# Cover Page for Protocol

| | |
|---|---|
| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT04992065 |
| Sponsor trial ID: | NN6435-4697 |
| Official title of study: | Dose response and safety of an oral PCSK9i, NNC0385-0434, in patients with established atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiringfurther LDL-C reduction |
| Document date*: | 21 September 2021 |

*Document date refers to the date on which the document was most recently updated.
Note: The date in the header of Page 2 is the date of compilation of the documents and not of an update to content.

### 16.1.1 Protocol and protocol amendments

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*Redacted protocol*
*Includes redaction of personal identifiable information only.*

.

# Protocol

**Protocol title:**

**Dose response and safety of an oral PCSK9i, NNC0385-0434, in patients with established atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction**

**Substance number: NNC0385-0434**

**Universal Trial Number: U1111-1252-3392**

**EudraCT Number: 2020-002630-32**

**IND Number: 151409**

# Protocol amendment summary of changes table

| DOCUMENT HISTORY | | |
|---|---|---|
| Document version | Date | Applicable in country(-ies) and/or site(s) |
| Protocol version 3.0 | 28 September 2021 | United States |
| Protocol version 2.0 | 29 April 2021 | All |
| Original protocol version 1.0 | 19 March 2021 | All |

## Protocol version 3.0 (28 September 2021), United States

This local amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety nor physical/mental integrity of participants nor the scientific value of the study.

## Overall rationale for preparing protocol, version 3.0:

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 10.9, Appendix 9: Country specific requirements | US specific contraceptive guidance for male patients in the trial have been updated | To align with the recommendation in comment 2 of the questions received from US FDA on 10 June 2021 (IND151409) |
| Section 10.4, Appendix 4: Contraceptive guidance and collection of pregnancy information | Appendix 9 has been cross-referred for US specific contraceptive requirements | To align with the recommendation in comment 2 of the questions received from US FDA on 10 June 2021 (IND151409) |

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

Protocol attachment II Country list of key staff and relevant departments.

# 1 Protocol summary

## 1.1 Synopsis

**Rationale:**

PCSK9 inhibition is a new therapy indicated for treatment of hypercholesterolaemia by lowering LDL-C and reduction of cardiovascular risk in patients with established atherosclerotic cardiovascular disease (ASCVD).

NNC0385-0434 is a new PCSK9 inhibitor in development for lowering LDL-C and offers oral administration. The rationale for conducting this trial is to acquire a robust dose-response understanding of oral NNC0385-0434 to allow for dose selection in a phase 3 programme. The trial includes a dose-range expected to cover the relevant therapeutic levels. The target population consists of patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C lowering according to current global treatment guidelines. The purpose of this trial is also to examine the steady state PK, safety and tolerability of oral NNC0385-0434.

**Objectives and endpoints:**

**Primary objective**

To demonstrate superiority of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

**Secondary objectives**

To compare the effect on lipid/lipoprotein parameters excluding LDL-C of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the effect on lipid/lipoprotein parameters of three dose levels of oral NNC0385-0434 versus s.c. evolocumab in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the safety and tolerability of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

**Estimands**

To address the primary objective, two estimands will be used:

- **Primary estimand**: Addresses the main question of interest: What is the efficacy of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy if all patients had remained on trial treatment. A hypothetical strategy is applied for the intercurrent event premature trial treatment discontinuation.

- **Additional estimand**: Addresses an additional question of interest: What is the efficacy of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy regardless of premature treatment discontinuation. A treatment policy strategy is applied for the intercurrent event premature trial treatment discontinuation.

## Primary endpoint

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in LDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |

## Supportive secondary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in total cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in HDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in VLDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in triglycerides | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Apo B | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Apo CIII | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Lp(a) | From baseline (week 0) to visit 9 (week 12) | Ratio |
| Treatment-emergent adverse events | From baseline (week 0) to visit 10 (19 weeks + 4 days) | Number of events |

## Overall design:

## Trial design

This is a randomised, multicentre, multinational, seven-armed, parallel group, dose finding trial. The trial will be double-blinded within dose level of oral NNC0385-0434 and size-matched placebo arm. The s.c. evolocumab arm will be open label. The trial population includes patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction. A PK sub-study in Japanese and non-Japanese patients will be performed following the 12 weeks of treatment.

Patients will be randomised 3:1:3:1:3:1:3 according to the following treatment arms:

- Oral NNC0385-0434 15 mg
- Oral placebo (size-matched to oral NNC0385-0434 15 mg)
- Oral NNC0385-0434 40 mg
- Oral placebo (size-matched to oral NNC0385-0434 40 mg)
- Oral NNC0385-0434 100 mg
- Oral placebo (size-matched to oral NNC0385-0434 100 mg)
- S.c. evolocumab

Randomisation will be stratified according to participation in the PK sub-study, country and population (inclusion criteria a/b). Within each stratum, each patient will be randomly allocated to one of the treatment arms. For the main statistical analyses, the 3 placebo arms will be pooled into one placebo group.

**Key inclusion criteria**

- Male patient or female patient of non-childbearing potential.
- Established atherosclerotic cardiovascular disease (ASCVD) (criteria a) or ASCVD risk (criteria b):
    a) Age ≥40 years at the time of signing informed consent and history of ASCVD
    b) Age >50 years at the time of signing informed consent and with ASCVD risk
- Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) as measured by the central laboratory at screening.
    - Japanese patients: Serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) for patients of ≥40 years of age and with a history of coronary heart disease, and serum LDL-C ≥3.1 mmol/L (≥120 mg/dL) for all other Japanese patients
- Patients must be on maximally tolerated dose of statins.
- Patients not receiving statin must have documented evidence of intolerance to all doses of at least two different statins.

**Key exclusion criteria**

- Treatment with PCSK9i therapy (alirocumab or evolocumab within 90 days prior to screening) or PCSK9 siRNA therapy (inclisiran within 12 months prior to screening).
- Fasting triglyceride >4.52 mmol/L (>400 mg/dL) as measured by the central laboratory at screening.
- Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
- Renal impairment with eGFR <30 ml/min/1.73 $m^2$ as measured by the central laboratory at screening.

**Number of patients:**

Approximately 255 patients will be randomly assigned to trial product. Out of the 255 patients, 30 Japanese and 30 non-Japanese patients will be randomised to the PK-sub-study.

**Treatment groups and duration:**

The total trial duration for an individual patient will be approximately 22 weeks divided into the following periods:

- Screening: up to 2 weeks
- Treatment period: 12 weeks
- Follow-up period: 7 weeks and 4 days

The following trial products will be supplied by Novo Nordisk for the duration of the trial:

- NNC0385-0434 A 15 mg, oral, once daily
- NNC0385-0434 A 40 mg, oral, once daily
- NNC0385-0434 A 100 mg, oral, once daily
- Placebo I A (for NNC0385-0434 A 15 and 40 mg), oral, once daily
- Placebo II A (for NNC0385-0434 A 100 mg), oral, once daily
- Evolocumab 140 mg/mL, Repatha®, subcutaneous, solution for injection, 1 mL pre-filled SureClick® autoinjector (single-use)

After end of trial, patients will continue suitable standard of care at the discretion of the investigator. The trial product will not be available to patients after end of treatment.

**Data monitoring committee:** No

## 1.2 Flowchart

### Table 1-1 Flowchart

| | Protocol Sections | Information visit | Screening | Randomisation | Treatment | | | | | | End of treatment | Treatment Discontinuation[f] | PK sub-study[g] | | | | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V0 | V1 | V2 | P3 | V4 | P5 | V6 | V7 | V8 | V9 | V9X | V9A | V9B | V9C | V9D | V10 |
| Timing of Visit | | Minimum 1 day prior to V1 | -2W | 0W | 1W | 2W | 3W | 4W | 6W | 9W | 12W | | V9/V9X +1D[h] | V9/V9X +1W | V9/V9X +2W | V9/V9X +3W | 138D |
| Visit Window | | -7/0D | 0/13D | ±0D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | | ±4H | ±3D | ±3D | ±3D | 0/5D |
| Informed Consent and Demography[a] | 8.1, 10.1.3 | X | | | | | | | | | | | | | | | |
| Eligibility Criteria | 5.1, 5.2 | | X | X | | | | | | | | | | | | | |
| Concomitant Medication | 6.5 | | X | X | | X | | X | X | X | X | X | X | X | X | X | X |
| Medical History/Concomitant Illness | 8.3 | | X | | | | | | | | | | | | | | |
| Tobacco Use | 5.3.2 | | X | | | | | | | | | | | | | | |
| Childbearing Potential | 10.4 | | X | | | | | | | | | | | | | | |
| Pregnancy Test | 10.4 | | X | X | | | | | X | | X | X | | | | | X |
| Body Measurements | 8.3.2 | | | X | | | | | | | X | X | | | | | X |
| Height | | | | X | | | | | | | | | | | | | |
| Body Weight | | | | X | | | | | | | X | X | | | | | X |
| Waist Circumference | | | | X | | | | | | | X | X | | | | | X |
| PK Sampling | 8.6 | | | X | | X | | X | X | X | X | X | X | X | X | X | X |
| Pre-dosing | | | | | | X | | X | X | X | X[e] | X | | | | | |
| Post-dosing[b] | | | | X | | X | | | X | | | | | | | | |
| Attend Visit Fasting[c] | 5.3.1 | | X | X | | X | | X | X | X | X | X | | | | | X |
| Adverse Event | 8.4 | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication Error, Misuse and Abuse | 8.4 | | | X | | X | | X | X | X | X | X | | | | | |
| Technical Complaint | 8.4.7 | | | X | | X | | X | X | X | X | X | | | | | |
| Laboratory Assessments | | | | | | | | | | | | | | | | | |

| | Protocol Sections | Information visit | Screening | Randomisation | Treatment | | | | | | End of treatment | Treatment Discontinuation[f] | PK sub-study[g] | | | | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V0 | V1 | V2 | P3 | V4 | P5 | V6 | V7 | V8 | V9 | V9X | V9A | V9B | V9C | V9D | V10 |
| Timing of Visit | | Minimum 1 day prior to V1 | -2W | 0W | 1W | 2W | 3W | 4W | 6W | 9W | 12W | | V9/V9X +1D[h] | V9/V9X +1W | V9/V9X +2W | V9/V9X +3W | 138D |
| Visit Window | | -7/0D | 0/13D | ±0D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | | ±4H | ±3D | ±3D | ±3D | 0/5D |
| Anti-NNC0385-0434 antibodies[d] | 8.11 | | | X | | X | | X | | X | X | X | | | | | X |
| Biochemistry | 10.2 | | X | | | X | | X | X | X | X | X | | | | | X |
| Coagulation Parameter | 10.2 | | X | | | X | | X | X | X | X | X | | | | | X |
| Haematology | 10.2 | | X | | | X | | X | X | X | X | X | | | | | X |
| Glucose Metabolism | 10.2 | | X | | | X | | X | X | X | X | X | | | | | X |
| Lipids | 10.2 | | X | X | | X | | X | X | X | X | X | | | | | X |
| PCSK9 | 8.9.1 | | X | X | | X | | X | X | X | X | X | | | | | X |
| ECG | 8.3.4 | | | X | | | | | X | | X | X | | | | | X |
| Physical Examination | 8.3.1 | | | X | | | | | | | X | X | | | | | X |
| Vital Signs | 8.3.3 | | X | | | X | | X | | X | X | X | | | | | X |
| Biomarker Sample (future analysis) | 8.9 | | | X | | | | X | | | X | X | | | | | X |
| Biosamples for Genetic (future analysis) | 8.10, 10.6 | | | X | | | | | | | | | | | | | |
| Administration of Trial Product | | | | X | | X | | X | X | X | X[e] | X | | | | | |
| IWRS Session | | | X | X | | X | | X | X | X | X | X | | | | | |
| Drug Dispensing | | | | X | | X | | X | X | X | X[e] | X | | | | | |
| Hand Out ID Card | | | X | | | | | | | | | | | | | | |
| Hand Out Direction for Use | | | | X | | X | | | | | | | | | | | |
| End of Trial | | | | | | | | | | | | | | | | | X |

**Notes**:

[a] Date of birth, age, sex, race and ethnicity (according to local regulation). Germany, The Netherlands: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

[b] Patients will receive a meal 30-60 min post dosing, and the PK sampling should be performed 60-90 minutes post dosing.
Date and exact time point for trial product ingestion at site, including start of meal must be collected in the laboratory requisition form.

[c] Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling.

[d] Pre-dosing

[e] Only applicable for patients in the PK sub-study to cover one dose given at site. Sampling scheme for PK sub-study is outlined in Table 1-2.

[f] V9X is only applicable for patients in the PK sub-study who have discontinued trial product prematurely. Visit 9X has to be performed as soon as site has been informed of prematurely trial product discontinuation by the patient.

[g] Patients part of the PK sub-study who discontinue treatment will be requested to take their last trial product dose at site and attend visit 9X followed by visit 9A, 9B, 9C and 9D.

[h] Visit 9 + 1 day (24 hours)

**Abbreviations:** ECG: Electrocardiogram; IWRS: Interactive web response system; P: Phone visit; PCSK9: proprotein convertase subtilisin/kexin type 9; PK: pharmacokinetics; V: Clinic visit

**Table 1-2 Sampling scheme for PK sub-study[a]**

| Visit | Week no. | Nominal time[c] | Time window allowance | Dosing of IMP | NNC0385-0434 PK |
|---|---|---|---|---|---|
| V9 | Week 12 | -15 min | - | | X[e] |
| | | 0 hour | - | X[d] | |
| | | 1 hour | 0 to 30 min | | X |
| | | 2 hours | ±15 min | | X |
| | | 4 hours | ±1 hour | | X |
| | | 8 hours | ±2 hours | | X |
| V9X[b] | | -15 min | - | | X[e] |
| | | 0 hour | - | X[d] | |
| | | 1 hour | 0 to 30 min | | X |
| | | 2 hours | ±15 min | | X |
| | | 4 hours | ±1 hour | | X |
| | | 8 hours | ±2 hours | | X |
| V9A | V9/V9X + 1 Day | 24 hours | ±4 hours | | X |
| V9B | V9/V9X + 1 Week | 7 days | ±3 days | | X |
| V9C | V9/V9X + 2 Weeks | 14 days | ±3 days | | X |
| V9D | V9/V9X + 3 Weeks | 21 days | ±3 days | | X |

[a] In addition to visit 9 assessments according to Table 1-1 for patients taking part in the PK sub-study.

[b] V9X is only applicable for patients in the PK sub-study who have discontinued trial product prematurely. Visit 9X has to be performed as soon as site has been informed of prematurely trial product discontinuation by the patient.

[c] From last dose.

[d] Patients will receive a meal 30-60 min post dosing, and post dosing PK sampling will be performed according to sampling scheme. Date and exact time point for trial product ingestion at site, including start of meal must be collected in the laboratory requisition form.

[e] Performed in the fasting state. Visit 9 assessments requiring fasting (lipids, fasting glucose and biosamples for future research) must also be taken pre-dosing.

**Abbreviations**: IMP: investigational medicinal products; PK: pharmacokinetic

# 2 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death globally[1]. Increased levels of LDL-C have been identified as a causal risk factor for ASCVD[2]. Furthermore, lowering LDL-C results in reduced risk of adverse cardiovascular outcomes[3]. In 2008, the global prevalence of hypercholesterolaemia among adults (total cholesterol ≥ 5.0 mmol/l) was 39% (37% for males and 40% for females)[1].

