Predicted exposure at the low dose level. Mean C_{max} of 10 daily doses with Inno8 (red) and 5th and 95th percentile (grey). The predicted exposure in NN7442-7582 SAD cohort 5 is shown in blue. Target C_{max} of Inno8 of at low dose level is shown as a dashed green line. The emicizumab equivalent of Inno8 is shown as a black dotted line. The emicizumab equivalent of Inno8 is the concentration of Inno8 that results in an in vitro response in the TGT assay that is equivalent to the TGT response to emicizumab at its therapeutic concentration.

4.3.2 Exposure limit

Due to the human specificity, and thus the lack of a relevant toxicology species for Inno8, an exposure limit of Inno8 could not be identified from a No Observed Adverse Effect Level (NOAEL) value. Instead, an alternative approach to defining an exposure limit was used. The method used was based on the NOAEL obtained for Mim8 and is described below.

The NOAEL C_{max} of Mim8 in monkeys was 730 nM or 730 nmol/L (1 nM = 1 nmol/L). For healthy participants in Mim8, the exposure limit was 2-fold lower than the NOAEL exposure (365 nM) due to a 2-fold lower potency of Mim8 in monkeys than in humans. To estimate the NOAEL for Inno8, the Mim8 NOAEL was adjusted for the potency difference (EC50) between Mim8 and Inno8 using the most sensitive assay, tissue factor triggered thrombin generation assay (TGA):

(Mim8 NOAEL exposure ×EC50 of Inno8) ÷ EC50 of Mim8= (365 nM×10 nM) ÷ 44 nM= 84 nM.

For Inno8, a concentration of 84 nM corresponds to 2480 ng/mL. Therefore, an exposure limit of 2480 ng/mL is proposed for Inno8. The target mean C_{max} to be achieved after the highest dose administered in the MAD part of NN7442-7582 study in healthy volunteers is 2.1 nM (62.1 ng/mL).

This corresponds to 60% of emicizumab equivalent therapeutic concentration of Inno8 (where 100% is 3.5 nM [103 ng/mL]). The emicizumab equivalent concentration is the concentration of Inno8 that results in an *in vitro* response in the TGT assay that is equivalent to the TGT response to emicizumab at its therapeutic concentration. The margin of target C_{max} of 2.1 nM (62.1 ng/mL) to the exposure limit of 84 nM (2480◦ng/mL) is 40-fold.

Cohort 1 of NN7442-8454 study in people with haemophilia A targets the same mean C_{max} of 2.1 nmol/L (62.1 ng/mL) after the last dose. In cohort 2 of NN7442-8454 study, up to two-fold higher C_{max} is targeted, i.e. a concentration of 4.2 nmol/L (124 ng/mL), which is slightly above the emicizumab equivalent concentration and 20-fold below the exposure limit.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he has completed all periods of the study including the last visit for the applicable study part. For details on number of participants that are needed to complete the study to reach the end of study, see Section 9.5.

The primary endpoint is evaluated from time of dosing (Visit 2 Day 1) to the end of study (Visit 17, Day 46). The primary completion date (PCD) is defined as the date of the follow up visit on which the last participant in the clinical study has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant would have completed the end of study visit.

5 Study population

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

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male, with age 18-64 years (both inclusive) at the time of signing the informed consent.
3. Body weight ≥45 kgs at screening visit.
4. Diagnosis of congenital haemophilia A with FVIII activity ≤ 15% with or without FVIII inhibitors, based on medical records.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous dosing in this study.
3. More than one rescreening for this study.
4. Current or prior exposure to any prophylactic treatment for haemophilia A within 5 half-lives of the medicinal product by the time of screening.
5. Current participation (i.e., signed informed consent) in any other interventional clinical study.
6. Exposure to an investigational medicinal product within 30 days or 5 half-lives of the investigational medicinal product (if known), whichever is longer, before screening.
7. Any condition, except for conditions associated with haemophilia A, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
8. BMI ≥30.0 kg/m^2 at screening visit.
9. Increased risk of thrombosis, e.g. known history of personal or first-degree relative(s) with unprovoked deep vein thrombosis.
10. Any clinical signs or established diagnosis of venous or arterial thromboembolic disease.
11. Presence of any of the thrombophilia markers listed below at screening:
    a) Protein C, protein S or antithrombin below the lower normal laboratory range,
    b) Lupus anticoagulant, anti-cardiolipin antibody (IgG and IgM) or anti-β2 glycoprotein I antibody (IgG and IgM) outside the normal laboratory range at screening,
    c) Heterozygosity or homozygosity for the factor V Leiden mutation (G1691A)[c] or heterozygosity or homozygosity for the prothrombin mutation (G20210A)[c] or compound heterozygosity for the factor V Leiden (G1691A) and prothrombin mutation (G20210A)[c].
12. Supine blood pressure at screening outside the range of 90−139 mmHg for systolic or 50−89 mmHg for diastolic (one re-assessment is allowed in case of suspected white-coat hypertension[a]).
13. Pulse (as part of vital signs) outside the range of 50−90 beats/minute at screening.
14. Use of prescription medicinal products or non-prescription drugs, except routine vitamins, within 14 days prior to the day of screening[b]. Occasional use of paracetamol (acetaminophen) and ibuprofen is permitted.
15. Diagnostic test results positive for active HIV-1 or HIV-2 infection at screening.

16. Diagnostic test results positive for ongoing hepatitis B or hepatitis C infection or SARS-CoV2-infection at screening.
17. Current use of tobacco and nicotine products, defined as any of the below:
    a) Smoking more than 5 cigarettes or equivalent daily.
18. Any laboratory safety parameter at screening outside the below laboratory ranges, see "Log of laboratory ranges used for laboratory exclusion criterion" for specific values:
    a) Alanine aminotransferase outside upper limit of normal (ULN)
    b) Aspartate aminotransferase outside ULN
    c) Bilirubin outside ULN
    d) Creatinine outside −5% of lower limit of normal (LLN) and ULN
    e) Thrombocytes outside −15% of LLN and ULN
    f) Troponin T ≥ 14.0 pg/mL
    g) NT-proBNP > 125.0 pg/mL.
19. Renal impairment defined as estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 for serum creatinine measured at screening.
20. Mental incapacity, language barriers or unwillingness to comply with the requirements of the protocol, which may preclude adequate understanding or co-operation during the study as judged by the investigator.
21. Participant depends on the sponsor, the investigator, or the study centre or participant is the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
22. Vulnerable participant (e.g. person kept in detention or participants committed to an institution by way of an official or judicial order) who may have an increased likelihood of being wronged or of incurring additional harm.
23. Any known coagulation disorders other than haemophilia A.
24. Ongoing or planned immune tolerance induction therapy.
25. Major surgery within 30 days prior to first trial product administration or major/minor surgery planned during the study.[b] For definition of surgeries, see Table 6-4.
26. Presence of clinically significant gastrointestinal disorders potentially affecting absorption of drugs and/or nutrients, as judged by the investigator.
27. History[b] of major surgical procedures involving the stomach potentially affecting absorption of trial products (e.g., subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery) or current presence of gastrointestinal implant[b].

[a] White coat hypertension is a condition in which a participant's blood pressure readings are higher when taken at the doctor's office compared to other settings due to heightened stress levels.

[b] As declared by the participant or reported in the medical records.

[c] If a participant is not willing to consent to genetic testing, then they will be tested factor II activity or activated protein C resistance at screening and will be excluded if these values are found outside the normal laboratory range.

5.3 Lifestyle considerations

To ensure alignment regarding performance of assessments across participants, participants will be informed about the below restrictions during the study.

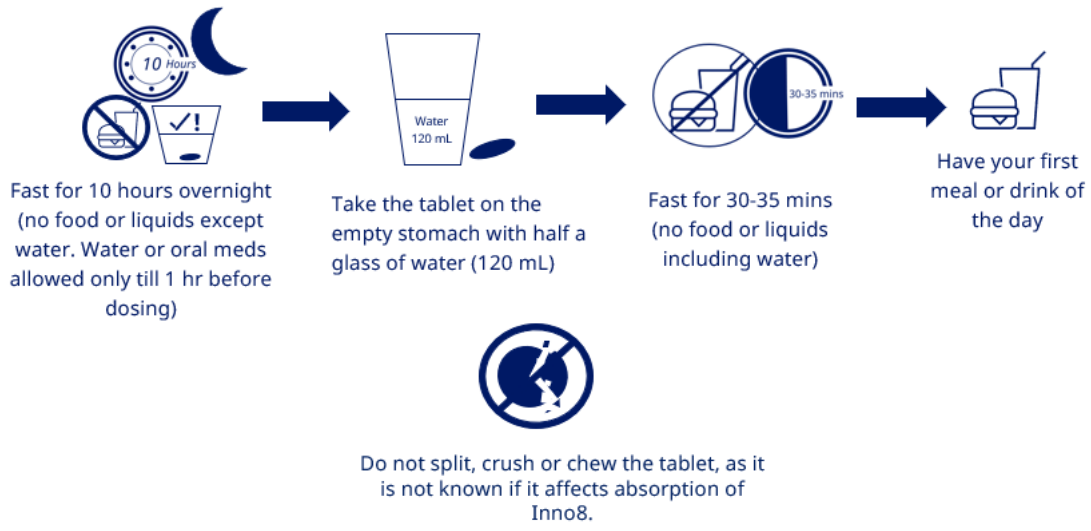
5.3.1 Meals and dietary restrictions

Participants must be instructed to refrain from consuming poppy-seed containing foods 48 hours before visit 2. Consumption of poppy-seeds may interfere with the drug screen.

All the participants must attend visits according to the SoA (Table 1-1), and must follow the dosing instructions (supervised by site staff) that are listed below (also shown in Figure 5-1):

- Take the tablet(s) daily as recommended.
- Take the tablet(s) in the morning after an overnight fasting. Fasting is defined as no food or liquid, except for water, for 10 hours before dosing. No water or oral medications is allowed 1 hour before dosing.
- Swallow the tablet(s) whole with a half a glass of water (120 mL).
- Do not split, crush or chew the tablet, as it is not known if it affects absorption of Inno8.
- After taking the tablet(s) wait 30-35 minutes before having the first meal or drink of the day or taking other oral medicines (please also see Section 6.8 on concomitant therapy). Waiting less than 30 minutes may lower the absorption of Inno8.