Reducing LDL-C levels is an important strategy for global cardiovascular risk reduction, which is reflected in US[4], European[5] and Japanese lipid lowering guidelines[6] with statins as recommended first line standard of care. Despite the widespread availability and use of statins many patients do not reach their target LDL-C levels[7, 8] giving rise to the need for additional effective pharmacotherapies.

PCSK9 inhibition is a new therapy indicated for treatment of hypercholesterolaemia by lowering LDL-C and reduction of cardiovascular risk in patients with established atherosclerotic cardiovascular disease (ASCVD)[9-12]. NNC0385-0434 is a new PCSK9 inhibitor in development for lowering LDL-C and offers oral administration.

## 2.1 Trial rationale

The rationale for conducting this trial is to acquire a robust dose-response understanding of oral NNC0385-0434 to allow for dose selection in a phase 3 programme. The trial includes a dose-range expected to cover the relevant therapeutic levels. The target population consists of patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C lowering according to current global treatment guidelines. The purpose of this trial is also to examine the steady state PK, safety and tolerability of oral NNC0385-0434.

## 2.2 Background

### PCSK9 inhibition

The LDL-receptor is located on liver cells and involved in the removal of LDL-C from the circulation. When LDL-C binds to the LDL-receptor, this complex moves into the cell. The LDL-receptor releases LDL-C in the endosome for degradation whilst the LDL-receptor is recycled back to the cell surface[13]. If PCSK9 binds to the LDL-receptor on its epidermal growth factor-like repeat A (EGF-A) domain[14], the LDL-receptor is no longer recycled back to the cell surface but degraded along with the bound LDL-C[15]. Therefore, when inhibiting PCSK9, more LDL-receptors will be recycled to the cell surface and more LDL-C can be taken up by the liver cells, reducing LDL-C in the circulation.

There are currently two approved PCSK9 inhibitors on the market, evolocumab[9] and alirocumab[10]. Both are s.c. administered monoclonal antibodies that have been shown to be safe, reduce risk of recurrent CV event and lower LDL-C levels by approximately 60% from baseline[16].

Recently, also inclisiran, a small interfering RNA therapeutic agent was approved in EU[17]. Inclisiran reduces the level of LDL-C by reducing PCSK9 hepatic production.

### Oral NNC0385-0434 – a new PCSK9 inhibitor peptide

NNC0385-0434 is a new medicinal product in development for lowering LDL-C. It is a peptide that binds to circulating PCSK9 and inhibits its interaction with the LDL-receptor by resembling the EGF-A domain of the human LDL-receptor. The molecule contains amino acid substitutions to increase PCSK9 affinity, peptide stability and allow for introduction of fatty acid moieties providing increased half-life.

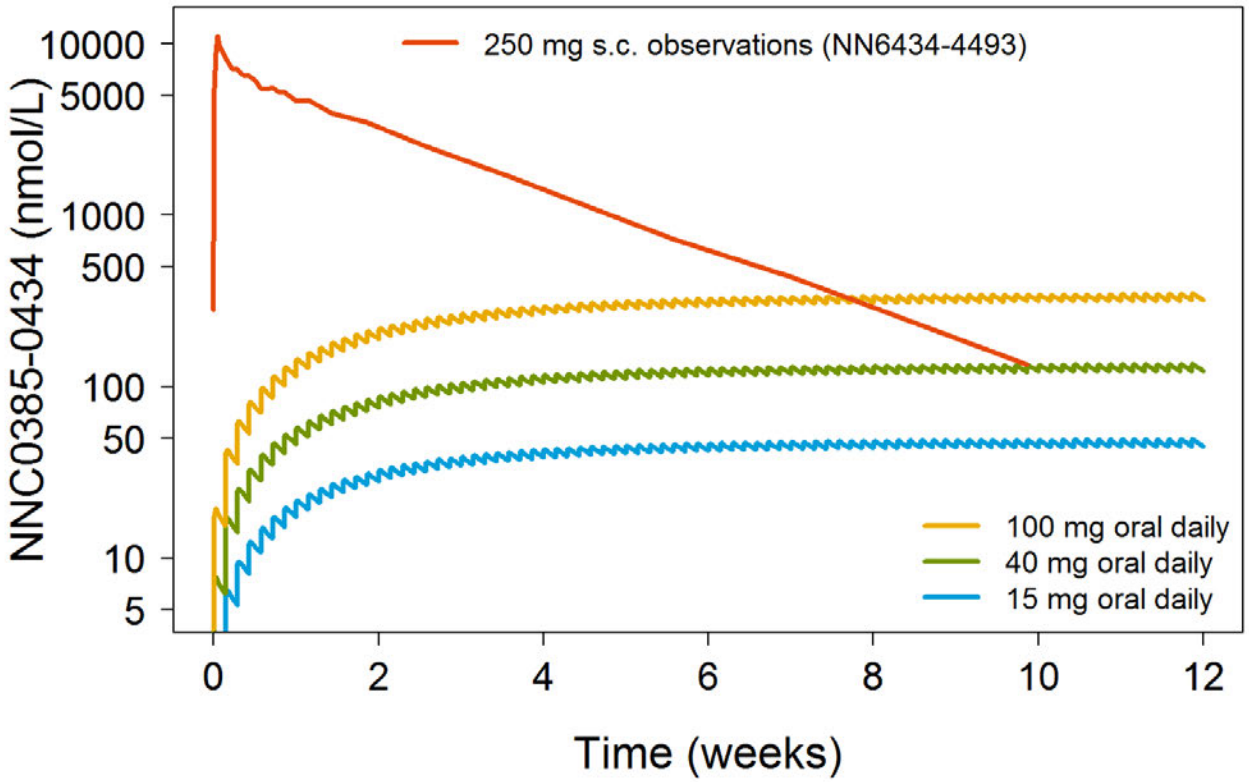
Preclinical data following s.c. and oral administration of NNC0385-0434 have demonstrated a robust dose-dependent reduction in LDL-C plasma levels (rat, cynomolgus monkey). In addition, NNC0385-0434 has shown a long systemic half-life across preclinical species (cynomolgus monkey, mini-pig and rat).

No safety or toxicity findings were found in the nonclinical studies after two-weeks repeated daily s.c. dosing in rats, and s.c. and oral dosing in cynomolgus monkeys. No adverse findings were found in toxicity studies of up to 13-week duration in rats and the NOAEL was established as the highest dose administered (12 mg/kg/day s.c. + 50 mg/kg/day orally) at an exposure >100 fold higher than the expected human exposure at 15-100 mg daily oral dose.

NNC0385-0434 administered s.c. has been investigated in a FHD trial (NN6434-4493) with single ascending doses up to 250 mg in 3 cohorts of healthy male subjects and 1 cohort of patients with hypercholesterolaemia treated with statins. High doses were explored in the FHD trial and NNC0385-0434 was found to be safe with no tolerability issues and resulted in clinically relevant lowering of LDL-C. The terminal half-life was approximately 10.5 days following single doses of 10-250 mg s.c. NNC0385-0434 in healthy male subjects and patients with hypercholesterolaemia. Mean $C_{max}$ was 11,133.3 nmol/L following single dose of the highest dose of 250 mg NNC0385-0434.

NNC0385-0434 is currently being developed as an oral treatment. Formulation with an absorption enhancing excipient is needed since NNC0385-0434 otherwise would have a very low bioavailability. Thus, NNC0385-0434 is co-formulated with SNAC, a fatty acid derivative protecting the peptide from enzyme degradation by local pH buffering and working as a absorption enhancer. In order to obtain best possible absorption from oral NNC0385-0434 tablets, a fasting condition is required. SNAC was fully qualified in the nonclinical and clinical development programme for oral semaglutide. Preclinical dog studies with NNC0385-0434 co-formulated with SNAC indicated a bioavailability in the same range as oral semaglutide. Based on the bioavailability estimate and data from the FHD trial, the treatment arm with the highest planned oral dose (100 mg) is predicted to have a lower exposure than the observed exposure reached with the s.c. 250 mg dose arm in the FHD trial (NN6434-4493) for up to 6 weeks. Furthermore, the steady state exposure ($C_{max}$) in a dosing interval is expected to be 32 times lower than what was achieved in the s.c. 250 mg dose arm in the FHD trial (Figure 2-1). Modelling data based on the FHD trial data indicate that a 28-60 % LDL-C reduction can be achieved with a once daily oral dosing of 15-100 mg NNC0385-0434 co-formulated with 500 mg SNAC. Thereby, the FHD trial data support proceeding to phase 2 and the further investigation of NNC0385-0434 as a once daily oral therapy for lowering LDL-C.

**Figure 2-1 Simulation of NNC0385-0434 exposure in the planned phase 2 trial vs. observed exposure in FHD trial (NN6434-4493)**




**Note:** Lines for NN6435-4697 treatment arms (15, 40, and 100 mg oral daily) represents geometric mean of 10,000 simulations for each treatment arm. The line for the 250 mg s.c. observations from NN6434-4493 represents the observed geometric mean concentration.

**Abbreviations**: FHD: first human dose

Throughout this protocol, the compound, NNC0385-0434 co-formulated with 500 mg SNAC administered once daily, will be named oral NNC0385-0434.

### Trial population

The trial population will consist of patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C lowering. According to the European ESC/EAS treatment guidelines[5] this trial population will benefit of obtaining LDL-C < 1.8 mmol/L (<70 mg/dL) in order to reduce their CV risk. Only women of non-childbearing potential are included since embryo-foetal development studies remain to be conducted.

## 2.3 Benefit-risk assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of oral NNC0385-0434 may be found in the investigator's brochure[18] and in the SmPC or US PI for evolocumab[19, 20].

### 2.3.1 Risk assessment

Potential risks describe undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with oral NNC0385-0434, but where there is currently insufficient evidence to conclude that this association is causal. Currently, there are no

identified risk with evidence of a causal association with oral NNC0385-0434. The risk assessment for oral NNC0385-0434 and s.c. evolocumab is presented in Table 2-1.

### 2.3.2 Benefit assessment

In this trial, patients with established ASCVD or ASCVD risk will continue their current treatment of maximally tolerated statin dose and other lipid-lowering therapy and be randomised to a 12-week LDL-C lowering treatment as an add-on therapy to statins and other lipid-lowering therapy or placebo. The 12-week LDL-C lowering treatment of oral NNC0385-0434 or s.c. evolocumab is expected to be efficacious on top of the background statin treatment.

All patients, including patients randomised to placebo, are expected to benefit from the frequent medical evaluations/examinations.

Furthermore, the data obtained from the present trial will form the basis for future development of oral NNC0385-0434 in patients with high ASCVD risk and dyslipidaemia.

### 2.3.3 Overall benefit-risk conclusion

Considering the measures taken to minimise risk to patients participating in this trial, the potential risks identified in association with oral NNC0385-0434 are justified by the anticipated benefits that may be afforded to patients with established ASCVD or ASCVD risk.

## Table 2-1 Risk assessment for oral NNC0385-0434 and s.c. evolocumab

| Identified/Potential risk of clinical significance | Summary of data/rationale for risk | Mitigation strategy |
|---|---|---|
| **Trial treatments (oral NNC0385-0434)** | | |
| **Potential:**<br>Hypersensitivity/allergic reaction | As with all protein-based pharmaceuticals, patients treated with oral NNC0385-0434 are at risk of developing immunogenic and allergic reactions. | As a precaution, patients with known or suspected hypersensitivity to trial product or related products are excluded. In addition, patients will be instructed to contact the site staff as soon as possible for further guidance if suspicion of a hypersensitivity reaction to the trial product occurs. |
| **Trial treatment (s.c. evolocumab)** | | |
| For detailed information regarding the known and expected benefits and risks of evolocumab, please refer to the current version of the SmPC[11] and the US PI[9], or any locally approved label. | | |
| **Trial procedures** | | |
| **Potential:**<br>COVID-19 infection in relation to participation in trial | Patients may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country. | The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical area. To minimize the risk as much as possible, the following measures have been taken:<br>• Cautious patient recruitment planning ensures controlled patient enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate.<br>• On-site visits will be well-prepared and as short as possible. Physical contact between patients and site staff will be limited to the extent possible, and protective measures will be implemented (e.g. use of masks, sanitizers, no aerosol-generating procedures etc. according to the local practice).<br>•Appendix 8 (Section 10.8), includes mitigations that can be implemented to ensure patient safety and data integrity in case a major emergency (e.g. COVID-19 outbreak) leads to lock-down of sites which affects the ability to perform trial related procedures. |

**Abbreviations**: EMA: European Medicines Agency, PI: prescribing information, s.c.: subcutaneous, SmPC: Summary of Product Characteristics

# 3 Objectives and endpoints

## 3.1 Primary, secondary and exploratory objectives and estimands

### 3.1.1 Primary objective

To demonstrate superiority of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

### 3.1.2 Secondary objectives

To compare the effect on lipid/lipoprotein parameters excluding LDL-C of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the effect on lipid/lipoprotein parameters of three dose levels of oral NNC0385-0434 versus s.c. evolocumab in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

To compare the safety and tolerability of three dose levels of oral NNC0385-0434 versus placebo in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

### 3.1.3 Exploratory objectives

To examine the population pharmacokinetic and immunogenic properties of three dose levels of oral NNC0385-0434 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

**PK sub-study**

To assess and compare the pharmacokinetic properties of three dose levels of oral NNC0385-0434 at steady-state between Japanese and non-Japanese patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

### 3.1.4 Estimands

For the primary objective, an estimand of primary interest and an additional estimand is defined. The estimands are used to address the trial objectives in terms of two different aspects of the treatment effect of three dose levels of oral NNC0385-0434. A single intercurrent event is considered: Premature treatment discontinuation. Intercurrent events are events occurring after treatment initiation that affect the interpretation, or the existence of the measurements associated with the question of interest.

The primary estimand will be used to address the primary objective and similar estimands will be used to address the secondary objectives for the corresponding supportive secondary endpoints. The additional estimand will be used to address the primary objective for the primary endpoint. The estimands are described below and the attributes of the estimands are presented in Table 3-1.

**Primary estimand**

The primary estimand addresses the main question of interest: What is the efficacy of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy if all patients had remained on trial treatment? A hypothetical strategy is applied for the intercurrent event premature trial treatment discontinuation. The population-level summary is difference in means.

Results based on the primary estimand quantifies the achievable treatment effect if all patients remain on the trial treatment.

**Additional estimand**

The additional estimand addresses an additional question of interest: What is the efficacy of three dose levels of oral NNC0385-0434 versus placebo on percent change in LDL-C from baseline to week 12 in patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy regardless of premature treatment discontinuation? For this estimand, the treatment policy strategy is applied for the intercurrent event premature trial treatment discontinuation. The population-level summary is difference in means.

Results based on the additional estimand are expected to mirror the clinical practice scenario because the estimand considers both the efficacy and tolerability of oral NNC0385-0434.

**Table 3-1 Estimand attributes**

| Estimand category | Treatment condition | Variable / endpoint | Population of interest | Intercurrent events and strategy | Population-level summary measure |
|---|---|---|---|---|---|
| Primary | The effect of three dose levels of oral NNC0385-0434 versus placebo, both in combination with maximally tolerated statin dose and other lipid-lowering therapy. | Change in LDL-cholesterol (%) from baseline to week 12 | Patients with established ASCVD or ASCVD risk. Further details can be found in Section 5. | Hypothetical strategy is applied for the intercurrent event 'premature trial treatment discontinuation' | Difference in means |
| Additional | The effect of three dose levels of NNC0385-0434 versus placebo, both in combination with maximally tolerated statin dose and other lipid-lowering therapy. | | | Treatment policy strategy is applied for the intercurrent event 'premature trial treatment discontinuation' | |

## 3.2 Primary, secondary and exploratory endpoints

### 3.2.1 Primary endpoint

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in LDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |

### 3.2.2 Secondary endpoints

#### 3.2.2.1 Confirmatory secondary endpoints

Not applicable.

#### 3.2.2.2 Supportive secondary endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Change in total cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in HDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in VLDL-cholesterol | From baseline (week 0) to visit 9 (week 12) | % |
| Change in triglycerides | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Apo B | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Apo CIII | From baseline (week 0) to visit 9 (week 12) | % |
| Change in total Lp(a) | From baseline (week 0) to visit 9 (week 12) | Ratio |
| Treatment-emergent adverse events | From baseline (week 0) to visit 10 (19 weeks + 4 days) | Number of events |

### 3.2.3 Exploratory endpoints

| Endpoint title | Time frame | Unit |
|---|---|---|
| Concentration of NNC0385-0434 at steady state | From visit 7 (week 6) to visit 9 (week 12) | nmol/L |
| Occurrence of NNC0385-0434 binding antibodies | From baseline (week 0) to visit 10 (19 weeks + 4 days) | Yes/no |
| Occurrence of NNC0385-0434 binding antibodies cross reacting with endogenous counterpart (EGF-A) | From baseline (week 0) to visit 10 (19 weeks + 4 days) | Yes/no |
| Titre of NNC0385-0434 binding antibodies | From baseline (week 0) to visit 10 (19 weeks + 4 days) | No unit |

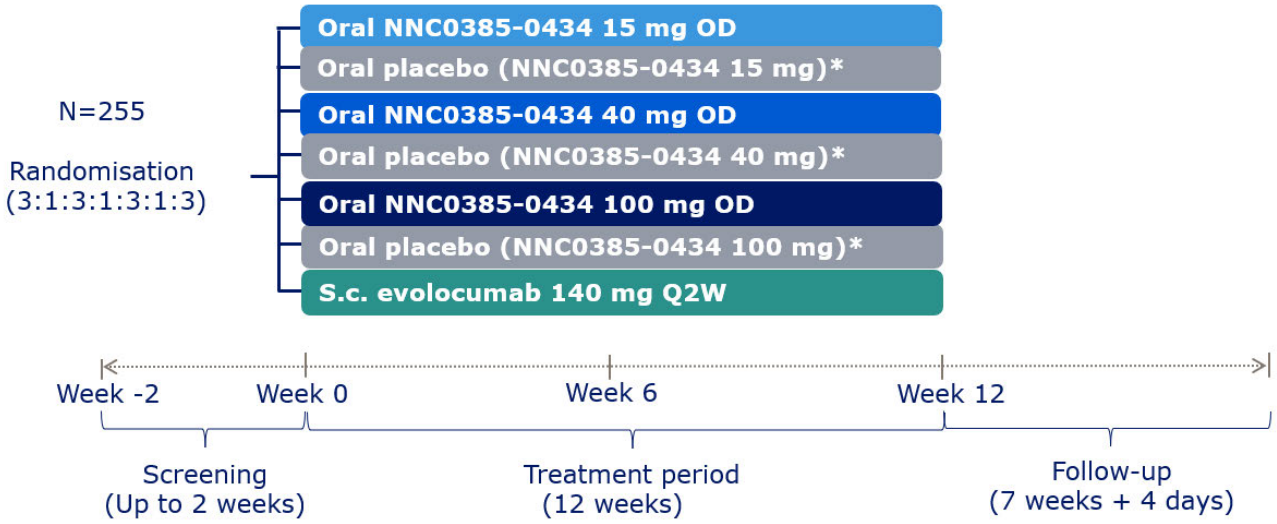
| **PK sub-study** | | |
|---|---|---|
| **Endpoint title** | **Time frame** | **Unit** |
| $AUC_{0\text{-}24h,SS}$ (area under the steady state plasma NNC0385-0434 concentration−time curve) | From 0 to 24 hours after end of treatment at visit 9 (week 12) | h*nmol/L |
| $AUC_{0\text{-}\infty,SS}$ (area under the steady state plasma NNC0385-0434 concentration−time curve) | From 0 hours to infinity after end of treatment at visit 9 (week 12) | h*nmol/L |
| $C_{max,SS}$ (maximum observed plasma NNC0385-0434 concentration at steady state) | From 0 to 24 hours after end of treatment at visit 9 (week 12) | nmol/L |
| $t_{max,SS}$ (time to maximum observed plasma NNC0385-0434 concentration at steady state) | From 0 to 24 hours after end of treatment at visit 9 (week 12) | Hours |
| $t_{½,SS}$ (terminal phase elimination half-life of NNC0385-0434 at steady state) | After end of treatment at visit 9 (week 12) | Hours |

# 4 Trial design

## 4.1 Overall design

This is a randomised, multicentre, multinational, seven-armed, parallel group, dose finding trial (Figure 4-1). The trial will be double-blinded within dose level of oral NNC0385-0434 and size-matched placebo arm. The s.c. evolocumab arm will be open label. The trial population includes patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C reduction.

**Figure 4-1 Schematic overview of the trial design**




**Notes**: *placebo tablets are sized match to the active arm within dose level. Placebo arms will be pooled in the statistical analyses.

**Abbreviations**: N: number of patients; OD: Once daily; Q2W: every 2 weeks; s.c. subcutaneous.

The trial includes a 2-week screening period followed by a 12-week treatment period. Additional PK sampling will be performed for 60 patients following the 12 weeks of treatment (referred as 'PK sub-study', see Section 4.1.1). The follow-up period for all patients is 7 weeks and 4 days. The total duration for each patient will be approximately 22 weeks. Throughout this protocol, the 'main trial' refers to the trial part without PK sub-study sampling.

Oral treatment arms (NNC0385-0434 or placebo) will be administered once daily. Each oral NNC0385-0434 treatment arm will be administered as tablets with varying sizes, but is blinded towards placebo with matching tablet sizes. The s.c. evolocumab treatment arm will be administered every 2 weeks.

The 7 treatment arms consist of 4 active treatment arms and 3 placebo arms, as follows:

- 15 mg NNC0385-0434 co-formulated with 500 mg SNAC tablet once daily (51 patients)
- 40 mg NNC0385-0434 co-formulated with 500 mg SNAC tablet once daily (51 patients)
- 100 mg NNC0385-0434 co-formulated with 500 mg SNAC tablet once daily (51 patients)
- 140 mg evolocumab s.c. injections every 2 weeks (51 patients)
- 3 placebo arms: placebo administered as tablets (without SNAC) once daily (17 patients in each placebo arm, 51 patients in total)

Patients will be randomised 3:1:3:1:3:1:3 according to Figure 4-1. Randomisation will be stratified according to participation in the PK sub-study (yes/no), country (Japan/non-Japan) and population (inclusion criteria 3a/3b). Within each stratum, each patient will be randomly allocated to one of the treatment arms (Section 6.3.1). For the main statistical analyses, the 3 placebo arms will be pooled into one placebo group.

The initial 15 patients (3 patients in each active treatment arm and 1 patient in each of the placebo arms) will be recruited from few pre-selected sites and treated for minimum 4 weeks before recruitment of the remaining 240 patients. Randomisation of the remaining patients will be initiated following medical monitoring of 4 week data of these 15 patients without identification of safety concerns, in addition to review of PK data from the 15 patients 2 weeks after dosing. Specifically, for Japanese patients, an evaluation of the safety and PK from the Japanese PK trial (NN6435-4748) will be performed before randomisation of Japanese patients into the current trial. The safety evaluation will include 12 healthy male Japanese subjects on a 10-day treatment with 15 mg, 40 mg or 100 mg oral NNC0385-0434, or placebo (3 subjects on each). The PK review will include data of the 15 mg and 40 mg cohorts.

Details on risk-based monitoring including medical monitoring and early PK evaluation is provided in Section 10.1.8.2.

### 4.1.1 PK sub-study

A PK sub-study in Japanese and non-Japanese patients will be performed following the 12 weeks of treatment. For PK sampling details, refer to Table 1-2.

For the PK sub-study, 30 Japanese and 30 non-Japanese patients will be randomised with ratio 3:1:3:1:3:1:3 as randomised in the main trial (for details on randomisation ratio, refer to Figure 4-1). For further details on randomisation, see Section 6.3.1.

The aim of the PK sub-study is to assess and compare the PK properties of three doses of oral NNC0385-0434 at steady-state between Japanese and non-Japanese patients (18 Japanese and 18 non-Japanese patients exposed to NNC0385-0434). The evolocumab arm is not part of the PK sub-study. Therefore, patients randomised to the evolocumab arm will not have additional visits or sub-study PK samples taken.

## 4.2 Scientific rationale for trial design

To allow evaluation of dose-response relationship of oral NNC0385-0434, a parallel randomised, double-blinded within dose level, controlled design has been chosen. To minimize bias in the assessment, the oral NNC0385-0434 treatment arms are double-blinded for each dose level of oral NNC0385-0434 with size-matched placebo arm. Three dose levels of NNC0385-0434, covering the expected range for clinically adequate LDL-C lowering, have been chosen to evaluate the dose-response relationship.

The rationale for including a s.c. evolocumab arm is to compare the efficacy of oral NNC0385-0434 against one of the already marketed PCSK9 inhibitors. The s.c. evolocumab arm is open-label to limit unnecessary injections (e.g., by use of double-dummy) as the primary aim of the trial is to investigate the effects of oral NNC0385-0434.

The trial population will consist of patients with established ASCVD or ASCVD risk on maximally tolerated statin dose and other lipid-lowering therapy requiring further LDL-C lowering. In alignment with the European ESC/EAS treatment guideline[4, 5], this is the target population that will benefit of obtaining LDL-C < 1.8 mmol/L (<70 mg/dL) in order to reduce their ASCVD risk. Specific LDL-C inclusion criteria have been defined for Japanese patients according to the Japanese guidelines for prevention of ASCVD (JAS guidelines)[6].

The treatment period is set to 12 weeks. The steady state exposure is expected to be reached at approximately 6 weeks into the trial and therefore the complete LDL-C lowering response should be observed within 12 weeks of treatment.

As a precautionary measure, 15 patients will be recruited initially before recruitment of the remaining 240 patients. Medical monitoring of minimum 4 week safety data for these 15 patients will be completed before dosing of the remaining 240 patients in the trial (see Section 10.1.8.2).

### PK sub-study

The rationale for including the PK sub-study is to assess and compare the steady state PK profiles of multiple doses of oral NNC0385-0434 in Japanese and non-Japanese patients. Therefore, PK assessments from the evolocumab arm are not relevant and this arm is not included in the PK sub-study.

## 4.3 Justification for dose

The dose range of oral NNC0385-0434 to be investigated in this trial has been selected based on the results from the FHD trial (NN6434-4493) and on modelling data for the expected exposure response and dose response.

Based on modelling analyses of the preliminary data from the FHD trial, the oral NNC0385-0434 dose of 100 mg/day is expected to have an exposure level lower than the exposure seen in the FHD trial s.c. 250 mg single dose arm for up to 6 weeks. The steady state exposure ($C_{max}$) in a dosing interval of the 100 mg/day dose is predicted to be 32 times lower than the exposure achieved in the s.c. 250 mg dose arm in the FHD trial. This is due to the relatively high s.c. dose investigated in the FHD trial (250 mg), the long half-life of NNC0385-0434 (10.5 days) and the predicted bioavailability of the oral dose (approximately 1% relative to s.c. dosing).

Moreover, no adverse findings were found in toxicity studies of up to 13-week duration in rats and the NOAEL was established as the highest dose administered (12 mg/kg/day s.c. + 50 mg/kg/day orally) at an exposure > 100 fold higher than the expected human exposure at 15-100 mg daily oral dose. Also, no adverse findings were found in local tolerance study after daily oral dosing of 100 mg NNC0385-0434 for 14 weeks in cynomolgus monkeys.

Oral NNC0385-0434 administered as once daily doses of 15, 40 and 100 mg are expected to be within the therapeutically relevant range. This dose range is expected to provide exposures to cover the exposure-response profile with mean LDL-C responses ranging from -28 to -60% change from baseline.

In summary, the exposure expected from simulated data for the oral NNC0385-0434 100 mg once-daily arm is lower than the exposure reached in the FHD trial. Oral doses of 15, 40 and 100 mg NNC0385-0434 are expected to be within the therapeutically relevant range and modelling predictions suggest corresponding LDL-C reductions of approximately 28, 46 and 60% from baseline, respectively.

## 4.4 End of trial definition

A patient is considered to have completed the trial if he/she has completed all phases of the trial including the last visit (Visit 10) according to the flowchart (Table 1-1).

The end of the trial is defined as the date of the last visit of the last patient in the trial globally.

# 5 Trial 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

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

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Male patient or female patient of non-childbearing potential. See Appendix 4 (Section 10.4), for the definition of a woman of non-childbearing potential.
3. Established atherosclerotic cardiovascular disease (ASCVD) (criteria a) or ASCVD risk (criteria b):
    a. Age ≥40 years at the time of signing informed consent and history of ASCVD defined as at least one of the following (i-iii):
        i. Coronary heart disease defined as at least one of the following:
            1. Prior myocardial infarction.
            2. Prior coronary revascularization (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)).
            3. ≥50% stenosis in a major epicardial coronary artery documented by cardiac catheterisation or computed tomography (CT) coronary angiography.
            4. Coronary heart disease with ischaemia documented by stress test with any imaging modality.
        ii. Cerebrovascular disease defined as at least one of the following:
            1. Ischemic Stroke.
            2. Prior carotid artery revascularisation procedure (surgical or endovascular).
            3. ≥50% stenosis in carotid artery documented by X-ray angiography, Magnetic resonance (MR) angiography, CT angiography or Doppler ultrasound.
        iii. Peripheral artery disease in the lower extremities defined as at least one of the following:
            1. Current symptoms of intermittent claudication and an ankle-brachial index (ABI) < 0.85 or toe-brachial index (TBI) < 0.7, both at rest.
            2. Current symptoms of intermittent claudication and ≥ 50% stenosis in lower extremity artery documented by X-ray angiography, MR angiography, CT angiography or Duplex ultrasound.
            3. Lower extremity artery revascularization procedure.
            4. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis).
    b. Age >50 years at the time of signing informed consent and with ASCVD risk defined by at least one of the following (i-ii):

i. Moderate chronic kidney disease (CKD) measured as estimated Glomerular Filtration Rate (eGFR) values of 30-59 mL/min/1.73 m2 (both inclusive) as measured by central laboratory at screening
ii. Diagnosed with type 2 diabetes mellitus

4. Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) as measured by the central laboratory at screening. For Japan only: See Table 5-1 for serum LDL-C inclusion criteria for Japanese patients.
5. Patients must be on maximally tolerated dose of statins (see Appendix 7 (Section 10.7)).
6. Patients not receiving statin must have documented evidence of intolerance to all doses of at least two different statins (see Appendix 7 (Section 10.7)).
7. Patients on any lipid-lowering therapies must be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation (for maximally tolerated statin dose, see Appendix 7 (Section 10.7); for other lipid-lowering therapies, see Section 6.5).