Figure 5-1 Dosing instructions



5.3.2 Physical activity

Participants should be encouraged not to change their physical exercise pattern from screening until completion of the follow-up visit, as judged by the investigator, to interfere with study results.

5.3.3 Other restrictions

Participants must adhere to the requirements regarding medication not permitted from screening to follow-up (Section 6.8). Participants must refrain from simultaneous participation in another clinical study from screening to follow-up.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set

of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, age, screen failure details (end of study form), eligibility criteria, results of laboratory safety samples (if collected and analysed).

Screening or rescreening activities must be stopped if it is confirmed that an individual cannot participate in the study for any reason to avoid unnecessary procedures being performed. A screen failure must be registered in the RTSM.

5.4.1 Rescreening

Individuals who do not meet the criteria for participation in this study may be rescreened.

One repeat procedure or one rescreening is allowed in the following cases:

- If an individual's condition has changed, e.g., after recovering from an intercurrent illness; or the individual failed screening due to practical circumstances (such as time since participation in a previous study).
- If the individual failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, re-sampling is allowed for any affected laboratory parameter(s) in case of technical issues (e.g., equipment failure, or sample is haemolysed or lost).
- Individuals who have been deemed eligible for the study but cannot be dosed within the screening window may be rescreened once. If the individual did not fail any eligibility criteria during the initial screening but fails one during rescreening, one repeat procedure is allowed in the same cases as listed above.

Individuals who are rescreened are required to sign a new informed consent form. Individuals who are rescreened will be provided with a new participant ID. Rescreening must be registered in the RTSM. For the re-screened individual, the end of study form will be completed for the first participation, indicating the reason participation ended. At the re-screening visit, the previous participant ID will be entered in the CRF. Data from both the first and the second screening visits will be entered in the CRF, as applicable.

Individuals who fail a repeat procedure or fail rescreening are considered a screen failure and cannot have an additional repeat procedure performed or be rescreened again.

5.5 Rescheduling criteria

Treatment allocation will be done at visit 2. Visit 2 can be rescheduled once if any of the rescheduling criteria is answered "yes". If not possible to reschedule within the screening time window, the participant may be rescreened once according to Section 5.4.1. If any of the below criteria are answered as "yes" on a rescheduled visit, then this will lead to withdrawal from the study according to Section 7.2.

1. Presence of any medical condition that may confound the results of the study or pose an unacceptable risk to the participants at administration of the trial products, as judged by the investigator at screening.
2. Clinical manifestation of an active treatment-requiring bleed at visit 2.

3. Unable to follow all the criteria mentioned in meals and dietary restrictions (Section 5.3.1) by the time of visit 2.
4. Use of any active treatment with haemostatic products within 5 half-lives of the medicinal product by the time of visit 2.

5.5.1 Participants screened but not dosed

All the eligible participants will be dosed until the planned number of participants are included in the study. The information collected from the eligible participants who are screened but not dosed will be limited to that collected in the screening visit.

6 Study intervention(s) and concomitant therapy

Study intervention is defined as all pre-specified investigational and auxiliary medicinal products, medical devices, IVDs and other intervention(s) (e.g., surgical and behavioural), intended to be administered to the study participants or otherwise used in relation to treatment or study assessments during the study conduct according to the study protocol.

Investigational interventions are a subset of study interventions that are being tested or used as a control (e.g., placebo or active control).

The term 'trial product' is used in the protocol when referring to specific actions to be taken (e.g., actions related to shipping and storage), that only apply for these products. In this study, 'trial products' comprise investigational medicinal products (IMPs).

6.1 Study intervention(s) administered

Table 6-1 provides an overview of the study interventions.

Table 6-1 Study interventions

Intervention/Arm name	**Inno8 for peroral administration**
Intervention name	NNC0442-0344 A (Inno8)[a]
Intervention type	IMP, test product
Investigational or non-investigational	Investigational intervention
Pharmaceutical form	Tablet
Route of administration	Oral
Trial product strength	10, 30, 50 and 100 mg per tablet
Dose and dose frequency	1-2 tablets (dose range: 10 mg to 200 mg) Once daily[b]
Dosing instructions and administration	1-2 tablets in the morning in a fasted state with 120 mL of water. Wait for 30–35 minutes before having the first meal or drink of the day.
Sourcing	Manufactured and supplied by Novo Nordisk A/S
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with EU CTR Annex VI,[8] local regulations and study requirements • Trial product is provided in a 40 mL HDPE bottle (10 tablets per bottle)
Authorisation status	The actual IMP is not approved

Abbreviations: IMP = investigational medicinal product.

[a] ProdEX name: NNC0442-0344 A 10032 ProdEX name for 10 mg = NNC0442-0344 A 10029; ProdEX name for 30 mg is NNC0442-0344 A 10030; ProdEX name for 50 mg is NNC0442-0344 A 10031; ProdEX name for 100 mg is NNC0442-0344 A 10032.

[b] The actual dose may be a single tablet or a combination of two tablets.

The investigator must document that 'instructions for use' were given to the participant verbally and in writing at the first dispensing visit (as specified in the SoA (Table 1-1)). The participant must be reminded of the instructions for use at subsequent visits during the on-treatment period.

Investigational medicinal products (IMP)

Absorption of peroral Inno8 is significantly affected by food and fluid in the stomach, hence all dosing occasions must be completed in the morning in a fasting condition as described in Section 5.3.1. For details on timing of trial product administration, please refer to the SoA (Table 1-1). Administration of trial product must be aligned with the peroral Inno8 PK sampling schedule (Table 1-2). Dosing performed at site will be supervised by site staff.

For dosing, the following data must be collected and recorded in the CRF:

- Has the participant been fasting overnight? (yes/no)
- Any fluid intake from 1 hour before dosing (yes/no)
- Date and time of trial product administration (hh:mm)
- Number of tablets taken and actual dose of each tablet
- Start time of breakfast meal after trial product administration (hh:mm)

6.2 Preparation, handling, storage and accountability

- Only participants enrolled in the study may use study intervention and only delegated site staff may supply study intervention.
- All trial products must be stored in a secure, controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).
- The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records).
- The investigator or designee must instruct the participant to bring the container to the site for dosing day 10 (visit 11).
- The investigator or designee must instruct the participant on how to manage the in-use time and storage requirements of the dispensed products as described in the latest edition of the Trials Materials Manual.
- Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor.
- All returned (used or unused), expired or damaged trial products (for technical complaint samples, see Appendix 6 (Section 10.6)) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products, including expired or damaged products, must be accounted by the site and reconciled by the monitor, at the latest at closure of the site.
- Drug accountability of the trial product dispensed is the responsibility of the investigator. The participant will be asked to return all the unused trial product as specified in the SoA (Table 1-1) and also in cases of participant withdrawal/discontinuation (see Section 7.2). Accountability after end of treatment will be recorded in the CRF.

For the US, see Appendix 7 (Section 10.7).

6.3 Measures to minimise bias: Randomisation and blinding

This is an open-label study; however, all participants will be screened and centrally enrolled using RTSM and assigned to the investigational intervention according to the enrolment schedule. Investigational intervention will be dispensed by the investigator at the study visit as summarized in Table 1-1. The RTSM will not be supporting kit dispensing or drug accountability.

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

During the visits 2, 3 and 11, the participants self-administer trial product on-site, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents. Site staff will observe ingestion of the trial product. If in doubt whether the trial product has been swallowed, site staff will enter into a dialogue with the participant, acknowledging non-compliance can happen and addressing barriers to compliance.

During the remaining visits, the participants self-administer trial product at home, compliance with trial product administration will be assessed, and the assessment is documented in source documents at each visit (phone/video call/on-site/home visit) where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information: counting returned trial product and visual inspection
- Questioning of participants at each contact with the site including phone/video call visits, home visits and on-site visits (see treatment compliance contact in Table 1-1).

When a participant misses to administer a dose, in cases of home dosing, the visit schedule will not be rescheduled and the participant will continue with the next planned visit as per the SoA (Table 1-1).

Trial product start and stop dates and treatment compliance questions will be recorded in the CRF.

6.5 Dose modification

6.5.1 Dose escalation studies

6.5.1.1 Sentinels

Sentinel dosing will be performed only for cohort 2 in the study as cohort 1 is the same as that of the highest dose administered in NN7442-7582 MAD cohort, which will be already safety cleared in healthy participants.

Two (2) sentinel participants in cohort 2 are dosed ahead of the remaining participants in the cohort, followed by a safety observation period of at least 72 hours (3 days). This will allow sufficient time

to evaluate sentinel data, and to implement any necessary restrictions, prior to dosing the remaining participants in cohort 2.

The investigators responsible for the sentinel participants must confirm that the stopping criteria have not been met and that there are no concerns to be raised. The investigators must provide a brief description, of the participant status at their site, including any AEs and a confirmation that the doses administered have been taken according to dosing conditions mentioned in Section 5.3.1. The decision to dose the remaining participants in the cohort will be made by the Novo Nordisk medical specialist based upon the recommendations by the investigators from the sites with sentinel participants, observed AEs and the results of the safety assessments. The decision will be communicated to all participating sites in the study.

6.5.1.2 Dose escalation

Two (2) multiple dose levels are planned to be investigated in this study. No separate study safety group has been employed for this study who would evaluate the dose escalation from cohort 1 to cohort 2. This is because, the dose in cohort 1 will be the same as the peroral dose that is already safety cleared in NN7442-7582 study MAD part by the study safety group in NN7442-7582 study, see Section 4.3 for further details.

6.6 Continued access to study intervention after end of study

The participants will not be provided with the study intervention beyond the end of treatment visit (visit 11), see Table 1-1. When discontinuing investigational intervention, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

6.7 Treatment of overdose

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.4 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the participant for overdose related AEs/SAEs and laboratory abnormalities as agreed with Novo Nordisk on an individual basis.

Decisions regarding dose interruptions will be made by the investigator based on the clinical evaluation of the participant and after consulting with Novo Nordisk.

For more information on overdose, also consult the current version of the Inno8 investigator's brochure (IB).

6.8 Concomitant therapy

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of visit 1 or receives during the study conduct (till end of study) must be recorded as concomitant medication along with:

- Trade name
- Primary indication
- Dates of administration including start and stop dates.

For participants in the study, the following medications must not be used from screening visit (V1) to the end of study visit:

- Prescription medicinal products or non-prescription drugs, except routine vitamins, and occasional use of paracetamol (acetaminophen) and ibuprofen.