**Inclusion criteria for PK sub-study (in addition to inclusion criteria 1-7)**

8. For Japanese patients only: Both parents of Japanese descent and from Japanese site
9. For non-Japanese patients only: Both parents of non-Japanese descent and from non-Japanese site

## Table 5-1 Inclusion criterium 4 (serum LDL-C) only for Japanese patients

| | |
|---|---|
| **Japanese patients aged ≥40 years with established ASCVD defined as at least one of the following:** | |
| History of coronary heart disease defined as at least one of the following[1]:<br>1. Prior myocardial infarction.<br>2. Prior coronary revascularization (PCI, CABG)<br>3. ⩾50% stenosis in a major epicardial coronary artery documented by cardiac catheterisation or CT coronary angiography.<br>4. Coronary heart disease with ischaemia documented by stress test with any imaging modality. | Serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) |
| History of cerebrovascular disease defined as at least one of the following:<br>1. Ischemic Stroke.<br>2. Prior carotid artery revascularisation procedure (surgical or endovascular).<br>3. ≥50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound. | Serum LDL-C ≥3.1 mmol/L (≥120 mg/dL) |
| History of peripheral artery disease in the lower extremities defined as at least one of the following:<br>1. Current symptoms of intermittent claudication and an ankle-brachial index (ABI) < 0.85 or toe-brachial index (TBI) < 0.7, both at rest.<br>2. Current symptoms of intermittent claudication and ≥ 50% stenosis in lower extremity artery documented by X-ray angiography, MR angiography, CT angiography or Duplex ultrasound.<br>3. Lower extremity artery revascularization procedure.<br>4. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis). | Serum LDL-C ≥3.1 mmol/L (≥120 mg/dL) |
| **Japanese patients aged >50 years and with ASCVD risk defined by at least one of the following:** | |
| 1. Moderate CKD measured as estimated Glomerular Filtration Rate (eGFR) values of 30-59 mL/min/1.73 m2 (both inclusive) as measured by central laboratory at screening<br>2. Diagnosed with type 2 diabetes mellitus | Serum LDL-C ≥3.1 mmol/L (≥120 mg/dL) |

**Notes**: serum LDL-C as measured by the central laboratory at screening.

[1] If a patient have a history of both coronary heart disease and cerebrovascular disease or peripheral artery disease, the LDL-C criteria for coronary heart disease (LDL-C ≥100 mg/dL) applies.

## 5.2 Exclusion criteria

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

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Participation in any clinical trial of an approved or non-approved investigational medicinal product within 30 days before screening.
4. Any disorder, which in the investigator's opinion might jeopardise a patient's safety or compliance with the protocol.
5. Treatment with PCSK9i therapy (alirocumab or evolocumab within 90 days prior to screening) or PCSK9 siRNA therapy (inclisiran within 12 months prior to screening).
6. Treatment with oral semaglutide therapy within 30 days prior to screening
7. Fasting triglyceride >4.52 mmol/L (>400 mg/dL) as measured by the central laboratory at screening.
8. Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.
9. Planned coronary, carotid or peripheral artery revascularisation.
10. History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery)
11. Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.
12. Impaired liver function, defined as Alanine Aminotransferase (ALT) ≥ 2.5 times or Bilirubin >1.5 times upper normal limit as measured by the central laboratory at screening.
13. Renal impairment with eGFR <30 ml/min/1.73 $m^2$ as measured by the central laboratory at screening.
14. Clinically significant arrhythmia or clinically significant conduction disorder as judged by the investigator at screening.
15. Inadequately treated blood pressure defined as Systolic ⩾180 mmHg or diastolic ⩾110 mmHg at screening.
16. Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years before screening.

**Exclusion criteria for PK sub-study (in addition to exclusion criteria 1-12)**

There are no additional exclusion criteria for the PK sub-study.

## 5.3 Lifestyle considerations

To ensure alignment with regards to performance of assessments across patients and trial sites, the below restrictions apply.

### 5.3.1 Meals and dietary restrictions

**Visits attended fasting**

- Patients must attend the relevant visits fasting according to the flowchart (Table 1-1).
- Fasting for blood sampling is defined as no food, liquid or any oral medication within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling.
- If the patient is not fasting as required, the patient should be called in for a new visit preferably the following morning or within the visit window to have the fasting procedures done.
- Assessments requiring patient to fast include blood sampling of lipids, fasting glucose and NNC0385-0434 PK (only pre-dose samples), and biosamples for future research.
- PK sub-study (Table 1-2):
  - Visit 9: PK blood sampling must be performed in a fasting state
  - Visit 9A-9D: PK blood sampling is not required to be performed in a fasting state
- A meal will be served 30-60 min post dosing at site visits for PK sampling (Table 1-1) and at visit 9 for patients in the PK sub-study (Table 1-2). Date and exact time point for start of meal must be collected in the laboratory requisition form.

### 5.3.2 Caffeine and tobacco

Patients should avoid caffeine and smoking for at least 30 minutes prior to measuring the blood pressure at site visits according to the flowchart (Table 1-1). Smoking is defined as smoking at least one cigarette or equivalent daily.

### 5.3.3 Physical activity

Patients should avoid unaccustomed strenuous physical exercise for 48 hours prior to blood sampling at site visits (including the screening visit) according to the flowchart (Table 1-1).

Patients should avoid physical activity for at least 30 minutes prior to measuring the blood pressure at site visits according to the flowchart (Table 1-1).

## 5.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible for participation according to inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria.

For Japanese sites: For Japanese patients screened for the PK sub-study, a screen failure is also defined as eligible patients who cannot be randomised due to closure of randomisation into the PK sub-study.

A screen failure session must be made in the interactive web response system (IWRS). The reason for failure will be captured in the eCRF.

Individuals who do not meet the criteria for participation in this trial may not be rescreened. If the patient has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g. haemolysed or lost), re-sampling is allowed for the affected parameters.

## 5.5 Run-in criteria, randomisation criteria and dosing day criteria

Not applicable for this trial.

# 6 Treatments

## 6.1 Treatments administered

### Investigational medicinal products (IMP)

The investigational medicinal products (trial products) provided are listed in Table 6-1.

**Table 6-1 Investigational medicinal product provided by Novo Nordisk A/S**

| Trial product name | Dosage form | Route of administration | Dose levels | Dosing instructions | Packaging |
|---|---|---|---|---|---|
| NNC0385-0434 A 15 mg (IMP, test product) | Tablet | Oral | 15 mg | Once daily<br>1 tablet in the morning in a fasting state[a] | HDPE bottle of 10 tablets |
| NNC0385-0434 A 40 mg (IMP, test product) | Tablet | Oral | 40 mg | Once daily<br>1 tablet in the morning in a fasting state[a] | HDPE bottle of 10 tablets |
| NNC0385-0434 A 100 mg (IMP, test product) | Tablet | Oral | 100 mg | Once daily<br>1 tablet in the morning in a fasting state[a] | HDPE bottle of 10 tablets |
| Placebo I A (for NNC0385-0434 A 15 and 40 mg) (IMP, reference therapy) | Tablet | Oral | - | Once daily<br>1 tablet in the morning in a fasting state[a] | HDPE bottle of 10 tablets |
| Placebo II A (for NNC0385-0434 A 100 mg) (IMP, reference therapy) | Tablet | Oral | - | Once daily<br>1 tablet in the morning in a fasting state[a] | HDPE bottle of 10 tablets |
| Evolocumab 140 mg/mL, Repatha® (IMP, reference therapy) | Solution for injection | Subcutaneous | 140 mg | Every 2 weeks<br>S.c. injection into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated<br><br>Dose volume: 1 mL | 1 mL pre-filled SureClick® autoinjector (single-use) |

**Note**: [a] The tablet should be taken at least 30 min before the first food, beverage or other oral medications of the day. The tablet can be taken with up to half a glass of water (approximately 120 mL/ 4 fluid ounces).

**Abbreviations**: HDPE: high density polyethylene, IMP: investigation medicinal product

### Directions for use

The investigator must document that directions for use are given to the patient verbally and in writing as a directions for use (DFU) for s.c. evolocumab is to be handed to the patient, at the first dispensing visit and at visit 4 (as specified in the flowchart, Table 1-1). The investigator should remind patients of dosing instructions throughout the trial, as applicable.

### Dosing instructions for tablets

Absorption of oral NNC0385-0434 could be affected by food, fluid (other than plain water) and other oral medications in the stomach. Therefore, patients must be instructed to take the tablet (either NNC0385-0434 or placebo) in the morning in a fasting state and at least 30 minutes before

the first food, beverage or other oral medications of the day. The tablet can be taken with up to half a glass of water (approximately 120 mL/4 fluid. The tablet must be swallowed whole. The tablet must not be cut, crushed or chewed.

**Training in pre-filled SureClick® autoinjector**

Patients will be instructed to inject every second week on the same day of the week (to the extent possible) throughout the trial. The patients must be trained according to the DFU in how to handle the pre-filled SureClick® autoinjector, when handed out the first time. Training must be repeated during the trial at regular intervals in order to ensure correct use of the pre-filled SureClick® autoinjector. The investigator must document that the DFU is given to the patient orally and in writing at the first dispensing visit and at visit 4 (documented in patient source notes).

**Auxiliary supplies**

Auxiliary supplies will be provided by Novo Nordisk A/S in accordance with the TMM (Table 6-2).

**Table 6-2 Auxiliary supplies provided by Novo Nordisk A/S**

| Auxiliary supply | Details |
|---|---|
| Directions for use | DFU for evolocumab (Repatha®) pre-filled SureClick® autoinjector<br>Not included in the dispensing unit and to be handed out separately. |

**Abbreviations**: DFU: directions for use, s.c. subcutaneous

### 6.1.1 Medical devices

#### 6.1.1.1 Investigational medical device(s)

Not applicable for this trial.

#### 6.1.1.2 Non-investigational medical device(s)

Non-investigational medical devices are listed in Section 6.1 as auxiliary supplies.

## 6.2 Preparation/handling/storage/accountability

Only patients randomised to treatment may use trial product and only delegated site staff may supply trial product.

- Acceptable temperature ranges and conditions for storage and handling of each trial product when not in use and when in use are described in the TMM and on the trial product label.
- Each site will be supplied with sufficient trial products for the trial on an ongoing basis. Trial product will be distributed to the sites according to screening and randomisation.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.
- All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated 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 patient 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 drug accountability and record maintenance (i.e. receipt, accountability and final disposition records).
- The investigator or designee must instruct the patient in what to return at next visit.
- Drug accountability must be done on tablet/pen level.
- 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, expired or damaged trial products (for technical complaint samples, see Section 10.5) must be stored separately from non-allocated trial products. No temperature monitoring is required.
- Non-allocated trial products including expired or damaged products must be accounted as unused, at the latest at closure of the site.

Japan: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

## 6.3 Measures to minimise bias: Randomisation and blinding

### 6.3.1 Randomisation

- This is a randomised, placebo-controlled trial.
- Patients will be randomised 3:1:3:1:3:1:3 according to Figure 4-1
- For the PK sub-study:
  - All Japanese patients will be included in the PK sub-study. Once 30 Japanese patients have been included in the PK sub-study and randomised to treatment, any Japanese patient ongoing screening procedures should be considered a screen failure (Section 5.4).
  - Selected non-Japanese sites will include 30 non-Japanese patients for the PK sub-study. Once 30 non-Japanese patients have been randomised to the PK sub-study, eligible non-Japanese patients will be randomised to the main study.
- Randomisation will be stratified according to participation in the PK sub-study (yes/no), country (Japan/non-Japan) and population (inclusion criteria 3a/3b). Within each stratum, each patient will be randomly allocated to one of the treatment arms.
- All patients will be screened and randomised centrally using an IWRS and assigned to the next available treatment according to randomisation schedule. Trial product will be dispensed/allocated at the trial visits summarised in the flowchart (Table 1-1).
- At screening, each patient will be assigned a unique 6-digit number which will remain the same throughout the trial. Each site is assigned a 3-digit number and all patient numbers will start with the site number.

### 6.3.2 Blinding

- This trial is double-blinded within dose level of oral NNC0385-0434 and size-matched placebo arm. Within dose level, oral NNC0385-0434 and placebo tablets are identical in appearance and will be packed in a manner that maintains blinding.
- The s.c. evolocumab arm is open label and treatment for a patient will be assigned using IWRS.

### 6.3.3 Blind break

The IWRS will be used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Novo Nordisk prior to unblinding a patient's treatment unless this could delay emergency treatment of the patient. If a patient's treatment is unblinded, Novo Nordisk (Global Safety department) must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the "code break confirmation" notification generated by the IWRS, sign and date the document. If IWRS is not accessible at the time of blind break, the IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

Treatment with trial product can be resumed if there are no safety concerns at the discretion of the investigator.

For the early PK monitoring the laboratory will also have access to the treatment allocation. The laboratory responsible for analysis of NNC0385-0434 (LC-MS/MS analysis) and the responsible bioanalytical scientist at special lab will have access to the treatment allocation. The Novo Nordisk scientific monitor for bioanalysis will have access to treatment allocation according to PK sample but will be blinded to subject level. Also, treatment allocation will be accessible to the laboratory responsible for analysis of anti-drug antibodies and the responsible immunogenicity scientist at Novo Nordisk.

## 6.4 Treatment compliance

### 6.4.1 Drug treatment compliance

Throughout the trial, the investigator will remind the patients to follow the trial procedures and requirements to encourage patient compliance.

When patients are dosed at the site in the main trial and in the PK sub-study (Table 1-1 and Table 1-2, respectively), they will receive trial product directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents. Site staff will observe ingestion of the tablet. If in doubt whether the tablet has been swallowed, site staff will enter into a dialogue with the patients, acknowledging non-compliance can happen and addressing barriers to compliance.

When patients self-administer trial product at home, compliance with trial product administration will be assessed and the assessment documented in source documents at each visit where information is available.

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the patient. Treatment compliance is defined as taking between 80-120% of the dose as prescribed between visits. The investigator must assess the amount of trial products returned compared to what was dispensed at the previous visit.

If any suspicion of non-compliance arises, apart from occasional missed doses, the site must enter into a dialogue with the patient, re-emphasising the importance of compliance and uncovering barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Drug accountability information; counting returned tablets
- Questioning of patients: Discussing treatment compliance and dosing conditions with the patient

Treatment start and stop dates will be recorded in the eCRF.

## 6.5 Concomitant medication

During the treatment period, all oral background medication must first be ingested 30 minutes after oral trial product has been taken in the morning.

### Lipid-lowering therapies

Patients must be on maximally tolerated dose of statins for at least 30 days before screening or have documented evidence of intolerance to all doses of at least 2 different statins
(see Appendix 7 (Section 10.7)).

Other lipid lowering therapies are allowed as background therapy (except PCSK9i therapy, see below section on Prohibited concomitant medication) if patients are on a stable dose for ≥30 days before screening (see Section 5.1).

Patients must continue their background medication (maximally tolerated dose of statins and other lipid-lowering therapies) throughout the entire trial. The background medication must be maintained at the same dose level as given at screening (visit 1) and with the same frequency during the entire treatment period unless any safety concerns related to the background medication arise. .