Use of not permitted concomitant medication may be necessary for treatment of acute illness for any participant in the study, as judged by the investigator. Study intervention can be continued if considered safe. In case there are no safety concerns for the participant and the consequences for the endpoint(s) are deemed acceptable, the participant will be allowed to continue in the study. The decision on whether the participant can continue study intervention must be based on mutual agreement between investigator and Novo Nordisk. All use of not permitted concomitant medication will be considered a protocol deviation.

Changes in concomitant medication must be recorded at each visit, see Table 1-1.

If a change in concomitant medication is due to an AE/SAE, then this must be reported according to Section 8.4. If the change influences the participant's eligibility to continue in the study, the monitor must be informed.

Sponsor should be contacted if there are any questions regarding concomitant or prior medication.

6.9 Bleeding episodes

Bleeding episodes should be treated at the discretion of the investigator. Novo Nordisk will not provide or reimburse treatment for bleeding episodes. Information about bleeding episodes will be collected as described in Section 6.9.2.

6.9.1 Treatment of bleeding episodes

The investigator must instruct the participants to contact the site in case of a suspected bleeding episode to evaluate the need for administration of haemostatic medication and/or other treatment, and to ensure correct choice of product and dose, irrespective of whether the participant is able to visit the site in person. However, serious or life-threatening bleeding should be treated promptly by the participant without delay, if necessary, before contacting the site. Exact dose, schedule and type of bleed treatment in such cases must be agreed with the investigator at the beginning of the study. Repeated dosing of bleed treatment with FVIII products or FVIIa should be performed only under medical supervision and consideration should be given to verifying bleeds prior to repeated dosing. If no other options are available, and aPCC or Byclot® is used for bleed treatment, the guidance specified in the below section "Participants with haemophilia A with FVIII inhibitors" is applicable.

If participants are unable to visit the site due to a bleed for mandatory on-site visits mentioned in Table 1-1, then the relevant blood samples for PK, PD and safety evaluation will not be collected for that missed on-site visit.

Participants with haemophilia A without FVIII inhibitors:

Treatment requiring bleeding episodes should be treated with one or more i.v. bolus injections of standard or extended half-life FVIII products at the lowest dose expected to achieve haemostasis.

Participants with haemophilia A with FVIII inhibitors:

For haemophilia A patients with inhibitors, when recent inhibitor titre is available and is >5 BU, rFVIIa is required as first-line treatment of bleeding episodes (Figure 6-1).

Bleeding in a participant with a low titre inhibitor (<5 BU) may in some instances be treated with FVIII concentrates. First line treatment for bleeding episodes requiring bypassing therapy should be rFVIIa, at an initial dose of no more than 90 µg/kg and otherwise administered according to approved prescribing information.

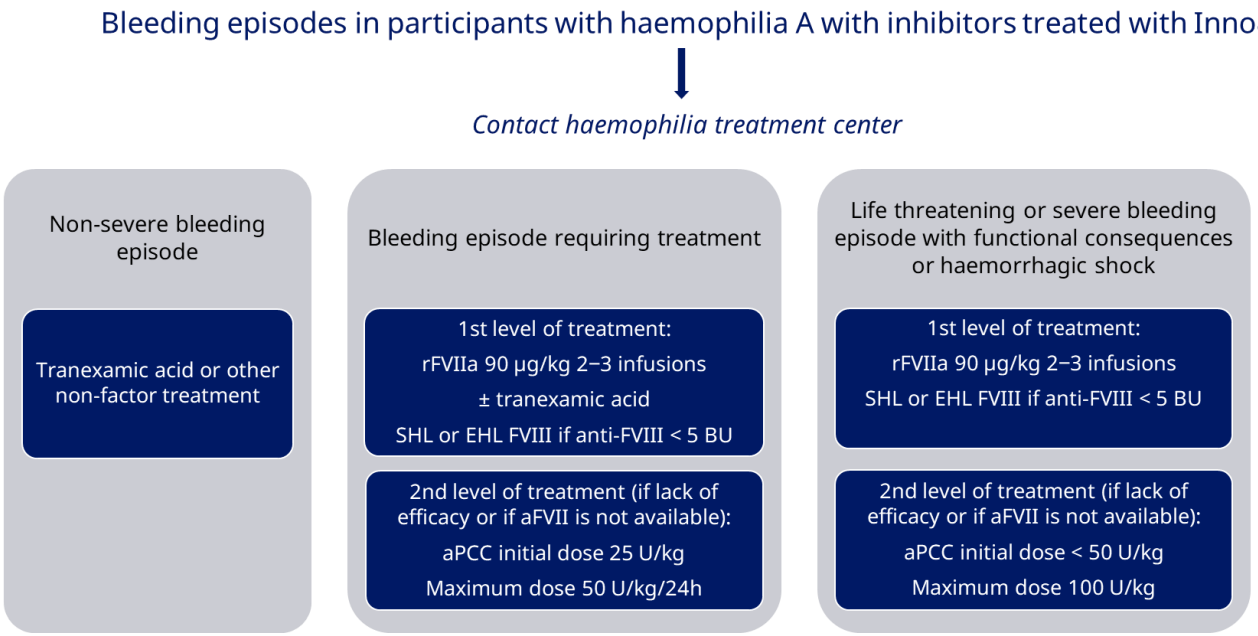
aPCC and ByClot® should only be considered for severe bleeding episodes if:

- haemostatic control of a severe bleed cannot be achieved with rFVIIa,
- no other therapeutic options are available,
- the clinical benefit is considered to outweigh the risk.

Decision to treat with aPCC or ByClot® should always be made in consultation with the investigator. For aPCC the initial dose should not be more than 25 U/kg and accumulated doses >50 U/kg/24 hours should be avoided. Life-threatening bleeding episodes may be treated with higher doses (≤50 U/kg) or with shorter intervals between infusions (not exceeding 100 U/kg/24 hours). For ByClot® the initial dose should not be more than 60 µg/kg. Recommendations for aPCC also apply for PCC.

It is recommended that participants treated with aPCC/PCC or ByClot® should have surveillance of thromboembolic events and thrombotic microangiopathy performed at the discretion of the investigator.

Figure 6-1 Breakthrough bleed treatment in participants with haemophilia A with inhibitors



Abbreviations: aPCC = activated prothrombin complex concentrate; BU = Bethesda unit; EHL = extended half-life; rFVIIa = recombinant activated factor VII; SHL = standard half-life.

For participants treated with aPCC or Byclot® prior to their study participation, administration must be discontinued at least 48 hours prior to Visit 2. The investigator must advise the participants to remove home supplies of aPCC and Byclot® prior to Visit 2. Prophylactic treatment with Inno8 should continue independent of bleeding episodes and their treatment, i.e. the original dosing schedule should be maintained unless investigator judges otherwise. Investigator must not administer prophylactic treatment other than Inno8 after the bleeding has stopped, as defined in Table 6-2.

Novo Nordisk will not provide or reimburse treatment for bleeding episodes.

6.9.2 Recording of bleeding episodes

The study site must be informed about the details of any bleeding episodes, including those that are treated outside the study site. Any contact with the participant related to the bleed must be recorded in the participant's medical record. Information about bleeding episodes prior to visit 2 will be recorded as medical history in the CRF as per Section 8.1, and those that occur after the investigational intervention (on or after visit 2), will be recorded in the CRF as disease-related events (DREs) as per Section 8.4.5.

The investigator must review the bleeding data collected in the CRF. It is the responsibility of the investigator to ensure timely completion of the CRF in cases of a bleeding episode. If corrections to the data in CRF are needed, the participant must be in agreement, and the outcome documented in source records prior to requesting the actual data change. The investigator must sign the CRF again if changes are made to it after signing it at the end of study, see Appendix 1 (Section 10.1.8.1).

The investigator/delegate must record the following in the CRF for all treatment-requiring bleeding episodes:

- Start date and time
- Stop date and time (Table 6-2)
- Anatomical location
- Cause of bleed:
  - 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)
- Severity:
  - mild/moderate or severe (see Table 6-3) (as evaluated by the investigator)
- Haemostatic medication:
  - brand name
  - type of the product
  - date and time of administration
  - dose(s) administered
  - dosing frequency.

Table 6-2 Definition of stop of bleed

Stop time is	When the participant experiences/observes signs of cessation of the active bleed such as pain relief, no increase in swelling/limitation of motion and improvement in other objective signs of the bleeding episode.
Stop time is <u>not</u>	When pain and objective signs of the bleeding episode are completely resolved.

6.9.3 Severity rating of bleeding episodes

Severity of all bleeding episodes must be evaluated by the investigator according to Table 6-3 and reported in the CRF. Haemostatic treatment must also be reported.

Table 6-3 Definition of bleeding episode severity

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

6.9.4 Treatment of bleeds in connection with a surgery

Definition of minor and major surgeries are provided in Table 6-4.

No surgeries are to be planned during the study duration and no interruptions in the study intervention are allowed due to any surgery.

In cases where a participant needs an acute major surgery during the study, he will be withdrawn from the study (see Section 7.2). However, in case where a participant is in need of an acute minor surgery during the study, the participant is allowed to continue the study and will be treated with haemostatic treatment as per the investigator's discretion.

Table 6-4 Definition of major and minor surgery

Minor surgery	Major surgery
Any invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated	Any invasive operative procedure where any one or more of the following occur: • A body cavity is entered • A mesenchyme barrier (e.g. pleura, peritoneum or dura mater) is crossed • A fascia plane is opened • An organ is removed • Normal anatomy is operatively altered

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, or compliance reasons.

Efforts should be made to have participants attend and complete all scheduled visit procedures.

The study intervention must be discontinued, if any of the following applies for the participant:
1. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study
2. If in need of a major surgery during the study (see Section 6.9.4 for details).

If study intervention is discontinued, the participant must be withdrawn from the study, see Section 7.2 for assessments to be performed.

The primary reason for discontinuation of study intervention must be specified in the CRF, and final trial product accountability must be performed. Discontinuation of study intervention must be registered in the RTSM.

7.1.1 Stopping criteria

Participant level and cohort level stopping criteria are continuously evaluated by each investigator.