### Prohibited concomitant medication

The following medications must not be used prior to the screening visit and during the trial:
- PCSK9i therapy: Alirocumab or evolocumab 90 days prior to screening
- PCSK9 siRNA therapy: Inclisiran 12 months prior to screening
- Oral semaglutide therapy within 30 days prior to screening

### Recording the use of concomitant medication

Any medication or vaccine (including over-the-counter and prescription medicines) other than the trial product that the patient is receiving at the time of the first visit (screening visit) or receives during the trial must be recorded along with:
- Trade name or generic name
- Indication
- Dates of administration including start and stop dates

For lipid-lowering and CV medication, the following should be also collected:

- Dose and unit
- Frequency
- Route of administration

Information on concomitant medication must be recorded in the concomitant medication form in eCRF.

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.4.

## 6.6 Dose modification

Deviations from the planned doses are not allowed.

## 6.7 Treatment after end of trial

After the end of trial (visit 10) the patient will continue suitable standard of care at the discretion of the investigator. The patients will not receive treatment after the end of treatment.

# 7 Discontinuation of trial treatment and subject discontinuation/withdrawal

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

Efforts must be made to have the patients attend and complete all scheduled visit procedures. Only patients who withdraw consent will be considered as withdrawn from the trial. Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

## 7.1 Discontinuation of trial treatment

Discontinuation of trial product can be decided by either the patient or the investigator.

The trial product must be discontinued, if any of the following applies for the patient:

1. Pregnancy
2. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical trial
3. Safety concern at the investigator´s discretion
4. Initiation of treatment with PCSK9i therapy (alirocumab, evolocumab), PCSK9 siRNA therapy (inclisiran) or oral semaglutide

See the flowchart (Table 1-1) for data to be collected at the time of treatment discontinuation (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

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

### Main trial

Patients who discontinue trial product should continue with the remaining scheduled site visits and assessments until the time of the originally scheduled end of trial visit (visit 10) to ensure continued monitoring and data collection. See the flowchart (Table 1-1).

If the patient does not wish to attend the scheduled site visits, efforts should be made to have the remaining visits converted to phone contacts. However, as a minimum, these patients must be asked to attend visit 9 to ensure final data collection related to the primary endpoint. Also, all efforts should be made to have patients attend visit 10 (end of trial). The information about the attempts to follow up with the patient must be documented in the patient's medical record

**PK sub-study**

For patients who have been randomised to the PK sub-study and who discontinue trial product prior to visit 9 (e.g. due to challenges with dosing conditions), efforts should be made to have the patient to take their last trial product dose at site.

- **If a patient accepts to take the last trial product dose at site**, the patient should attend visit 9X as soon as possible followed by the PK sub-study specific visits 9A, 9B, 9C and 9D (see flowchart, Table 1-1 and PK sub-study sampling scheme Table 1-2). Visit 9X should be performed before patients may initiate new lipid-lowering treatment. After completion of the sub-study specific visits, patients should continue with the remaining scheduled site visits and assessments until the time of the originally scheduled end of trial visit (visit 10).
- **If a patient does not wish to take the last trial product dose at site**, the patient should continue with the remaining scheduled site visits and assessments (except visit 9A, 9B, 9C and 9D) until the time of the originally scheduled end of trial visit (visit 10).
- **If premature discontinuation of trial product is decided during a scheduled visit**, the visit will be converted into a visit 9X and trial procedures must be performed accordingly. All efforts should be made to have patients attend the PK sub-study specific visits 9A, 9B, 9C and 9D (see flowchart, Table 1-1 and PK sub-study sampling scheme Table 1-2). After completion of the sub- study specific visits, patients should continue with the remaining scheduled site visits and assessments until the time of the originally scheduled end of trial visit (visit 10).

### 7.1.1 Temporary discontinuation of trial treatment

If a patient has discontinued trial treatment temporarily, continuation of trial product is allowed. In such cases a treatment discontinuation session should not be made in the IWRS. Temporarily trial product treatment discontinuation must be specified in eCRF.

## 7.2 Subject discontinuation/withdrawal from the trial

A patient may withdraw consent at any time at his/her own request or the patient's LAR.

If a patient withdraws consent, the investigator must ask the patient if he/she is willing, as soon as possible, to have assessment performed according to visit 9. See the flowchart for data to be collected.

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

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

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

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

### 7.2.1 Replacement of subjects

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

## 7.3 Lost to follow-up

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

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

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

# 8 Trial assessments and procedures

- The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.
- Informed consent must be obtained before any trial related activity, see Section 10.1.3.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, patients will be provided with a card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit bias between assessments. The suggested order of the assessments:
  - Electrocardiogram (ECG) and vital signs
  - Blood sampling
  - Other assessments
- Review of ECG, laboratory reports etc. must be documented either on the documents or in the patient's source documents.
- 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 Information visit and screening

### Demography

The following information has to be recorded after informed consent at the information visit (visit 0):

- Date of birth, unless not permitted by local regulations
- Year of birth
- Sex
- Race, unless not permitted by local regulations
- Ethnicity, unless not permitted by local regulations

For countries participating in the PK sub-study, randomisation will be stratified by being of Japanese descent. The following has to be assessed at screening (visit 1):

- Japanese descent and living in Japan (yes/no), assessed at screening visit (visit 1).

Germany, The Netherlands: For country-specific requirements, please refer to Appendix 9 (Section 10.9)

**Tobacco use**

Details of tobacco use must be recorded at screening (visit 1). Smoking is defined as smoking at least one cigarette or equivalent daily. The collected information should include whether or not the patient smokes or has smoked.

Smoking status information to be collected:
- Never smoked
- Previous smoker (smoking stop date)
- Current smoker

**Woman of non-childbearing potential**

The assessment of a woman of non-childbearing potential should be performed at the screening visit (visit 1) and recorded as specified in the flowchart and Appendix 4 (Section 10.4).

## 8.2 Efficacy assessments

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

### 8.2.1 Clinical efficacy laboratory assessments

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

## 8.3 Safety assessments

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

**Concomitant illness and medical history**

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 trial procedures performed before exposure to trial product.

**Medical history** is a medical event that the patient experienced. Only relevant medical history should be reported prior to the time point from which AEs are collected.

In case of an abnormal and clinically significant finding fulfilling the definition of a concomitant illness or medical history, the investigator must record the finding on the Medical History/ Concomitant Illness form. The information collected for concomitant illness and medical history should include diagnosis, date of onset and date of resolution or continuation, as applicable.

The following Medical History/Concomitant Illness should be reported in the eCRF:
- **History of cardiovascular disease**
- **History of moderate chronic kidney disease**
- **History of type 2 diabetes mellitus**
- **History of dyslipidaemia**

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

### 8.3.1 Physical examinations

A physical examination will include assessments of the:

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

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

Any abnormal, clinically significant findings at visit 2 must be recorded as concomitant illness. Any clinically significant worsening from visit 2 must be reported as an AE (see Section 8.4).

### 8.3.2 Body measurements

Body measurements (e.g. height and weight) will be measured and recorded as specified in the flowchart (Table 1-1).

#### Body weight

Body weight should be measured with an empty bladder, without shoes and only wearing light clothing on a calibrated (digital) scale. Body weight is recorded in kilograms (kg) or pounds (lb) with a precision of one decimal. The body weight should be assessed on the same calibrated weighing scale throughout the trial. The scale must be calibrated yearly as a minimum, unless the manufacturer certifies that calibration of the weighing scale is valid for the lifetime of the scale.

#### Height

Height is measured without shoes in centimetres (cm) or inches (in) and recorded with a precision of one decimal.

#### Waist circumference

Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured using a non-stretchable measuring tape. The waist circumference should be measured to the nearest half cm or quarter inch when the patient is in a standing position, with an empty bladder, and wearing light clothing. The patient should be standing feet together, with arms down their sides and waist accessible. The tape should touch the skin but not compress the soft tissue, and twists in the tape should be avoided. The patient should be asked to breathe normally, and the measurement should be taken when the patient is breathing out gently.

### 8.3.3 Vital signs

Pulse rate, as well as systolic and diastolic blood pressure will be assessed:

- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the patient 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.

Any clinically significant worsening from visit 1 must be reported as an AE (see Section 8.4).

**Blood pressure**

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. Systolic blood pressure is to be documented as the mean of the last 2 systolic blood pressure readings, and diastolic blood pressure as the mean of the last 2 diastolic blood pressure readings. Only the last 2 systolic and last 2 diastolic blood pressure readings must be recorded in the eCRF.

**Pulse rate**

Pulse rate will be measured in connection to the blood pressure measurements. Record the pulse rate for the last 2 blood pressure measurements in the eCRF. The pulse rate is to be documented as the mean of the last 2 measurements.

### 8.3.4 Electrocardiograms

12-lead ECG will be obtained as outlined in the flowchart (Table 1-1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals.

The ECG should preferably be performed as the first trial assessment, prior to blood sampling and other assessments. At each site, ECG assessments should be performed on the same ECG machine throughout the trial.

The ECG should be recorded after at least 5 minutes resting in supine position. The ECG will be evaluated by the investigator or designee and the outcome must be specified in the eCRF as either “normal” or “abnormal”.

If “abnormal”, a comment must be given together with an assessment of clinical significance (yes/no). The investigator or designee must sign and date the ECG on the day of evaluation. The data will be transferred to the eCRF.

Abnormal clinically significant findings at visit 2 should be recorded as concomitant illness in the eCRF. At the following visits, any new abnormal clinically significant findings or clinically significant deterioration from baseline should be reported as an AE.

### 8.3.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the protocol flowchart.

## 8.4 Adverse events and serious adverse events

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

The definition of AEs and SAEs can be found in Appendix 3, along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. This always includes medication error, misuse and abuse of IMP. The relevant events are listed below in Table 8-1.

**Table 8-1 AEs requiring additional data collection (serious and non-serious AEs)**

| Event type | AE requiring additional data collection |
|---|---|
| Medication error | X |
| Misuse and abuse | X |
| Hypersensitivity reactions | X |

A detailed description of the events mentioned in the above table can be found in Appendix 3.

### 8.4.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs must be collected from the randomisation visit and until the end of trial visit at the time points specified in the flowchart.

Medical occurrences that take place or have onset prior to the time point from which AEs are collected will be recorded as concomitant illness/medical history. AE and SAE reporting timelines can be found in Appendix 3. All SAEs must be recorded and reported to Novo Nordisk within 24 hours, and the investigator must submit any updated SAE data to Novo Nordisk within 24 hours of it being available.

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

### 8.4.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

### 8.4.3 Follow-up of AEs and SAEs

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

### 8.4.4 Regulatory reporting requirements for SAEs

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

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

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

### 8.4.5 Pregnancy

Only female patients of non-childbearing potential are eligible for inclusion in the trial (see Section 5.1 for inclusion criteria). The definition of a woman of non-childbearing potential is provided in Appendix 4 (Section 10.4).

Should a pregnancy occur, details of pregnancies in female patients will be collected after first exposure to trial product and until the end of trial visit.

If a female patient becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

No data collection of pregnancy information will be performed for female partners of male patient as the risk of seminal transfer of NNC0385-0434 in a magnitude that could impact a foetus in a female partner is highly unlikely[18].

### 8.4.6 Cardiovascular and death events

Cardiovascular and death events will be handled and reported according to Section 8.4.

### 8.4.7 Technical complaints

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

Instructions for reporting technical complaints can be found in Appendix 5.

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 Treatment of overdose

Decisions regarding dose interruptions will be made by the investigator based on the clinical evaluation of the patient.

There is no previous experience of an overdose with oral NNC0385-0434 in humans and no known antidote. NNC0385-0434 administered s.c. with single ascending doses up to 250 mg, and at maximum concentrations more than 32 fold higher than expected in this trial, have been found safe and well tolerated (see Section 2.2 and Figure 2-1 for details). In the event of an overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

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 10.3.3) for further details.

In the event of an overdose, the investigator should closely monitor the patient for overdose-related AE/SAE and laboratory abnormalities until clinically safe, taking into account the long half-life of NNC0385-0434.

For more information on overdose, please refer to the current version of the NNC0385-0434 investigator's brochure[18] and in the SmPC or US PI for evolocumab[19, 20].

### 8.6 Pharmacokinetics

Blood samples will be used to evaluate the PK of NNC0385-0434. Samples will be collected in accordance with the flowchart Table 1-1.

For visits with pre-dosing PK sampling (Table 1-1):

- Patients must be instructed to withhold their trial product dose in the morning of the clinic visit until blood sampling has been performed.
- The date, exact time and dose of the latest trial product administration prior to pre-dose PK sampling will be obtained by patient interview at site and must be collected in the laboratory requisition form

Procedures for sampling, handling, storage, labelling, and shipments of samples must be performed in accordance with the laboratory manual.

Bioanalysis of NNC0385-0434 plasma samples will be performed at a special lab using a validated Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) assay. The exact method will be described in a bioanalytical report, and the bioanalytical report must be provided before finalisation of the CTR.

Residual plasma PK samples may be used for exploratory metabolite analysis.

Potential metabolite analysis will be carried out by department of Development ADME, Novo Nordisk, and will be reported separately from the CTR.

Residual PK samples will be discarded after performance of the experimental work. All samples will be destroyed at latest 15 years from end of trial (last patient last visit, LPLV)

#### 8.6.1 PK sub-study

For the PK sub-study, samples will be used to evaluate the PK of NNC0385-0434. Samples will be collected in accordance with the flowchart (Table 1-1) and the sample scheme for the PK sub-study

provided in Table 1-2. Window allowance for nominal times specified in Table 1-2 should be followed.

- Visit 9:
  - Trial product must be taken at site and the PK blood sampling must be performed in a fasting state (as defined in Section 5.3.1)
  - The exact time of trial product administration, start of meal and blood sampling must be collected in the laboratory requisition form
  - The date, exact time and dose of the latest trial product administration prior to pre-dose PK sampling will be obtained by patient interview at site and must be collected in the laboratory requisition form

- Visits 9A-9D:
  - PK blood sampling is not required to be performed in a fasting state
  - The exact time of blood sampling must be collected in the laboratory requisition form

Bioanalysis of NNC0385-0434 plasma samples will be performed as described in Section 8.6

### 8.7 Pharmacodynamics

Not applicable.

### 8.8 Genetics

Not applicable.

### 8.9 Biomarkers

#### 8.9.1 PCSK9 levels

Blood samples will be collected for exploratory analysis of the endogenous levels of PCSK9 (pending on assay development) as specified in the flowchart (Table 1-1) and Appendix 2 (Table 10-1). The analyses will be performed by special laboratory contracted by Novo Nordisk. The samples will be processed as detailed in the laboratory manual.

### 8.10 Biosamples for future analysis

Collection of additional blood samples for future research (stored in a biobank) is also a component of this trial. Participation in the biobank component is optional, and patients must sign a separate informed consent form to indicate their participation in each biobank component of the trial:

- Biobank, genetic analysis
- Biobank, circulating biomarkers

Patients who do not wish to participate in the optional biobank component may still participate in the trial. For the biobank, blood samples for each biobank component will be collected according to the flowchart (Table 1-1) and stored for future use.

The biobank samples are collected for the purpose of allowing future analyses of biomarkers, both genetic and circulating biomarkers, at a later point in time when new knowledge or improved

measurement techniques may have become available. The analysis may include biomarkers currently known or discovered in the future.

Genetic analyses may include analysis of candidate genes or genetic markers throughout the genome.

Potential biomarker and genetic analyses (for both DNA and mRNA extractions) will be performed with the purpose of understanding and predicting response to NNC0385-0434 as well as understanding cardiometabolic disease or other related diseases. The patient will not be informed about potential results as the analyses are intended for finding trends in the population and not in the individual patient.

The analyses will be performed after the trial has come to an end, and results will, therefore, not be part of the CTR.

The biobank samples will be processed as detailed in the laboratory manual. The biobank samples will be stored up to 15 years after end of trial at a central laboratory. Refer to Appendix 6 (Section 10.6) for further details on the storage and intended use of these samples.

### 8.11 Immunogenicity assessments

Anti-drug antibody samples will be collected according to the flowchart (Table 1-1). All samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

Assessment of antibodies against NNC0385-0434 (anti-drug antibodies) in serum will be performed at Novo Nordisk A/S.

For details on blood sampling, serum preparation and storage, please refer to the laboratory manual.

Analysis for anti-drug antibodies in patients treated with NNC0385-0434 will be done as listed in the flowchart (Table 1-1) with a binding anti-drug antibody assay. Positive samples will be further characterised for neutralising activity by correlation to PK and PD (with a validated LDL-C assay) i.e. the highly sensitive PD marker LDL-C. Any potential clinical effect of ADAs will be evaluated by correlation to PK, efficacy and safety parameters. Detailed description of the anti-drug antibody assay methods will be included in an analytical report. Antibody assays will be validated according to international guidelines and recommendations. Furthermore, samples will be banked for possible future analysis in a dedicated neutralising anti-drug antibody analysis if this assay would be deemed necessary (for further details, see Section 10.6.2).

Results from the binding anti-drug antibody analyses from visit 2, 4, 6, 8, 9 and 10 will be available at the end of trial.

At the end of the trial, the following data will be electronically transferred to the Novo Nordisk database:

- Anti-NNC0385-0434 binding antibodies (positive/negative)
- Anti-NNC0385-0434 binding antibodies cross-reacting with endogenous EGF-A (positive/negative)
- Anti-NNC0385-0434 binding antibody titre (no unit)

Patients who have tested positive for antibodies against NNC0385-0434 (high titre of antibodies) at visit 10 (end-of-trial visit) will be requested to have a follow-up analysis performed 12 months after visit 10. If the anti-NNC0385-0434 antibody titre has not declined at the follow-up analysis, the patient may be requested to have an additional follow-up analysis performed. The result from additional follow-up analyses will be reported in a separate analytical report. Thus, the results will not be part of the CTR.

The investigator will not be able to review the results of antibody measurements in relation to AEs as these will be analysed after LPLV.

Refer to Section 10.6.2 for further details.

### 8.11.1 Assessments in case of suspicion of hypersensitivity to trial product

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

- Local reactions
- Systemic reactions, including anaphylaxis.

In the event of a hypersensitivity reaction:

- The patient should contact the site for advice on further action as soon as possible.
- Additional data collection will be performed on the event
- Treatment should be provided by the investigator according to local clinical practice.

**Additional blood samples and other tests**

In the event of a **systemic** hypersensitivity reaction (i.e. not local reactions), as judged by the investigator, the patient should be called in as soon as possible to have additional blood samples taken in order to analyse the following parameters:

- Tryptase (optimal 0.5 – 2 hours post the hypersensitivity reaction)
- Anti-NNC0385-0434 binding antibodies
- Anti-NNC0385-0434 IgE antibodies
- Anti-EGF-A IgE antibodies
- Total IgE

The following additional exploratory tests may be performed on the already taken blood samples, if deemed relevant:

- Histamine release assay (basophil activation test)

The blood sampling should if possible be repeated 1, 2 and 4 weeks following the systemic hypersensitivity reaction. In addition, the test should also be performed on samples drawn prior to first administration of trial drug.

Prick test/intra-dermal test may be performed if deemed relevant. Complement may be measured in case of suspicion of immune complex mediated hypersensitivity reactions.

Analysis of anti-NNC0385-0434 IgE, anti-EGF-A IgE, total IgE and tryptase will be performed at Novo Nordisk A/S. If deemed relevant, histamine release (basophil) assay will be performed at [redacted], as an exploratory analysis. Prick test/intra-dermal test should be performed at the hospital allergy unit.

Data from the additional blood samples and tests will be reported in a separate report and attached to the clinical trial report. Furthermore, the results will be included in the narratives of the clinical trial report.

### 8.11.2 Digital pictures

The investigator or the patient should take digital pictures of the hypersensitivity reaction as applicable (for example rash, urticaria, swelling of face) for reactions possibly related to the administration of NNC0385-0434 at time of identification and thereafter as often as judged necessary by the investigator.

The pictures should include patient identification number, date and time, time after dosing and a ruler for scaling. All pictures should be stored as part of source documentation at site.

## 8.12 Health economics

Not applicable.

# 9 Statistical considerations

## 9.1 Statistical hypotheses

Confirmation of superiority for each oral NNC0385-0434 dose vs. placebo (pooled from all 3 placebo arms) will be evaluated using a hierarchical testing procedure starting with the treatment difference between the highest oral NNC0385-0434 dose (100 mg) and placebo and ending with the lowest dose (15 mg). In case of a non-significant treatment difference the testing procedure will stop. This will protect the family-wise type 1 error in the strong sense on a 5% level of significance.

The superiority test for oral NNC0385-0434 vs. placebo will be carried out as follows. Let $\mu_{\text{NNC0385-0434 ,x}}$ and $\mu_{\text{placebo}}$ denote the true mean of percent change in LDL-C from baseline for dose level x of oral NNC0385-0434 and placebo, respectively. The null and alternative hypotheses tested are

$$H_0: \mu_{\text{NNC0385-0434 ,}x} \geq \mu_{placebo} \text{ vs. } H_A: \mu_{\text{NNC0385-0434 ,}x} < \mu_{placebo}$$

The null hypothesis will be rejected if the upper limit of the estimated two-sided 95% CI for the treatment difference is below 0.

## 9.2 Sample size determination

To characterise the shape of the curve for the dose-response relationship it is considered adequate to test 3 doses of oral NNC0385-0434 and the sample size for each dose is determined in order to achieve a sufficient precision on this relationship. Furthermore, sample size calculation is done for analyses addressing the primary estimand. Here, measurements of the primary endpoint from patients that have discontinued treatment prematurely but continuing in the trial (retrieved dropouts) are treated as missing.

In the sample size calculations addressing the primary estimand, missing values and assessments from retrieved dropouts are assumed to be similar to treatment completers within the same treatment group.

The sample size calculation assumes at least 45 eligible measurements of the primary endpoint in each treatment arm (eligible assessment defined as non-missing and obtained during the on-treatment observation periods, see Section 9.3 for definition of the on-treatment observation period). The sample size calculation assumes an SD of 30%-points for the percent change in LDL-C from baseline to week 12.

Data from the currently approved PCSK9 inhibitors are as follows:

- Alirocumab: lowering percentage LDL-C after 24 weeks by 61 percent with SE=0.7 for n=1530, corresponding to an SD of 27%-points[21]
- Evolocumab: lowering percentage LDL-C after 52 weeks by 46.8 percent with SE=3.0 for n=126, corresponding to an SD of 34%-points[22]

Table 9-1 includes different scenarios for the probability of the 95% confidence interval for the treatment difference to have the given halfwidth for different scenarios of number of patients per treatment arm.

A standard deviation of 30%-points and at least 45 eligible measurements in each treatment arm will allow the 95% confidence interval for the estimated difference between an oral NNC0385-0434 dose and the placebo group, with 94% probability, to be contained within ±14%-points of the estimate. This is considered to be a sufficient precision for determining which doses to use for the continued development of oral NNC0385-0434.

The calculations in Table 9-1 also apply for the comparison between oral doses of NNC0385-0434 and s.c. evolocumab.

In total this requires a sample size of 255 patients.

**Table 9-1 Probability of desired CI half-width**

| N per active arm/N for placebo group (Eligible) | SD (%-points) | CI half-width (%-points) | Probability |
|---|---|---|---|
| 51 (45) | 30 | 14 | 94% |
| 60 (54) | 30 | 14 | >99% |
| 51 (45) | 30 | 13 | 69% |
| 60 (54) | 30 | 13 | 98% |
| 51 (45) | 34 | 14 | 42% |
| 60 (54) | 34 | 14 | 88% |
| 51 (45) | 34 | 13 | 13% |
| 60 (54) | 34 | 13 | 52% |

### PK sub-study

Based on the PK endpoint $AUC_{0\text{-}24h}$, a common race ratio across doses will be estimated including the 18 Japanese and 18 non-Japanese patients exposed to oral NNC0385-0434. Assuming that the true common race ratio is 1, and that the SD of $\log(AUC_{0\text{-}24h})$ is 0.5, and accounting for a 10% withdrawal rate, the 95% confidence interval of the common race ratio of $AUC_{0\text{-}24h}$ will, with a probability of 80%, be within the range from 0.67 to 1.5 times the estimated ratio.

## 9.3 Populations for analyses

The following populations are defined:

| Population | Description |
|---|---|
| Full analysis set | Full analysis set (FAS): All patients randomised. Patients will be analysed according to the randomised treatment. |
| Safety analysis set | Safety analysis set (SAS): All patients randomly assigned to trial treatment and who take at least 1 dose of trial product. Patients are analysed according to the treatment they actually received. |

The patients or observations to be excluded, and the reasons for their exclusion must be documented before unblinding. The patients and observations excluded from analysis sets, and the reason for this, will be described in the CTR.

Efficacy endpoints will be analysed using the FAS; safety endpoints will be analysed using the SAS.

For both the primary estimand and the additional estimand, patients are analysed according to the randomised treatment.

Two observation periods are defined for each patient:

- The *in-trial period* is defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site. Follow-up time for antibody positive patients is not included in the in-trial period.
- The *on-treatment* period is a subset of the 'in-trial' observation period and represents the time period where patients are considered exposed to trial product. The observation period starts at the date of first dose of trial product and ends at the first date of any of the following:
- The follow-up visit
- The last date on randomised treatment regimen + 58 days
- The end-date for the 'in-trial' observation period

The in-trial and on-treatment periods define the patient years of observation (PYO) and patient years of exposure (PYE), respectively, as the total time duration in the periods.

## 9.4 Statistical analyses

The statistical analysis plan will be finalised prior to first patient first visit and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and confirmatory secondary endpoints.

### 9.4.1 General considerations

**Handling of missing baseline data**

The last available and eligible observation at or before randomisation is used as the baseline value. If no assessments are available, the mean value at randomisation across all patients is used as the baseline value.

### 9.4.2 Primary endpoint

Definition of primary endpoint: Percent change in LDL-C

Change from randomisation at week 0 to week 12 in LDL-C (%) is defined as:

$$\%\ \text{LDL-c change} = \frac{(\text{LDL-C at week 12} - \text{LDL-C at baseline})}{\text{LDL-C at baseline}} \times 100\%$$

The primary estimand for percent change in LDL-C addresses the efficacy of oral NNC0385-0434 and will be estimated based on the FAS using the on-treatment observation period.

The primary analysis for the primary estimand for percent change in LDL-C is an analysis of covariance (ANCOVA) with randomised treatment (each oral NNC0385-0434 dose, pooled placebo group, and s.c. evolocumab) and strata as factors (population strata (inclusion criteria 3a/3b), country (Japan/non-Japan)) and baseline LDL-C as a covariate.

The estimated treatment difference between individual oral NNC0385-0434 doses and placebo will be reported together with the associated two-sided 95% CI and corresponding two-sided p-value.

**Handling of missing week 12 values for the primary estimand**

The primary estimand will be estimated based on the FAS using post-baseline measurements up to and including week 12 from the on-treatment observation period. Missing data and observations outside the on-treatment observation period such as week 12 assessments for retrieved dropouts will be imputed using multiple imputation assuming missing at random (MAR). Missing post-baseline data will be imputed sequentially within each treatment using the observed post-randomisation assessments for visits prior to the one in question obtained during the on-treatment observation period. The imputation model will include strata as factors (population strata (inclusion criteria 3a/3b), country (Japan/non-Japan)) and baseline and post-baseline LDL-C values prior to the visit in question as covariates. The proportion of missing LDL-C change data at week 12 is assumed to be no more than 10% and is expected to be similar in all treatment arms.

**Analysis addressing the effect of oral NNC0385-0434 vs. s.c. evolocumab**

This analysis will evaluate the treatment difference between oral NNC0385-0434 and s.c. evolocumab using the same analysis as the primary analysis for the primary estimand described above. However, the treatment differences between oral NNC0385-0434 doses and s.c. evolocumab will be estimated but no confirmatory testing will be carried out.

**Analyses addressing the additional estimand**

The analysis model for percent change in LDL-C is an ANCOVA with randomised treatment and strata as factors (population strata (inclusion criteria 3a/b), country (Japan/non-Japan)) and baseline LDL-C as a covariate.

**Handling of missing week 12 values for the additional estimand**

The additional estimand will be estimated based on the FAS using week 12 measurements from the in-trial observation period. Missing week 12 data will be imputed using multiple imputation assuming missing at random (MAR). Imputation will be done within groups defined by randomised treatment and treatment status at week 12. The imputation model will include strata as factors (population strata (inclusion criteria 3a/3b), country (Japan/non-Japan)) and baseline LDL-C as a covariate. In case of sparse data in some of the groups, a common treatment discontinuation group across treatments will be created and randomised treatment will be added to the model as factor. If this is still not sufficient, the model will be thinned in the following order, starting with the one that will be removed first; strata, randomised treatment, and baseline value.

**Dose-response modelling**

In order to evaluate the effect of oral NNC0385-0434 dose vs. placebo on percent change in LDL-C and to characterise the dose-response relationship the mean percent LDL-C change will be estimated using dose as a continuous variable.

The dose-response candidate models in Table 9-2 will be fit.

**Table 9-2 Dose-response candidate models**

| Model | Functional form f(d,θ) |
|---|---|
| $E_{max}$ | $E_0 + E_{max}\frac{d}{ED_{50}+d}$ |
| Linear | $E_0 + \beta d$ |

The candidate models will be fit to the estimated percent change in LDL-C means at week 12 for the employed oral NNC0385-0434 doses and placebo from the primary analysis model described above. Thus, all patients in the FAS will be included and the same assumptions regarding missing values and the impact of explanatory variables will be applied.

The model used to evaluate dose-response will be selected among the candidate models based on the best fit to data. The best fit will be evaluated based on convergence, model complexity, Akaike information criterion (AIC) value and visual evaluation.

### 9.4.3 Secondary endpoints

#### 9.4.3.1 Confirmatory secondary endpoint

Not applicable

#### 9.4.3.2 Supportive secondary endpoints

For details on analyses of additional supportive secondary endpoints, please refer to the SAP.

### 9.4.4 Exploratory endpoints

For details on analyses of the exploratory endpoints, please refer to the SAP.

### 9.4.5 Other safety analyses

All safety analyses will be made on the safety analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively; including any notable changes of clinical interest in laboratory parameters.

### 9.4.6 Other analyses

For other analyses, please refer to the SAP.

#### 9.4.6.1 Pharmacokinetic and/or pharmacodynamic modelling

Population PK and exposure-response analyses will be used as supportive evidence for the evaluation of efficacy and safety as well as to support the dose selection of oral NNC0385-0434 for future clinical development in patients with established ASCVD or ASCVD risk. Firstly, plasma NNC0385-0434 concentrations will be analysed using a population PK model, quantifying covariate (such as baseline body weight, age, sex, race, ethnicity) effects on oral NNC0385-0434 exposure. Secondly, model-based estimates of steady-state average concentrations will be derived for each patient, to facilitate subsequent exposure-response analyses. Relevant efficacy and safety endpoints will be related to steady-state average concentrations and subjected to model-based analysis.