Each investigator must ensure prompt communication of any event potentially triggering a cohort level stopping criterion to all the sites and the sponsor. Such communication is needed in case of reporting of an SAE, or a severe AE, or a thromboembolic event, probably or possibly related to the study intervention, see Section 7.1.1.2. The communication must be in the form of an immediate e-mail sent from the site at which the event occurred to the e-mail distribution list VOYAGER2_Stopping_Criteria@novonordisk.com. This list includes responsible investigators at all the other sites and the sponsor. This will enable all investigators to stop any on-going treatment with Inno8 as soon as possible. The e-mail communication does not substitute AE reporting as described in Section 8.4, but ensures a fast information flow independent of entering into the eCRF.

Stopping criteria for the sentinel group are evaluated in accordance with Section 6.5.1.1.

7.1.1.1 Participant level

A participant will be discontinued from study intervention if he experiences an unacceptable AE defined as any SAE or severe AE judged as probably or possibly related to trial product by the investigator.

7.1.1.2 Cohort level

If any of the following stopping criteria are met, the administration of trial product must be stopped. Furthermore, the Inno8 safety committee must be informed immediately:

- If one or more participants on a dose level experiences an SAE judged as probably or possibly related to trial product by the investigator.
- If two or more participants on a dose level experience a severe non-serious AE judged as probably or possibly related to trial product by the investigator.
- If one or more participants on a dose level experiences a thromboembolic event judged as probably or possibly related to trial product by the investigator.

If any of the above stopping criteria are met, dosing of further participants must be stopped at all sites. In addition, if either of the 2 sentinel participants in cohort 2 experience a serious or severe adverse event or a thromboembolic event judged as probably or possibly related to trial product by the investigator, the dosing of further participants in cohort 2 must be stopped. In both cases, an immediate ad-hoc safety committee meeting will be held to review all relevant data and to make a recommendation on how to proceed with the study and the treatment of the participants.

In each case the Inno8 safety committee will decide whether:

- The study or study part should stop or continue without modification
- Any actions should be taken regarding participants in ongoing cohorts

If required, an amendment/modification of the protocol will be submitted to the regulatory authorities and IECs before restarting the study.

For information about Novo Nordisk Inno8 safety committee refer to Appendix 1 (Section 10.1.6.1).

7.2 Participant discontinuation/withdrawal from the study

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

A participant may withdraw consent at any time at his own request.

If a participant wants to withdraw consent or the investigator wants to withdraw the participant prior to the receipt of study intervention, he will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, available eligibility criteria, date of informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant wants to withdraw consent or the investigator wants to withdraw the participant after the receipt of study intervention, the investigator must ask the participant if he is willing, as soon as possible, to have assessments performed according to visit 11. If possible, an end of study visit should be performed at least 35 days after last administration of study intervention, corresponding to visit 17. See SoA (Table 1-1) for data to be collected. The end of study form must be completed.

The purpose of the visit(s) after participant discontinuation/withdrawal from the study is to safeguard the participant. If the participant is unwilling to attend one or both visits, the investigator will judge if the participant's safety is jeopardised.

The withdrawal date is considered to be the participant's last visit, assessment or contact in the study, whichever is the latest.

Final trial product accountability must be performed even if the participant is not able to come to the site. Discontinuation of investigational intervention must be registered in the RTSM.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected up until the withdrawal date for the purpose of the study and scientific research. This will also apply in any country(ies) relying on explicit informed consent as legal basis for processing personal data. If a participant wants to exercise any of his rights, he must follow the description in the 'Agreement to take part' form (See Section 10.1.3).

If a participant withdraws from the study, he may request destruction of any samples taken and not tested; the investigator must document this in the medical record and notify the sponsor as soon as possible.

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

7.2.1 Replacement of participants

In cases where participants discontinue the study intervention or withdraw consent or is withdrawn by the investigator, a participant can be replaced up until 2 times to ensure enough participants complete the study. Novo Nordisk will decide whether a participant should be replaced or not based on the number of remaining participants at the time of discontinuation or withdrawal. If discontinuation or withdrawal is caused by one or more unexpected AEs possibly or probably related to trial product, the participant will not be replaced. The replacement participant will be allocated to the same treatment and dose level as the participant that he replaces, see the TMM for more information on treatment allocation.

7.3 Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts must be documented in the participant's source documents.

- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up' recorded in the end of study form.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all study participants. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the SoA.

Informed consent must be obtained before any study-related activity, see Appendix 1, (Section 10.1.3).

Adherence to the study design requirements, including those specified in the SoA (Table 1-1), is essential and required for study conduct.

Review of ECG, laboratory reports, etc., must be documented in the source documents. In case of detection of an AE, this should be reported if applicable according to the protocol.

Assessments should be carried out according to the site's standard practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments. When multiple assessments occur at the same time in a visit schedule, blood samples should be collected after ECG and vital signs.

Blood sampling

- The maximum amount of blood collected from each participant over the duration of the study will not exceed 500 mL.
- Procedures for blood sampling will be described in the laboratory manual.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Screening/baseline assessments and procedures

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

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

At visit 2, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Demography will be recorded in the CRF at screening and consists of:

- Age
- Year of birth (according to local regulation)
- Sex, defaulted to male
- Ethnicity (according to local regulation)
- Race (according to local regulation)

Ethnicity and race must be self-reported by the participant.

The term **medical history** covers medical events that the participant experienced prior to the time point from which AEs are collected. Only relevant medical history as judged by the investigator should be reported.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before exposure to investigational intervention.

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form in the eCRF. Any new finding fulfilling the definition of an AE (see Appendix 3 (Section 10.3.1)) during the study and any clinically significant worsening must be reported as an AE (see Section 8.4).

Details of haemophilia

The following information about the participant's underlying disease will be recorded in the CRF:

- FVIII inhibitor:
  - Current inhibitor status
  - Inhibitor test performed within the last year
  - If the participant had inhibitor status in the last 5 years from the screening visit (visit 1):
    - Date of last inhibitor test
    - Peak inhibitor result and the date of peak inhibitor result
- Family history of:
  - Haemophilia
  - FVIII inhibitors.

Haemophilia treatment and bleed history

The following information about the participant's haemostatic treatment and bleed history up to 6 months prior to screening will be recorded in the CRF:

- Type of treatment regimen:
  - prophylaxis or on-demand
  - start date
  - stop date
- Number of treated bleeding episodes
- Coagulation factor products
  - type of product
  - brand name (if available)
- Dosage used for prophylaxis (for participants who were on prophylaxis only)
- Dosing frequency during prophylaxis (for participants who were on prophylaxis only).

8.2 Efficacy assessments

Efficacy assessments are not applicable for this study. Refer to Section 8.5 for PK and Section 8.6 for PD assessments included in this study.

8.3 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1-1).

8.3.1 Physical examinations

A physical examination will include assessments of:

- General appearance.
- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Neurological system (central and peripheral nervous system)
- Skin
- Thyroid gland
- Lymph node palpation.

Body measurements will also be measured as follows and recorded as specified in the SoA:

- Height should be measured without shoes (in meters with two decimals).
- Body weight should be measured without shoes only wearing light clothing (in kg with one decimal). If the scale measures body weight in kg with two decimals, common rounding rules should be applied, i.e., a second decimal of 0-4 is rounded down and 5-9 is rounded up (e.g., a measured body weight of 80.84 kg is rounded down to 80.8 kg, while 80.85 kg is rounded up to 80.9 kg).
- BMI should be calculated in the CRF as body weight (in kg with one decimal) divided by height (in meters with two decimals) squared (in kg/m2 with one decimal). BMI calculation should be done in an appropriate data handling system. Any rounding of body weight and/or height must be avoided when calculating BMI.

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

In the CRF, only data on whether the physical examination was performed will be collected (Yes/No). A physical examination with an abnormal and clinically significant finding will be handled as described in Section 8.1.

8.3.2 Vital signs

Body temperature, pulse rate, respiratory rate, as well as systolic and diastolic blood pressure will be assessed at visits as mentioned in the SoA (Table 1-1).

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).

Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. No more than four measurements will be performed.

- The mean systolic blood pressure and diastolic blood pressure values are calculated based on the last 2 measurements.
- The last 2 systolic and last 2 diastolic blood pressure measurements will be recorded in the CRF. The CRF will calculate the mean of the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements.

- The mean pulse rate value is calculated based on the last 2 pulse rate measurements.
- The pulse rate for the last 2 measurements will be recorded in the CRF. The CRF will calculate the mean of the last 2 measurements.

The records of vital signs will be specified in the CRF as either “normal” or “abnormal”. If “abnormal”, a comment must be given together with an assessment of clinical significance (yes/no).

8.3.3 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (Table 1-1) using an ECG machine. The heart rate will be calculated and PR, QRS, RR, QT and QT_cF intervals will be measured either manually or through the ECG machine.

- ECG measurements should be preceded by at least 5 minutes of rest in a supine position for the participant in a quiet setting without distractions (e.g., no use of television, cell phones).
- ECG will be evaluated by the investigator or designee and the outcome must be specified in the CRF as either “normal” or “abnormal”. An overall interpretation will be performed by the investigator and recorded in the CRF.
- The signed and dated versions of the ECGs will be filed together with the investigator’s study documentation.

8.3.4 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Table 1-1) and the laboratory manual.

8.4 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE or adverse events of special interest (AESI) or AEs requiring additional data collection.

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AESIs and AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. The relevant event(s) are listed below in Table 8-1, together with AESI(s) and other events requiring collection of additional information.

Table 8-1 AEs requiring additional data collection, AESIs and other events requiring collection of additional information

Event type	AE requiring additional data collection	AESI	Other events requiring collection of additional information
Medication error	X		
Misuse and abuse	X		
Elevated liver enzymes			X
Hypersensitivity	X		
Thromboembolic events		X	
Bleeding episodes[a]			X

[a] The recording and reporting of bleeding episodes depends on the causality, intensity, frequency or duration, severity and outcome of the events, see Section 8.4.5 for details.

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.4.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the first administration of investigational intervention and until the end of study visit in accordance with the SoA (Table 1-1) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs and AESIs must be recorded and reported to Novo Nordisk without undue delay but not later than within 24 hours of obtaining knowledge of the events. Similarly, the investigator must submit any updated data on SAEs and AESIs to Novo Nordisk without undue delay, but not later than within 24 hours of obtaining knowledge of the information.

Investigators are not obligated to actively seek for AEs or SAEs in former study participants. However, if the investigator learns of any SAE with a suspected causal relationship to the investigational intervention, or to study participation, occurring after a participant has discontinued/completed the study, the investigator must notify Novo Nordisk without undue delay.