A modelling analysis plan will be prepared before data base lock, outlining details of the analyses. The modelling will be performed by Quantitative Clinical Pharmacology at Novo Nordisk and will be reported separately from the CTR.

## 9.5 Interim analyses

Not applicable for this trial.

## 9.6 Data monitoring committee

Not applicable for this trial.

## 9.7 Reporting of the main part of the trial

Not applicable for this trial.

# 10 Supporting documentation and operational considerations

## 10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

### 10.1.1 Regulatory and ethical considerations

- This trial will be conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[23] and applicable ICH Good Clinical Practice (GCP) Guideline[24]
- 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 trial is initiated.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate safety hazard to trial patients.
- Before a site is allowed to start screening patients, written notification from Novo Nordisk must be received.
- The investigator will be responsible for:
- providing written summaries of the status of the trial annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CTR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately after discovery

Japan: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

### 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 trial and one year after completion of the trial.
For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

### 10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the trial to the patient or the patient's LAR and answer all questions regarding the trial.

- The investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.
- Patients must be informed that their participation is voluntary.
- Patients must be informed about their privacy rights.
- Patients or their LAR will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines[24], Declaration of Helsinki[23] and the IRB/IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any trial related activity.
- The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Patients or their LAR must be re-consented to the most current version of the informed consent form*(s)* during their participation in the trial.
- A copy of the informed consent form*(s)* must be provided to the patient or the patient's LAR.
- A separate informed consent form intended for collection of additional blood samples for future research (circulating biomarkers) is available for this trial (see Section 8.10)
- A separate informed consent form intended for collection of additional blood samples for future research (genetic analysis) is available for this trial (see Section 8.10)
- A separate informed consent form intended for a male partner of a female patient in case of an abnormal pregnancy is available for this trial (Appendix 4 (Section 10.4))

### 10.1.4 Information to patients during trial

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

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

### 10.1.5 Data protection

- Patients will be assigned a 6-digit unique identifier, a patient number. Any patient records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the patient are transferred to Novo Nordisk.
- The patient and any biological material obtained from the patient will be identified by patient number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of patients as required by local, regional and national requirements.

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

### 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 NNC0385-0434 safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal trial independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

### 10.1.7 Dissemination of clinical trial data

Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE)[25], the Food and Drug Administration Amendment Act (FDAAA)[26], European Commission Requirements[27-29] and other relevant recommendations or regulations. If a patient requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the patient. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The primary completion date (PCD) is the last assessment of the primary endpoint and is for this trial last patient first treatment (LPFT) + 12 weeks + 3 days visit window corresponding to visit 9. If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed visit 9. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

### 10.1.8 Data quality assurance

#### 10.1.8.1 Case report forms

- Novo Nordisk or designee is responsible for the data management of this trial including quality checking of the data.
- All patient data relating to the trial will be recorded on electronic CRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The following will be provided as paper CRFs:
  - Pregnancy forms
- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
  - AE forms

- Safety information forms
- Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a patient)

- 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, preferably within 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 trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of patients are being protected, to monitor drug accountability and collect completed paper CRF pages, if applicable, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.
- Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.
- Monitors will review the patient's medical records and other source data to ensure consistency and/or identify omissions compared to the CRF.

**Medical monitoring and early PK evaluation**

Bi-weekly medical monitoring of safety data including AEs, vital signs, ECG, and laboratory safety parameters will be performed according to the medical monitoring plan.

The centralised monitoring will include early PK evaluation to ensure that the PK parameters after oral dosing are in the expected range. The early PK evaluation will be performed at 3 early timepoints during the trial and will include all available blinded accumulated plasma concentration data from patients that have initiated treatment. PK data will be related to treatment arm. The early

PK evaluation will be based on nominal time points for the dose administration and PK sampling. Additional PK evaluations may be added if deemed necessary.

- Timepoint 1: After PK data is available from visit 4 (2 weeks of dosing) for the initial 15 patients.
- Timepoint 2: After PK data is available from visit 7 (6 weeks after dosing) for the initial 15 patients
- Timepoint 3: After PK data is available from visit 8 (9 weeks after dosing) for the initial 15 patients and from visit 4 (2 weeks of dosing) for the following 20 patients.

Further details are described in the interim modelling analysis plan.

The Novo Nordisk NN6435 Safety Committee will be informed immediately in case any of the following criteria are met:

- if the exposure of NNC0385-0434 exceeds the NOAEL exposure observed in the 13-week non-clinical toxicity study (12 mg/kg/day s.c. + 50 mg/kg/day orally)
- if the geometric mean $C_{max}$ of NNC0385-0434 for patients treated with any dose arm of NNC0385-0434 is numerically higher than the geometric mean $C_{max}$ observed in the FHD trial NN64334-4493 (11,015.5 nmol/L).

The initial 15 patients (3 patients in each active treatment arm and 1 patient in each of the placebo arms) will be recruited and treated for minimum 4 weeks before recruitment of the remaining 240 patients. Recruitment of the remaining patients will be initiated following medical monitoring of 4 week data of these 15 patients without identification of safety concerns, in addition to review of PK data from the 15 patients 2 weeks after dosing

If unexpected safety findings occur, a Novo Nordisk Safety Committee will be informed immediately and will take appropriate actions to the information received.

#### 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 trial database.

### 10.1.9 Source documents

- 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 trial staff making the entry.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data reported on the paper CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify patient's medical history in source documents, such as patient's medical record
- The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

### 10.1.10 Retention of clinical trial documentation

- Records and documents, including signed informed consent forms, pertaining to the conduct of this trial must be retained by the investigator for 15 years after end of trial unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.
- The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other patient 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 patient 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.
- Patient's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

United States of America: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

### 10.1.11 Trial and site closure

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

Sites will be closed upon trial completion. A site is considered closed when all required documents and trial 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 patients by the investigator
- discontinuation of further trial product development.

### 10.1.12 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients.

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

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

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. 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 patients to a specific qualified physician who will be readily available to patients during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

### 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 trials in any country, unless others have shown negligence.

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

Novo Nordisk accepts liability in accordance with:

Belgium: For country specific indemnity statement, see Appendix 9 (Section 10.9)

### 10.1.14 Publication policy

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

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial.

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

Novo Nordisk may publish on its clinical trials website a redacted CTR for this trial.

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

#### 10.1.14.1 Communication of results

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

The results of this trial will be 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 CTR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

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

In all cases, the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. 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 trial concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[30]

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 publication(s) by investigator(s)

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

#### 10.1.14.4 Investigator access to data and review of results

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

Individual investigators will have their own research patients' data and will be provided with the randomisation code after results are available.

## 10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1, Table 10-2 and Table 10-3 will be performed by the central laboratory unless otherwise noted.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g. to follow up on AEs, this must be done at a local laboratory.
- The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their lab SOPs. These data will not be transferred to the trial database. 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.
- Laboratory samples will be destroyed no later than at finalisation of the CTR, except for the following:
- Human biosamples for retention will be stored as described in Appendix 6 (Section 10.6).
- For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations.

**Table 10-1 Protocol-required efficacy laboratory assessments**

| Laboratory assessments | Parameters |
|---|---|
| Lipids | • Lipoprotein a (Lp(a))<br>• Apolipoprotein B (ApoB)<br>• Apolipoprotein C III (ApoCIII)<br>• Total cholesterol<br>• High density lipoprotein (HDL) cholesterol<br>• Low density lipoprotein (LDL) cholesterol<br>• Very low density lipoprotein (VLDL) cholesterol<br>• Triglycerides |
| Target engagement | • PCSK9 levels[a] |
| NOTES:<br>[a] Analysis performed by special laboratory contracted by Novo Nordisk | |

## Table 10-2 Protocol-required safety laboratory assessments

| Laboratory assessments | Parameters |
|---|---|
| Haematology | • Lymphocytes<br>• Eosinophils<br>• Basophils<br>• Monocytes<br>• Neutrophils<br>• Haematocrit<br>• Mean corpuscular haemoglobin, concentration<br>• Mean corpuscular volume<br>• Reticolyctes<br>• Haemoglobin<br>• Erythrocytes<br>• Leukocytes<br>• Thrombocytes |
| Biochemistry[a] | • Bicarbonate Serum<br>• High Sensitive C-Reactive Protein<br>• eGFR Using CKD-EPI Formula (Chronic Kidney Disease Epidemiology Collaboration)<br>• Aspartate Aminotransferase<br>• Albumin<br>• Urea<br>• Calcium<br>• Sodium<br>• Potassium<br>• Creatinine<br>• Alkaline Phosphatase<br>• Alanine Aminotransferase<br>• Gamma-glutamyl transferase (GGT)<br>• Bilirubin<br>• Creatine Kinase<br>• Lactate plasma |
| Coagulation parameters | • Prothrombin Time<br>• INR |
| Pregnancy Testing | • Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test[b] |
| Glucose metabolism | • Fasting plasma glucose<br>• $HbA1_c$ |
| Antibodies | • Anti NNC0385-0434 Antibodies[c] |

**Notes:**
[a] Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Section 10.3 (Hy's Law) and Section 7.1.
[b] Only applicable for female patients who have stopped menstruating within the last 5 years (Appendix 4 (Section 10.4))
[c] Analysis performed at Novo Nordisk A/S

**Table 10-3 Protocol-required PK assessments**

| Laboratory assessments | Parameters |
|---|---|
| Pharmacokinetics | • NNC0385-0434 plasma concentrations[a] |
| **Notes:**<br>[a] Analysis performed by special laboratory contracted by Novo Nordisk | |

Laboratory results that could unblind the trial (e.g. antibodies and PK) will not be reported to the sites until the trial has been unblinded.

## 10.3 Appendix 3: Adverse events: Definitions and procedures for recording, evaluation, follow-up, and reporting

### 10.3.1 Definition of AE

**AE definition**

An AE is any untoward medical occurrence in a clinical trial subject that is temporally associated with the use of an investigational medicinal product (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 meeting the AE definition** |
|---|
| • 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<br>• Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected<br>• Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition<br>• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction<br><br>• Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent |
| **Events NOT meeting the AE definition** |
| • Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or other trial procedures performed before exposure to IMP.<br>• Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.<br>• Medical or surgical procedures (e.g. endoscopy, appendectomy). The condition that leads to the procedure is the AE.<br>• 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:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalisation or prolongation of existing hospitalisation**<br>• Hospitalisation signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other 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.<br>Note:<br>• Hospitalisations for administrative, trial related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs.<br>• Hospital admissions for medical or surgical procedures, planned before trial inclusion, are not considered AEs or SAEs. |
| **d. Results in persistent or significant disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect** |
| **f. Important medical event:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.<br>• The following adverse events must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:<br>• Suspicion of transmission of infectious agents via the IMP<br>• Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x UNL and total bilirubin >2 x UNL where no alternative aetiology exists (Hy's law) |

### 10.3.3 Description of AEs requiring additional data collection

| **Description of AEs requiring additional data collection (on specific event form)** |
|---|
| **Adverse events requiring additional data collection**<br><br>**Hypersensitivity reactions**<br>All drug allergies, drug hypersensitivities and autoimmunity<br><br>**Medication error**<br>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 patient, such as:<br>• administration of wrong drug or use of wrong device<br>Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.<br>• wrong route of administration, such as intramuscular instead of subcutaneous<br>• accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although they did not necessarily occur. |

**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)

Medication error, misuse and abuse must always be reported as an AE (e.g. accidental overdose, intentional overdose or other) on a separate AE form, and a medication error, misuse and abuse form must be completed. In case of a medication error and/or misuse and abuse resulting in a clinical consequence (e.g. hypoglycaemia or other), this must be reported on an additional AE form.

### 10.3.4 Recording and follow-up of AE and/or SAE

**AE and SAE recording**

- The investigator will record all relevant AE/SAE information 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 patient identifiers, with the exception of the patient number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms, refer to "AE and SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

**Assessment of severity**

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

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

| **Assessment of causality** |
|---|
| • The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE.<br>• Relationship between an AE/SAE and the relevant IMP(s) should be assessed as:<br>  • Probable - Good reason and sufficient documentation to assume a causal relationship.<br>  • Possible - A causal relationship is conceivable and cannot be dismissed.<br>  • Unlikely - The event is most likely related to aetiology other than the IMP.<br>• 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, will be considered and investigated.<br>• The investigator should use the investigator's brochure and/or product information, for marketed products, for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.<br>• 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.**<br>• The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.<br>• The causality assessment is one of the criteria used when determining regulatory reporting requirements. |
| **Final outcome** |
| The investigator will select the most appropriate outcome:<br>• **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented<br>• **Recovering/resolving:** The condition is improving, and the patient is expected to recover from the event. 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).<br>• Note: For SAEs, this term is only applicable if the patient has completed the follow-up period and is expected to recover.<br>• **Recovered/resolved with sequelae:** The patient has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.<br>• **Not recovered/not resolved:** The condition of the patient has not improved, and the symptoms are unchanged, or the outcome is not known.<br>Note: 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).<br>• **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.<br>• **Unknown:** This term is only applicable if the patient is lost to follow-up. |

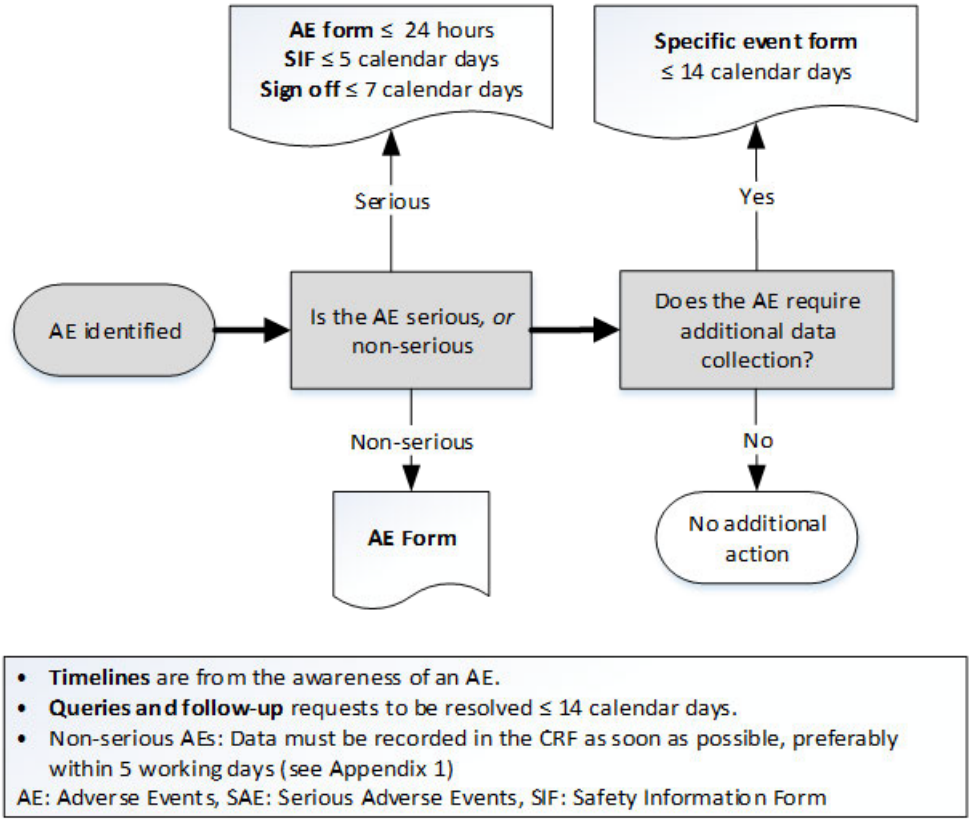
| Follow-up of AE and SAE |
|---|
| The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity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

### 10.3.5 Reporting of SAEs

| SAE reporting via electronic CRF |
|---|
| • Relevant forms (AE and safety information form) must be completed in the CRF.<br>• For reporting and sign-off timelines, see Figure 10-1 below.<br>• If the CRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the CRF is unavailable for more than 5 calendar days, then the site will use the safety information form (see box below).<br>• The site will enter the SAE data into the CRF as soon as it becomes available.<br>• After the trial is completed, the trial database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after CRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone. |

| AE and SAE reporting via paper CRF |
|---|
| • Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.<br>• For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting timelines (as illustrated in the figure below):<br>  • AE form within 24 hours<br>  • Safety information form within 5 calendar days<br>  • Both forms must be signed within 7 calendar days after first knowledge by the investigator.<br>• The specific event form for AEs requiring additional data collection within 14 calendar days |

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




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

## 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Documentation of non-child-bearing potential must be recorded in the eCRF.