8.4.2 Method of detecting AEs

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting reports on SAEs are provided in Appendix 3 (Section 10.3).

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

8.4.3 Follow-up of AEs

After the initial AE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs will be followed until the outcome is final of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and outcome of AEs is given in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE and AESI is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an investigational intervention are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

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

8.4.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with haemophilia A, and can be serious/life threatening:

- Bleeding episodes.

Bleeding episodes

Because bleeding episodes are typically associated with the disease under study, they will not be reported according to the standard process for reporting of AEs/SAEs, even though the episodes may meet the definition of an AE or qualify as an SAE according to Appendix 3 (Section 10.3.2). These episodes will be recorded in the CRF (see Section 6.9.2).

Note: The bleeding episode must be recorded and reported as both a DRE and an AE/SAE if one of the following applies:

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

8.4.6 Adverse event of special interest

Please refer to Section 8.4 and Appendix 3 (Section 10.3).

8.4.7 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form on a continuous basis.

Instructions for reporting technical complaints can be found in Appendix 6 (Section 10.6).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.5 Pharmacokinetics

Samples used to evaluate the PK of Inno8 will be collected as specified in the schedule of PK, PD and safety assessments in Table 1-2.

For each specific PK sample, two aliquots (one as primary PK sample and one as backup) should be stored. Sampling, handling, storage, labelling and shipments of the collected samples must be performed in accordance with the laboratory manual.

The actual date and time of collection of individual PK samples must be recorded in the CRF.

PK bioanalysis of analyte will be performed at Novo Nordisk, or a special laboratory designated by Novo Nordisk (see Attachment I). Analytes for Inno8 plasma will be assayed in the PK samples by validated assays. The bioanalytical method will be described in a bioanalytical report.

Genetic analyses will not be performed on these plasma/serum/whole blood samples. Participant confidentiality will be maintained.

Residual sample material may be used for primary purposes i.e., bioanalysis assay development and/or assay validation, or further characterisation of antibody responses towards drug and antibody analysis method validation and assay maintenance purposes. For storage of residual PK samples after final clinical study report (CSR), Novo Nordisk will ensure that third party collaborators live up to the regulations on data protection, see Appendix 1 (Section 10.1.5). Samples may be stored within expected analyte stability but no longer than 5 years from end of study. The relevance of storing the residual PK samples after final CSR will be evaluated no later than at final CSR. Only relevant Novo Nordisk staff, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored samples and associated data. Potential exploratory metabolite analysis, bioanalysis assay development and anti-drug antibody assay development will be reported separately from the CSR.

Approval by clinical pharmacology specialist in Novo Nordisk must be obtained before samples can be destroyed. A destruction certificate must be sent to Novo Nordisk if samples are stored at a special laboratory.

8.6 Pharmacodynamics

All protocol-required PD laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with schedule of PK, PD and safety assessments in Table 1-2 and the laboratory manual.

Inno8 activity

For each specific Inno8 activity sample, two aliquots (one as primary sample and one as backup) should be stored. Sampling, handling, storage, labelling and shipments of the collected samples must be performed in accordance with the laboratory manual.

The actual date and time of collection of individual Inno8 activity samples must be recorded in the CRF.

Inno8 activity bioanalysis of analyte will be performed at Novo Nordisk, or a special laboratory designated by Novo Nordisk (see Attachment I). Inno8 activity will be determined using validated bioanalytical assays. The bioanalytical method will be described in a bioanalytical report.

Thrombin generation

Thrombin generation will be determined using validated bioanalytical assays. It will be measured in platelet-poor plasma initiated with activated coagulation factor XI (FXIa). The participants with haemophilia included in this study will still have FVIII activity but only up to 15%. Therefore, thrombin generation will be measured in plasma both with and without neutralisation of endogenous FVIII to evaluate PD effects of Inno8 appropriately. In addition, pre-dose FVIII-neutralised samples will be spiked in parallel with increasing amounts of Inno8. The exact method will be described in an analytical report.

Activated partial thromboplastin time

Blood samples for determination of activated partial thromboplastin time (aPTT) will be collected to evaluate PD effects of Inno8. aPTT will be measured in plasma, with and without neutralisation of endogenous FVIII. Results from the neutralisation will be described in an analytical report.

Retention of residual samples

Residual sample material may be used for bioanalysis assay development and/or assay validation, or further characterisation of antibody responses towards drug and antibody analysis method validation and assay maintenance purposes. For storage of residual samples after final CSR, Novo Nordisk will ensure that third party collaborators live up to the regulations on data protection, see Appendix 1 (Section 10.1.5). Samples may be stored within expected analyte stability but no longer than 5 years from end of study. The relevance of storing the residual samples after final CSR will be evaluated no later than at final CSR. Only relevant Novo Nordisk staff, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored samples and associated data. Potential bioanalysis assay development, and anti-drug antibody assay development will be reported separately from the CSR.

Approval by clinical pharmacology specialist in Novo Nordisk must be obtained before samples can be destroyed. A destruction certificate must be sent to Novo Nordisk if samples are stored at a special laboratory.

8.7 Genetics

Genetic testing (factor V Leiden (G1691A)) and prothrombin mutation (GA20210A)) will be performed at screening (Visit 1), as part of thrombophilia screening to exclude participants with increased risk of thrombosis. The DNA samples will only be used for the purpose of determining whether these mutations are present. Only central laboratory staff will have access to the samples. The samples will be coded and the participant's identity will remain anonymous.

During the conduct of the study the samples will be stored at the central laboratory and no later than at the end of study samples will be destroyed according to local laws and regulations. Participation in the genetic testing is optional. Participants who do not wish to participate in the genetic testing may still participate in the study. In case participants do not consent to genetic testing, exclusion will be based on factor II activity or activated protein C resistance outside the normal laboratory range at screening.

Refer to Appendix 5 (Section 10.5) for further details.

8.8 Biomarkers

Not applicable for this study.

8.9 Immunogenicity assessments

Anti-Inno8 antibody plasma samples will be collected according to the SoA (Table 1-1). All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day. Analysis for anti-Inno8 antibodies will be done using a validated anti-drug binding antibody assay in a tiered manner with screening, confirmation and titre. Detailed description of the assay method will be included in the analytical report. Antibody assays will be validated according to international guidelines and recommendations.

Assessment of antibodies against Inno8 in plasma will be performed by Novo Nordisk and reported at the end of study. For details on blood sampling, plasma preparation and storage, please see the laboratory manual.

Results from immunogenicity assessments will be available at the end of study and will be reported in the CSR.

Anti-drug antibody samples may be retained for further characterisation of immune responses towards the trial product if required by health authorities or for safety reasons. These samples may also be used for assay maintenance or further development of anti-drug antibody assays, or for exploratory investigation of antibodies.

The antibody samples will be stored at Novo Nordisk after end of study until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed. The samples might be transferred to other countries, if not prohibited by local regulations. Only relevant Novo Nordisk staff, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored samples and associated data.

Assessments in case of suspicion of hypersensitivity to trial product

Participants and investigators will be instructed to detect signs and symptoms of hypersensitivity reactions:

- Local reactions and
- Systemic reactions, including anaphylaxis

In the event of a systemic hypersensitivity reaction (i.e., not local reactions or infusion site reactions), probably or possibly related to investigational drug, as judged by the investigator, the participant should be called in as soon as possible to have additional blood samples taken to analyse the following parameters:

- Tryptase (optimal 0.5 – 2 hours after the hypersensitivity reaction). Only relevant if the tryptase sample can be collected no more than 3 hours following the onset of reaction.
- Total IgE
- Anti-Inno8 IgE antibodies
- Anti-Inno8 binding antibodies

The blood sampling should be repeated 1-2 weeks and if possible, 3-5 weeks after the systemic hypersensitivity reaction. The follow-up sample will serve as baseline sample. If possible, the drug-specific IgE and binding antibodies should also be performed on samples drawn prior to first administration of trial product.

The investigator or the participant should take digital pictures of the hypersensitivity reaction at time of identification and thereafter as often as judged necessary by the investigator. The pictures should include participant ID, date and time, time after dosing and a ruler for scaling. All pictures should be stored as part of source documentation at site.

Analysis of anti-Inno8 IgE and anti-Inno8 binding antibodies in samples from participants treated with Inno8 (NNC0442-0344) will be performed at Novo Nordisk. The results of the analysis will not be available to the investigator until the end of study and cannot be used for medical decisions or diagnostic purposes.

Tryptase and total IgE will be performed at sites or relevant central lab or CROs, as agreed with Novo Nordisk. Tryptase and total IgE results can also be generated at local laboratory at the discretion of the investigator.

Other relevant tests may be performed as exploratory analyses by Novo Nordisk or Novo Nordisk designated laboratories.

Data from the above hypersensitivity measurements will be loaded into the clinical database. This includes both the data generated from CROs (Tryptase and total IgE) as well as that generated at Novo Nordisk (anti-Inno8 IgE and anti-Inno8 binding antibodies). In addition, the analysis of anti-drug IgE and anti-drug antibodies will be reported in a separate report and attached to the CSR.

In case of a systemic hypersensitivity reaction, the additional blood samples taken in relation to the reaction may be retained to follow-up on the hypersensitivity reaction. If measured, such data will be reported in a separate report. Hypersensitivity samples may be retained for later analysis for

further characterisation of antibody response towards drug, if required by health authorities, for up to 15 years from end of study after which they will be destroyed.

8.10 Human biosamples for future research

Not applicable for this study.

9 Statistical considerations

The analysis and reporting will be done after the global end of study.

9.1 Statistical hypotheses

No formal statistical hypotheses will be tested in the study.

9.1.1 Multiplicity adjustment

Not applicable.

9.2 Analysis sets

The safety analysis set (SAS) includes all participants exposed to Inno8. All participants with at least one valid PK or PD assessment will be included in the full analysis set (FAS). Safety data will be reported based on SAS, while all PK and PD endpoints will be reported based on FAS.

Any participants or observations to be excluded from the FAS, and the reasons for their exclusion, will be documented and signed before DBL. The participants and observations excluded from analysis sets, and the reason for this, will be listed and described in the CSR.

9.3 Statistical analyses

9.3.1 General considerations

An ample description of the statistical analyses will be provided in this document. Due to the exploratory nature of this study a separate statistical analysis plan (SAP) will not be prepared.

Data will be summarised by dose cohort. All documented data will be summarised descriptively according to their data type. Categorical data are displayed by number and percentage by visit. Continuous data are displayed by location and variation measures by visit, including change from baseline where appropriate. No confirmatory statistical tests will be performed.

Missing endpoint data will not be imputed unless specified for selected endpoints.

9.3.2 Primary endpoint analysis

9.3.2.1 Definition of endpoints

The primary endpoint is the number of treatment emergent adverse events (TEAEs). TEAEs are defined as AEs occurring from the time of dosing and until Day 46.

9.3.2.2 Main analytical approach

The safety of Inno8 will be evaluated based on the proportion of participants with TEAEs. The number of treatment emergent, serious, severe, possible or probably related AEs will be summarised together with the number and percentage of participants experiencing the event, by system organ class and preferred term (coded using Medical Dictionary for Regulatory Activities (MedDRA)).

All treatment emergent AEs will be listed and summarised by dose level.

9.3.2.3 Sensitivity analysis

Not applicable.

9.3.2.4 Supplementary analysis

Not applicable.

9.3.3 Secondary endpoint analysis

9.3.3.1 Pharmacokinetic analysis

All PK endpoints will be derived based on non-compartmental methods after multiple administrations of Inno8. The actual sampling time with respect to time since dosing will be used for the derivations. All AUCs will be calculated using the linear trapezoidal method. All PK endpoints will be listed and summarised by dose level (mean, median, standard deviation, min, max, coefficient of variation (CV%), geometric mean, and 95% confidence interval of the geometric means).

Approximate dose proportionality may be evaluated for C_{max} and AUC if data permits. This will be done by an ANOVA on log-transformed parameters with log-transformed dose as a covariate. The estimated slope will be provided with 95% confidence intervals.

Inno8 plasma concentration below the lower level of quantification (LLoQ) in the last part of the PK profiles will be treated as left-censored data e.g. when deriving the terminal elimination rate constant (λz) from the profiles.

Inno8 plasma concentration will be summarised by dose level and time point. Individual and mean value curves will be presented on both the linear and the logarithmic scale over the sampling time.

For graphical presentation of Inno8 plasma concentration, values below LLoQ will be imputed as follows:

- values before the last quantifiable value will be imputed as LLoQ/2
- values after the last quantifiable value will be imputed as LLoQ/2 for the first value and as 0 for the subsequent values

Table 9-1 Calculation of pharmacokinetic endpoints

Endpoint	Definition	Calculation
AUC_{0-24h}	Area under the concentration-time curve in the dosing interval after multiple doses.	AUC_{t0-24h} is calculated using the linear trapezoidal method from time 0 to 24 hours.
C_{max}	The maximum concentration of Inno8 after multiple doses.	Based on actual measurements.
T_{max}	The time to C_{max} after first dose (Day 1 to Day 2) and after last multiple dose (Day 10 to Day 11).	The actual time since dose administration.

Endpoint	Definition	Calculation
$T_{1/2}$	Terminal half-life.	$\ln(2) / \lambda_z$
λ_z	Terminal elimination rate constant.	The terminal elimination rate constant will be estimated using linear regression on the terminal part of the log (concentration or activity) versus actual time profile. If data at the terminal part is below LLoQ, these data will be treated as left-censored data when estimating the λ_z.

9.3.3.2 Pharmacodynamic analysis

Peak thrombin generation and changes in activated partial thromboplastin time will be summarised descriptively and with profile plots.

Inno8 activity levels will be summarised in the same way as Inno8 plasma concentration data, see Section 9.3.3.1.

9.3.3.3 Safety analysis

All safety laboratory assessments (haematology, biochemistry, coagulation parameters eGFR and urinalysis) will be summarised by visit (visit value as well as absolute and percent change from baseline). For D-dimer, prothrombin fragment 1 and 2, fibrinogen, platelets and other safety parameters listed as endpoints, individual profiles will also be displayed graphically over time. Incidence of anti-Inno8 antibodies will also be presented. Vital signs and ECG will be summarised correspondingly.

9.3.4 Exploratory endpoint analysis

Changes in FIX and FX antigens will be summarized as described in Section 9.3.3.

9.3.5 Other safety analyses

Not applicable.

9.3.6 Other analyses

Pharmacokinetic and/or pharmacodynamic modelling

Data from this study may be used for exploratory pharmacokinetic analysis as needed, of which some pre-determined exploratory analyses are explained below.

Inno8 plasma concentration versus time profiles will be participant to exploratory non-linear mixed effects PK modelling analysis. The objective of this modelling analysis is to study the Inno8 PK after multiple peroral doses of Inno8 in people with haemophilia A.

PK/PD relationships for PD endpoints may be investigated if deemed relevant. The analysis may include graphical investigation of PD data versus exposure and/or model-based analyses. The final analyses are considered exploratory, and no formal analysis plan will be developed. The results of the final analyses will be reported separately from the CSR.

9.4 Interim analysis

No formal interim analysis will be conducted for this study. However, as this is an open label study, the sponsor may review the data during the study for the purpose of decision-making during clinical development and/or health authority interactions. It is not considered a protocol deviation, if the data is not reviewed after a cohort.

9.5 Sample size determination

No formal power calculations will be performed. The plan is to include up to 10 participants in each cohort with a minimum of 8 participants for adequate assessment of safety, PK and PD data, to achieve the objectives of the study whilst exposing as few participants as possible to the study product.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[9] and applicable ICH Good Clinical Practice (GCP) Guideline[10].
- Applicable laws and regulations

The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

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

Any amendments/modifications to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants. In case of changes made to eliminate an immediate safety hazard, the actions must be reported to Novo Nordisk immediately (within 24 hours after the action was taken).

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The list of investigator responsibilities below reflects global GCP requirements. Certain activities related to IRB/IEC submission can be carried out by the sponsor, in accordance with local or regional regulatory requirements.

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC, as applicable according to local requirements (not applicable for sites in EU/EEA submitting via CTIS).
- reporting any potential serious breaches to the sponsor immediately (within 24 hours after discovery). A serious breach is a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of data generated in the clinical study. This includes persistent or systematic non-compliance with ICH GCP E6 and/or the protocol.

The sponsor will report any serious breach occurring in any participating country to the health authorities according to applicable regulations/laws.

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure that the participant has ample time to read and understand the written information and come to a decision on whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign and date a statement of informed consent ('Agreement to take part' form) that meets the requirements of local regulations, ICH GCP[10] guidelines, Declaration of Helsinki,[9] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

The responsibility of 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.

Participants must be re-consented to the most current version of the informed consent form(s) during their participation in the study according to sponsor instructions.

A copy of the informed consent form(s) must be provided to the participant.

10.1.4 Recruitment and information to participants during the study

Recruitment of potential participants to the study can include activities such as review of patient medical records, handing out study information and database review. Such activities are carried out prior to obtaining participant consent to participate, or any screening activities, and should be documented by the investigator.

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of

the investigator. The participant may receive a “thank you for your participation letter” after completion of the study. Further, the participant may receive other written information during the study.

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

10.1.5 Data protection

Participants will be assigned a participant ID as an identifier. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by participant ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants.

The participant must be informed about his privacy rights, including that his personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The sharing and disclosure of the data must also be explained to the participant.

The participant must be informed that his medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members and by inspectors from regulatory authorities.

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

Personal data may be collected from participants due to process requirements from Novo Nordisk’s suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the CSR. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including implementation of appropriate security measures, handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

In case of a data security breach, appropriate actions will be taken promptly to mitigate any potential adverse effects, in accordance with the sponsor’s procedures on how to respond in the event of unauthorized access, use or disclosure of sponsor information or systems.

For Spain and UK, see Appendix 7 (Section 10.7).

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal Inno8 safety committee. The safety committee is a multi-disciplinary team with members from all relevant functional areas. The committee works according to a written guideline and is responsible for providing integrated assessments of safety data and for endorsing appropriate actions.

10.1.7 Dissemination of clinical study data

This is a multinational study including both EU/EEA and non-EU/EEA sites, and the end of study is defined as the global end of study. The summary of study results and layperson summary of results will be submitted within 12 months after the global end of study, as the planned statistical analyses cannot be performed until data from all sites are available.

Study information will be disclosed at clinicaltrials.gov and euclinicaltrials.eu and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[9] the International Committee of Medical Journal Editors (ICMJE),[11] the Food and Drug Administration Amendment Act (FDAAA),[12] European Commission Requirements[1, 13, 14] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The privacy of each participant providing data for the clinical study, and the confidentiality of his information shall be preserved in reports, communications and when publishing any data.

10.1.8 Data quality assurance

10.1.8.1 Case report forms (CRF)

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator will sign the CRF at the end of the study, as described in the CRF completion guideline.

The term "case report form (CRF)" in this protocol means "electronic CRF (eCRF)" unless otherwise specified.

All participant data relating to the study will be recorded on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data). The investigator is responsible for verifying that data entries in CRFs are accurate and correct by electronically signing the CRF.

CRFs will be provided in an electronic format except the following that are provided as paper CRFs, when the access to the electronic format is revoked or temporarily unavailable:

- Safety information form
- Technical complaint form
- AE form

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, no later than 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Remote access to the source data documents by Novo Nordisk monitors and auditors can be agreed in countries where this is acceptable according to regulatory requirements and national legislation. Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[10] and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

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

Quality tolerance limits (QTLs) will be predefined for relevant study level risks, if any, in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. Predefined QTLs will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay 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 CRF or via listings from the study database.

Note: Throughout the protocol, the term 'should' indicates an expectation that applies unless an alternative scenario is described.

10.1.9 Source documents and source data

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

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site. Data that is transcribed into the CRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator/institution must have control of all essential documents and records generated by the investigator/institution before, during and after the study. The investigator must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

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

Novo Nordisk will retain study documentation for 25 years or longer as required by local law, or as long as the information contributes to scientific purposes or product safety.

For US, see Appendix 7 (Section 10.7).

10.1.11 Study and site start and closure

First act of recruitment

The start of study is defined as the date when the clinical study will be open for recruitment of participants, i.e., the 'first act of recruitment.' The first act of recruitment is defined as the first site activation in the study.

First participant's first visit

First participant's first visit in the study is defined as the date the first participant is screened in the study.

Study or site termination

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

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

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

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

10.1.12 Responsibilities

The investigator is responsible for conducting the study in accordance with the protocol at his/her site and must ensure adequate supervision of the conduct of the study at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's

responsibility to supervise the conduct of the study and to protect the rights, safety, dignity and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related medical decisions.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised 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. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). 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 participants to a specific qualified physician who will be readily available to participants 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).

A detailed responsibility split between Novo Nordisk and the CRO and the central and special laboratories is provided in the contract between the parties.

10.1.13 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 studies 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 study or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with local laws/acts/guidelines as described for Poland and Spain, in Appendix 7 (Section 10.7).

10.1.14 Publication policy

The information obtained during the conduct of this study 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 study intervention. All information supplied by Novo Nordisk in connection with this study 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 study.

The information obtained during this study may be made available to other investigators who are conducting other clinical studies with the study intervention, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same or related diseases and/or study intervention studied in this study.

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One or more investigators will be appointed by Novo Nordisk to review and sign the CSR (signatory investigator(s)) on behalf of all participating investigators.

10.1.14.1 Communication of results

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

The results of this study will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CSR 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 study.

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

10.1.14.2 Authorship

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

Authorship of publications will be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[15]

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

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

10.1.14.3 Site-specific publications by investigators

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

As owner of the study database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research participants' data.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory or the special laboratory with the exception of urinalysis done by dipstick (pH, glucose, protein, blood and leucocytes), which will be performed at the study site.

Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations e.g., to follow up on AEs. Such additional tests should be analysed at local laboratory. If the additional tests are sent to central laboratory for analysis by error or if the additional tests are sent to the local laboratory, which is also used for study related analyses, the results of such additional tests can be transferred to the study database if the assessment is already mentioned in the protocol. Assessments not mentioned in the protocol should not be transferred to the study database.

The central laboratory or local laboratory used for study related analyses may include testing of additional parameters not requested in the protocol due to their internal laboratory equipment and/or processes. These data results will not be transferred to the study database, but any abnormal values should be communicated to the investigator. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

The investigator must keep an overview, e.g., a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log, of laboratory samples stored at site.

Clinical laboratory samples will be destroyed no later than at finalisation of the CSR, except for PK, PD and anti-Inno8 antibodies/hypersensitivity samples.

Residual samples collected for immunogenicity will be stored as described in Section 8.9.

Table 10-1 Protocol-required clinical laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes (platelets) Differential count: • Lymphocytes • Monocytes • Neutrophils • Basophils • Eosinophils

Laboratory assessments	Parameters
Biochemistry[a]	• Alanine Aminotransferase (ALT) • Albumin • Alkaline phosphatase • Aspartate Aminotransferase (AST) • Bilirubin, total • Creatinine • Potassium • Sodium • C-reactive protein (CRP) • Lactate dehydrogenase (LDH) • Urea • Troponin T • NT-proBPN
Lipids	**Screening only:** • Cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Coagulation parameters	• D-dimer • Prothrombin fragment 1+2 (F1+2) • Antithrombin • Prothrombin time and international normalised ratio (PT/INR) • Fibrinogen • FIX antigen • FX antigen • Dilute Russell's Viper Venom Time Ratio • FVIII activity[b] **Screening only:** • Protein C antigen • Protein S antigen • Lupus anticoagulant • Anti-β2 glycoprotein-1 antibody (IgM and IgG) • Anti-cardiolipin antibodies (IgM and IgG) • Activated protein C (APC) resistance • Factor II (FII) activity
Serology[c]	**Screening only:** • HIV 1 and 2 antibody • Hepatitis B surface antigen (HBsAg) • Hepatitis C virus antibody
Urinalysis	• pH, glucose, protein, blood and leucocytes by dipstick • Albumin/creatinine ratio
Other tests	eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation 2021 List of genetic testing (**at screening only**): • Factor V Leiden mutation (G1691A) • Prothrombin mutation (G20210A)

Laboratory assessments	Parameters
Antibodies	• Anti-Inno8 antibodies
SARS-CoV-2[c,d]	• Reverse transcription polymerase chain reaction or Antigen Rapid test for SARS-CoV-2
Notes: [a] See Appendix 3 (Section 10.3) (Hy's Law) for details of required actions and follow-up assessments for increased liver parameters. Discontinuation and/or stopping criteria are given in Section 7.1. [b] FVIII activity will be assessed only at screening, visit 2 and visit 11. [c] Results will be kept in source data and not recorded in the CRF or transferred to the study database. [d] Can be performed as per local guidance.	

Table 10-2 Protocol-required PK and PD laboratory assessments

Laboratory assessments	Parameters
Pharmacokinetics	• Inno8 plasma concentration
Pharmacodynamics	• Thrombin generation • aPTT • Inno8 activity

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up and reporting

10.3.1 Definition of AE

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

Events to be reported as AEs

In addition to events falling under the AE definition above, the following are examples of events that also are to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected.
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected.
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms or the clinical sequelae of a suspected drug–drug interaction.
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent.

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. Record such conditions as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

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

- **Results in death**
- **Is life-threatening**
  - The term ‘life-threatening’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the

event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs.

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

10.3.3 Description of AESIs, AEs requiring additional data collection and other events requiring collection of additional information

AESIs

An AESI is an AE which, in the evaluation of safety, has a special focus due to requirements from regulatory authorities or sponsor. AESIs follow the same reporting timeline as an SAE, please see Figure 10-1 in Section 10.3.5. For AESIs both an AE form and a safety information form must be completed, regardless of seriousness.

Thromboembolic events

Thromboembolic events include, but are not limited to:

- disseminated intravascular coagulation (DIC)
- thrombotic microangiopathy (TMA)
- myocardial infarction
- pulmonary embolism
- stroke
- deep vein thrombosis
- other clinically significant thromboembolic events and peripheral artery occlusion

In case of suspicion of thromboembolic events, further investigations and appropriate medical treatment should be initiated immediately.

Definition of disseminated intravascular coagulation

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

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

Definition of thrombotic microangiopathies

Thrombotic microangiopathies (TMA) are a group of disorders characterized by microangiopathic haemolytic anaemia, thrombocytopenia and microthrombi leading to ischemic tissue injury that can affect e.g. the kidneys and the CNS.

TMA is a clinicopathologic diagnosis. The constellation of thrombocytopenia, anaemia and red blood cell fragmentation (i.e. schistocytes) on the blood film is consistent with a diagnosis of TMA. The finding of concomitant anaemia and thrombocytopenia should prompt a request for a peripheral blood film to look for red blood cell fragmentation.

If TMA is suspected the following laboratory assessment workup is suggested: standard haematology, haemolytic parameters (reticulocytes, haemoglobin, bilirubin, LDH, haptoglobin), Direct Anti-Globulin (DAT) test (also referred to as Coombs test), peripheral blood smear to look for schistocytes, creatinine, ADAMTS13 Antigen and ADAMTS13 Antibody.

Definition of myocardial infarction

Myocardial infarction is defined according to the "Third Universal Definition of Myocardial Infarction". 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.

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.

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

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".

Accordingly, the term "stroke" should be broadly used to include all of the following:

- Definition of central nervous system (CNS) infarction: CNS infarction is brain, spinal cord or retinal cell death attributable to ischemia, based on: pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or clinical evidence of cerebral, spinal cord or retinal focal ischemic injury based on symptoms persisting 24 hours or until death, and other aetiologies excluded.
- 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
- 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 oedema 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.

Definition of deep vein thrombosis

The "Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians" on diagnosis of venous thromboembolism recommends

ultrasound scanning for patients with intermediate or high pre-test probability of deep vein thrombosis in the lower extremities. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

Definition of other clinically significant thromboembolic events

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

Definition of peripheral artery occlusion

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

Adverse events requiring additional data collection

A specific event form needs to be completed for the following events.

Medication error:

- A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  - administration of wrong drug
    Note: Use of wrong Kit ID is not considered a medication error unless it results in administration of wrong drug.
  - wrong route of administration, such as intramuscular instead of subcutaneous.
  - accidental administration of a higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm).

Note: Medication error, misuse and abuse must always be reported on an AE form and the specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Hypersensitivity events

Since Inno8 is a biological product, acute, systemic hypersensitivity reactions, including anaphylaxis and anaphylactic reactions may occur.

In cases of clinical signs of a severe and immediate hypersensitivity reaction with possible or probably relation to Inno8, as judged by the investigator, additional blood should be sampled. See Section 8.9 for further guidance on additional laboratory testing to be performed.

Attention should be paid to any sign or symptom of a hypersensitivity reaction. If, according to the investigator's judgement, hypersensitivity reactions that require systemic treatment are suspected, dosing with Inno8 should be stopped immediately and treatment initiated at the discretion of the treating physician.

Other events requiring collection of additional information

Elevated liver enzymes

In all cases where one or more results from liver laboratory parameters (ALT, AST or ALP) measured in a blood sample at the central laboratory are increased above the limits defined below, the Elevated Liver Enzymes form must be completed.

- Alanine aminotransferase (ALT): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- Aspartate aminotransferase (AST): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- Alkaline phosphatase (ALP): >2.5 x ULN if baseline was normal; >2.5 x above baseline if baseline was abnormal

Bleeding events

Bleeding episodes in this study should be recorded in the CRF as per Section 6.9.2, regardless of whether or not it is considered as an AE/SAE. Please refer to Section 8.4.5 for details on when a bleeding episode is considered as an AE/SAE and a DRE.

10.3.4 Recording and follow-up of AEs and/or SAEs

10.3.4.1 AE and SAE recording

The investigator will record all relevant information about AEs/SAEs in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

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

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

participant ID, must be redacted on the copies of the source documents before submission to Novo Nordisk, see Section 10.1.5.

Please refer to Figure 10-1 for reporting of non-serious AEs. For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to Section 10.3.5.

If an SAE/AESI is considered to have a causal relationship with a concomitant medication, it is important that the suspected relationship is reported to Novo Nordisk in e.g., the alternative aetiology section on the safety information form. Novo Nordisk may need to report it to relevant regulatory authorities.

If an SAE/AESI is a suspected drug – drug interaction with the IMP, the investigator should report this to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form.

10.3.4.2 Assessment of severity

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

- **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

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

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

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

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

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

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

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

10.3.4.4 Outcome of AEs

The investigator will select the most appropriate outcome that reflects the event outcome status at the time of reporting:

- **Recovered/resolved**: The participant has fully recovered from the event, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death is due to another AE).
  Note: SAEs can be closed with the outcome 'recovering/resolving' only if the participant has withdrawn or completed the study, or end of study is near, and the investigator confirms that the participant is expected to fully recover from the event.
- **Recovered/resolved with sequelae**: The participant has recovered from the event but with long-lasting or permanent effect(s) 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 has not improved. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs that occurred before the participant died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: The outcome is unknown.
  Note: AEs can be closed with the outcome 'unknown' only if the participant is lost to follow-up.

10.3.4.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with the autopsy results including histopathology.

New or updated information will be recorded in the CRF.

The investigator will submit any updated SAE data to Novo Nordisk without undue delay, but not later than within 24 hours of receipt of the information.

10.3.5 Reporting of SAEs and AESIs

SAE and AESI reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE forms and safety information forms within the designated reporting timelines (see Figure 10-1):

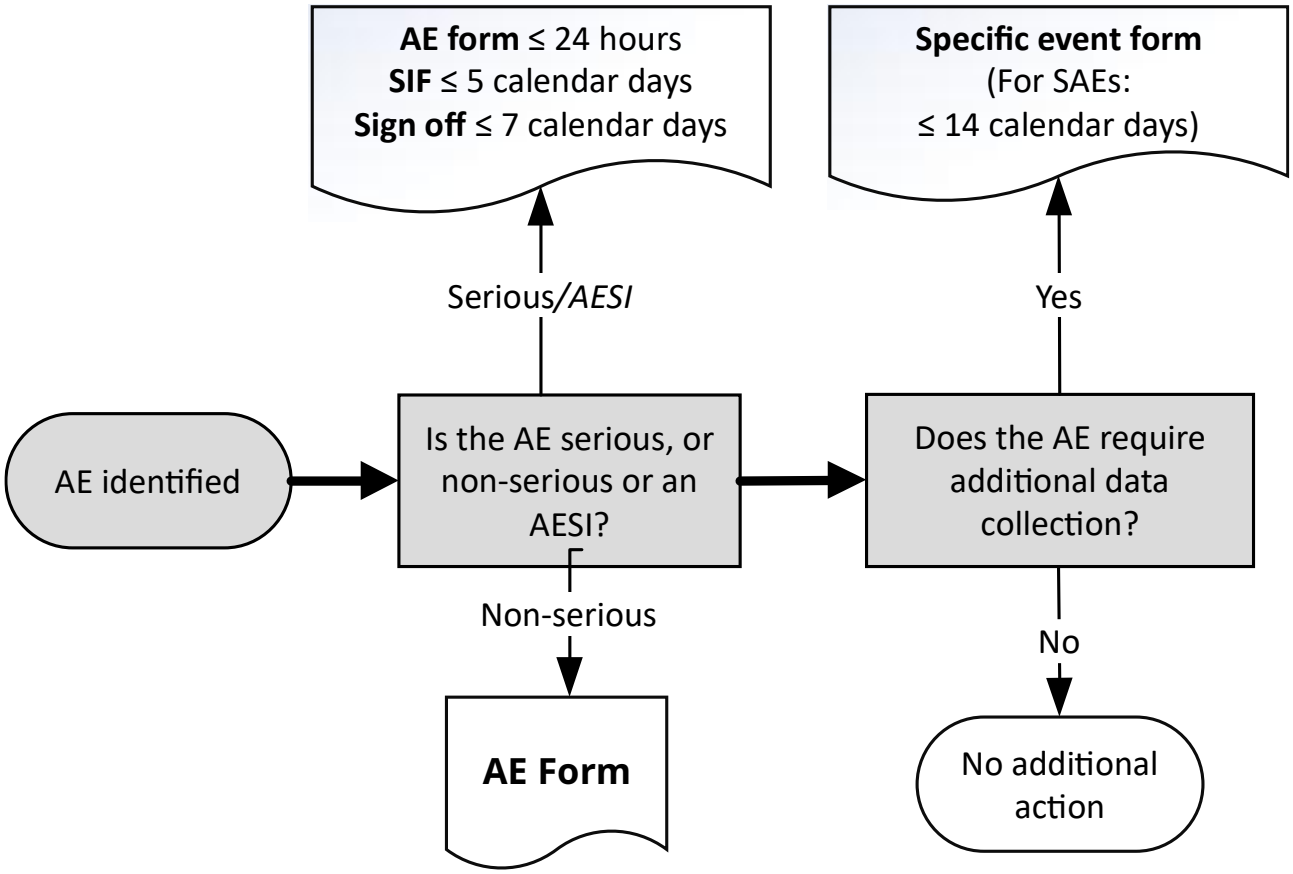
- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both the AE form and the safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

If the eCRF is unavailable for more than 24 hours, then the sites will use the paper backup AE form for SAE reporting, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper backup safety information form. The information from the paper backup AE form and the safety information form will be entered in the eCRF as soon as it becomes available.

All CRFs that are sent to Novo Nordisk in accordance with Section 10.1.5. Contact details for SAE reporting can be found in the investigator trial master file and in Attachment I of the protocol.

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a new SAE from a participant or updated information on a previously reported SAE needs to be reported after CRF decommission, a paper AE form and safety information form will be used to notify Novo Nordisk.

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



- **Timelines** are from the awareness of an AE.
- **Queries and follow-up** requests to be resolved ≤ 14 calendar days.
- In general data must be recorded in the CRF as soon as possible, preferably within 5 working days (see Appendix 1)

AE: Adverse Events, AESI: Adverse Events of Special Interest, SAE: Serious Adverse Events, SIF: Safety Information Form

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

The guidance for contraceptive methods is not applicable for this study as it includes only male participants and Inno8 is not considered to be transferred in clinically relevant amounts to a female partner via seminal transfer. Refer to the IB for further details.

10.5 Appendix 5: Genetics

Use/analysis of DNA

- Genetic variation in factor V Leiden and prothrombin can be used to determine a participant's risk of thrombosis. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for thrombophilia screening
- DNA samples will be analysed for factor V Leiden mutation (G1691A) and the prothrombin mutation (G20210A).
- During the conduct of the study the samples will be stored at the central laboratory and no later than at the end of the study, samples will be destroyed according to local laws and regulations.

10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.6.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges inadequacy related to any of the following for a product (drug or device): identity, quality, labelling, durability, reliability, usability, safety, performance or malfunction.

The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints include:
- Problems with the physical or chemical appearance of study interventions (e.g., discoloration, particles or contamination).
- Problems with packaging material including labelling.

Time period for detecting technical complaints

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

10.6.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:
1. For products with Kit ID: One technical complaint form must be completed for each affected Kit ID.
2. For products without Kit ID: One technical complaint form must be completed for each batch, code or lot number.

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete and forward the technical complaint form to Customer Complaint Center, Novo Nordisk, within the following timelines of obtaining knowledge of the technical complaint:
- 24 hours if related to an SAE
- 5 calendar days for all other technical complaints

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at site.

The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form.

The technical complaint sample should contain the batch, code or lot number and, if available, the Kit ID.

If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form.

If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

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

10.7 Appendix 7: Country-specific requirements

For Poland:

10.01.13 Indemnity statement:

Novo Nordisk carries liability for the study exclusively in the scope defined by the local applicable laws.

For Spain:

10.01.05 Data protection:

The study will be conducted in accordance with the Spanish Organic Law 3/2018, of 5th December, on the protection of personal data and the guarantee of digital rights.

10.01.13 Indemnity statement:

Novo Nordisk accepts liability in accordance with Article 10 "Liability regime" of the Royal Decree 1090/2015, of 4 December 2015, which regulates clinical trials with medicinal products, the Ethics Committees for Research with medicinal products and the Spanish Clinical Trials Register.

For United Kingdom:

10.01.05 Data protection:

In the UK the IRB/IEC does not have access to the participants' medical records.

For United States:

06.02 Preparation, handling, storage and accountability:

Once accountability has been finalised, alternative ways of reconciliation and trial product destruction can be performed if agreed at the site selection visit.

10.01.10 Retention of clinical study documentation:

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained for 25 years after end of study unless local regulations or institutional policies require a longer retention period.

10.8 Appendix 8: Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANOVA	analysis of variance
APC	activated protein C
aPCC	activated prothrombin complex concentrate
aPTT	activated Partial thromboplastin time
AST	aspartate transferase
AUC	area under the curve
BMI	body mass index
BNP	B-type natriuretic peptide
BU	Bethesda units
CKD-EPI	chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
CRF	case report form (The term “case report form (CRF)” in this protocol means “electronic CRF (eCRF)” unless otherwise specified.)
CRO	contract research organisation
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
DBL	database lock
DNA	deoxyribonucleic acid
DRE	disease-related event
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDAA	Food and Drug Administration Amendment Act
FHD	first human dose
FII	factor II
FIX	factor IX
FVIII	factor VIII
FX	factor X
GCP	good clinical practice
HDL	high density lipids
HDPE	high Density Polyethylene
HIV	human immunodeficiency virus
IB	investigators brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
IRB	institutional review board
IVD	in vitro diagnostic device
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLN	lower limit normal
MAD	multiple ascending dose
MI	myocardial infarction
NCT	National Clinical Trial number
NOAEL	no observed adverse effect level
PCD	primary completion date
PD	pharmacodynamics
PK	pharmacokinetics
PT/INR	Prothrombin time and international normalised ratio
QTL	quality tolerance limits
RTSM	randomisation and trial supply management
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SIA	sequence identical analogue
SNAC	sodium N-(8-[2-hydroxybenzoyl] amino) caprylate caprylate)
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TGA	thrombin generation assay
TGT	thrombin generation test
TMA	thrombotic microangiopathy
TMM	trial materials manual
ULN	upper limit normal
V_HH	single variable domain on a heavy chain
WFH	World Federation of Haemophilia

11 References

1. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 27 May 2014.
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1-47.
3. World Federation of Hemophilia. Report on the annual global survey 2022. 2023.
4. European Medicines Agency. ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals Step 5 (EMA/CHMP/ICH/731268/1998). June 2011.
5. den Uijl IE, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. Haemophilia. 2011;17(1):41-4.
6. Mahlangu J, Kaczmarek R, von Drygalski A, Shapiro S, Chou SC, Ozelo MC, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. N Engl J Med. 2023;388(8):694-705.
7. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158.
8. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Annex VI - Labelling of Investigational medicinal products and auxiliary medicinal products. 27 May 2014.
9. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
10. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Current step 4 version. 09 Nov 2016.
11. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
12. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
13. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.
14. The European Parliament and the Council of the European Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, article 41. Official Journal of the European Communities. 27 Dec 2006.
15. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.