**Definitions**

**Female patients in the following categories are considered women of non-childbearing potential**

- Premenopausal woman with one or more of the following:
  - Documented total hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site staff's review of patient's medical records, medical examination or medical history interview.

- Postmenopausal woman:
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females ≥ 60 years of age can be considered postmenopausal.

Female patients on HRT and whose menopausal status is in doubt are considered of childbearing potential.

**Contraception guidance**

There are no contraception requirements in this trial.

US: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

**Pregnancy testing**

Only women of non-childbearing potential are eligible for inclusion in this trial.

- Serum hCG pregnancy tests must be performed at the following five site visits for female patients who have stopped menstruating within the last 5 years. Criteria applies also if patient has prematurely discontinued trial product treatment:
- Visit 1 (screening)
- Visit 2 (week 0/randomisation)
- Visit 7 (week 6)
- Visit 9 (week 12)
- Visit 10 (week 19+4 day/end of trial)
- Serum hCG pregnancy test must be repeated at any time during the trial if pregnancy is suspected.

- Additional pregnancy testing should be performed during the treatment period, if required locally (Germany: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

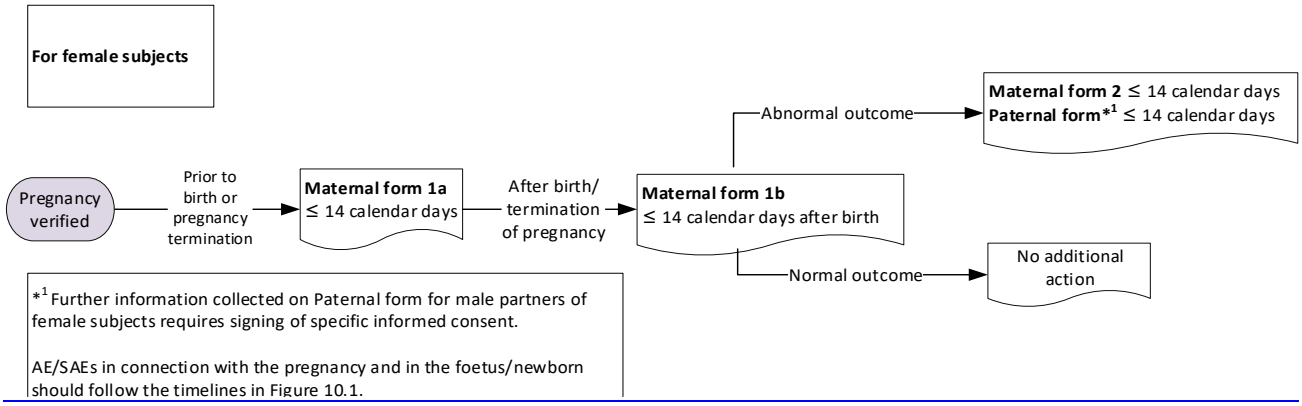
**Collection of pregnancy information**

***Female patients who become pregnant***

Only women of non-childbearing potential are eligible for inclusion in this trial. In the unlikely event of a female patient becoming pregnant while participating in the trial, the female patient will discontinue IMP and pregnancy information will be collected.

- Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this trial.
- Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a patient's pregnancy (see Figure 10-2).
- Patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on patient and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding ‘gestational’, ‘pregnancy related’ or a similar term when reporting the AE/SAE.
- Pregnancy outcome should be documented in the patient's medical record. Abnormal pregnancy outcome (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE.
- For abnormal pregnancy outcomes collection of information on the paternal form for male partners of female patients require signing of specific informed consent (see Section 10.1.3).
- Any SAE occurring as a result of a post-trial pregnancy which is considered possibly/probably related to the IMP by the investigator will be reported to Novo Nordisk as described in Section 10.3. While the investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.

**Figure 10-2 Decision tree for determining the forms to complete with associated timelines for pregnancy.**



## 10.5 Appendix 5: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

### 10.5.1 Definition of technical complaint

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

Examples of technical complaints:

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

| 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. |

### 10.5.2 Recording and follow-up of technical complaints

| Reporting of technical complaints to Novo Nordisk |
|---|
| Contact details for Customer Complaint Center, please refer to Attachment I.<br><br>Technical complaints must be reported on a separate technical complaint form:<br>3. One technical complaint form must be completed for each affected DUN.<br>4. If DUN is not available, a technical complaint form for each batch, code or lot number must be completed. |

| Timelines for reporting of technical complaints to Novo Nordisk |
|---|
| The investigator must complete the technical complaint form in the CRF within:<br>• 24 hours if related to an SAE<br>• 5 days calendar for all other technical complaints<br><br>If the CRF is unavailable, or when reporting a technical complaint on a trial product that is not yet allocated to patient, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF. |

| 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 that were packed in the same DUN 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 DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.<br><br>Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. |

## 10.6 Appendix 6: Retention of human biosamples

In countries where allowed, the trial will involve collection of human biosamples to be stored in a central laboratory facility for future use.

### 10.6.1 Biosamples for future research

- Patients who do not wish to contribute with biosamples for storage may still participate in the trial.
- Patients must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis.
- The material to be collected is:
  - ~~o~~ Genetic analysis (whole blood): visit 2
  - o Circulating biomarkers (serum and plasma): visits 2 (two samples), 6, 9 and 10
- Biosamples will be used to improve the understanding of cardiometabolic disease or related diseases, mechanism of action and disease aetiology. Biosamples may also be used to identify responders and non-responders to oral NNC0385-0434. The analysis of biosamples may include DNA sequencing, epigenetic analysis and other methods in 'omics' used to characterise the disease. As new knowledge may arise related to cardiometabolic disease and/or safety, efficacy or mechanism of action of oral NNC0385-0434 may evolve during or after the conduct of the trial, the analyses of the stored biosamples may include biomarkers presently not known, which have not been included up-front in the scientific hypotheses of this trial.
- The biosamples will be stored at a central laboratory for up to 15 years after end of trial. Only relevant Novo Nordisk staff and consultants, auditors, research organisations or laboratories working for Novo Nordisk and biorepository personnel will have access to the stored samples and associated data.
- The biosamples may be transferred to other countries for analysis, if not prohibited by local regulations, and will be destroyed at the latest 15 years after end of trial.
- The patient may request the stored biosamples to be destroyed by withdrawing the designated informed consent. The results obtained from any already-performed analyses of the samples will still be used.
- In case the patient withdraws his/her informed consent for the biobank components of the trial, the monitor must contact the trial manager at Novo Nordisk as soon as possible in order to have the biosamples withdrawn from storage.
- The patient's identity will remain confidential and the samples will be identified only by subject number, visit number and trial identification number. No direct identification of the patient will be stored together with the samples.

### 10.6.2 Immunogenicity samples

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons.

The samples will be stored at Novo Nordisk (or a Novo Nordisk designated referral bio-repository with access to the samples). The samples might be transferred to other countries, if not prohibited by local regulations. Only Novo Nordisk staff and biorepository personnel (if applicable) will have access to the stored samples.

Samples will be anonymised (marked and identified only by a unique sample ID, visit number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of trial and no direct identification of the patient will be stored together with the samples.

The potential future assessments may address issues such as unexpected safety events, refinement of the PK or anti-drug antibody assessments and to improve the understanding of the mechanism of action of NNC0385-0434. As new biomarkers related to the disease and/or safety, efficacy, or mechanism of action of NNC0385-0434 may evolve during the conduct of the trial, the analyses of the stored biospecimens may also include biomarkers that are unknown at present or have not been included in the scientific hypotheses at initiation of the trial.

In the event that the collected biospecimens (specific whole blood, plasma and serum samples) will be used in the future, the investigator will be informed directly by Novo Nordisk about the results if the findings are deemed clinically relevant and analytically valid and quantifiable. In such case, a written summary of the findings, including listings of patient specific values, will be provided once a firm conclusion from the results has been drawn by Novo Nordisk.

Potential further analyses of the samples will not have any medical consequences for patient and their relatives. Patients can contact the investigator if they wish to be informed about results derived from stored biosamples obtained from their own body.

The samples might be transferred to other countries, if not prohibited by local regulations. Only Novo Nordisk staff and biorepository personnel will have access to the stored biospecimens. The samples will be stored after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of trial after which they will be destroyed.

Remaining blood from the samples already collected may be used for further development of Anti-NNC0385-0434 antibody assays, and will not be reported in this study. Residual samples may also be used to generate reagents for in study validation or control of future assay performance inside or outside this study. Selected samples would be pooled, and not be traceable to any individual. Pooling would not be done if it prevented retention of sufficient sample material for possible further characterisation of antibody responses in this trial.

## 10.7 Appendix 7: Requirements for maximally tolerated dose of statins and documented evidence of intolerance to statins

There should be no plans at the time of screening and randomization to modify the dose of statin or other lipid lowering medication for the duration of the trial.

### Maximally tolerated dose of statins

Patients must be treated with one of the following highly effective statins at the specified daily doses and at a stable dose for at least 30 days prior to screening for the trial:

- atorvastatin, 40 or 80 milligrams (mg) once a day;
- rosuvastatin, 20 or 40 mg, once a day;
- simvastatin 40 mg, once a day or, if a patient has been on that dose for >1 year, 80 mg, once a day.

Combination medications that contain atorvastatin, rosuvastatin, or simvastatin components described at the aforementioned doses will be permitted.

Exceptions to maximally tolerated dose of statins are described below.

### Documented evidence of intolerance to statins (exceptions to background statin treatment)

The following background statin treatment exceptions are permitted:

- **Lower doses of statins due to partial statin intolerance**: Patients may be on a lower dose of one of the highly effective statins described above if there is documented intolerance to any one of them (atorvastatin, rosuvastatin, or simvastatin) at the aforementioned doses. Intolerance to any dose of any statin must be documented as medical history linked to the statin in question as documented/reported by the patient in the source documentation and eCRF.
- **Regulatory limitations**: Patients may be on a lower dose of one of the highly effective statins described above if the highest locally approved dose for one of the stated statins is lower than those doses shown above (e.g. in some countries, atorvastatin 20 mg, once a day, is the highest locally approved dose).
- **Alternative statins**: Patients may be treated with other statins (pravastatin, fluvastatin, pitavastatin, or lovastatin), different from the highly effective statins listed above, if there is documented intolerance to any two different highly effective statins (atorvastatin, rosuvastatin, simvastatin) at the lowest available daily dose for at least one of those highly effective statins. Intolerance to any statin must be documented as medical history linked to the statin in question as documented/reported by the patient, in the source documentation and eCRF.
- **No background statin therapy**: Patients may be enrolled who are only on non-statin lipid lowering therapy, if complete statin intolerance has been documented. Patients with complete statin intolerance must be unable to tolerate at least two statins: one statin at the lowest available daily dose AND another statin at any dose. Intolerance to any statin must be documented as medical history linked to the statin in question as documented/reported by the patient, in the source documentation and eCRF. The sole exception, for which a patient may participate in the study with documentation of intolerance to only one statin, is a documented history of rhabdomyolysis attributed to that statin.

## 10.8 Appendix 8: Mitigations to ensure patient safety and data integrity during an emergency situation

### 10.8.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for patients and/or sponsor representatives – i.e. pandemics (COVID-19) or natural disasters such as hurricanes, floods and large-scale fires.

In case local restrictions due to a major emergency as described above leading to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

Table 10-4 indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in the original flowchart (Table 1-1) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

### 10.8.2 Visits

- Screening (Visit 1) and randomisation/baseline (Visit 2) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new patients at that site should be on hold until on-site visits are possible.
- Visits (V4, V6, V7, V8, V9, V9A-D, V10) should be performed as on-site visits, if in any way possible. If not, assessments can be conducted remotely as home visits and if not possible then as video or phone visit to follow up on patient safety. Video or phone visits are not required for V9A-D in case these visits cannot be performed as on-site or home visits.
- If permitted by local regulations, the investigator may engage with a Health Care Professional from a third party home health care service provider to perform the home visits. Prior to the arrangement, the investigator must obtain the patient's consent by means of separate and locally approved consent form. The third party Health Care Professional must have a licence to practice and have received adequate protocol training.
- If the end of treatment visit (V9) cannot be performed on-site or as home visit within the given visit window, the visit window for the assessment can be extended for +/- 1 week.
- At each visit, the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

### 10.8.3 Assessments

- Assessments used for safety or the confirmatory endpoints (i.e., [Lipids, PK samples, blood sample for antibody testing, biochemistry and haematology, reporting of adverse events]) should be prioritised.

- The preferred order for the method of assessment is: on-site, home visit, video, phone. Video or phone visits can only be used to assess safety by AE reporting. Specifications regarding how to perform these assessments using home visits will be provided by Novo Nordisk or the vendor.
- Assessments performed as home visits should follow the minimum requirements as shown in Table 10-4 if on-site visits are not possible and if deemed feasible for the patient.
- If the assessments indicated in Table 10-4 cannot be performed as on-site visits or home visits they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

### 10.8.4 Study intervention

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

**Table 10-4 Minimum assessments following randomisation**

| | Protocol Sections | Information visit | Screening | Randomisation | Treatment | | | | | | End of treatment | Treatment Discontinuation[f] | PK sub-study[g] | | | | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V0 | V1 | V2 | P3 | V4 | P5 | V6 | V7 | V8 | V9 | V9X | V9A | V9B | V9C | V9D | V10 |
| Timing of Visit | | Minimum 1 day prior to V1 | -2W | 0W | 1W | 2W | 3W | 4W | 6W | 9W | 12W | | V9/V9X +1D[h] | V9/V9X +1W | V9/V9X +2W | V9/V9X +3W | 138D |
| Visit Window | | -7/0D | 0/13D | ±0D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | | ±4H | ±3D | ±3D | ±3D | 0/5D |
| Informed Consent and Demography[a] | 8.1, 10.1.3 | X | | | | | | | | | | | | | | | |
| Eligibility Criteria | 5.1, 5.2 | | X | X | | | | | | | | | | | | | |
| Concomitant Medication | 6.5 | | X | X | | X | | X | X | X | X | X | X | X | X | X | X |
| Medical History/Concomitant Illness | 8.3 | | X | | | | | | | | | | | | | | |
| Tobacco Use | 5.3.2 | | X | | | | | | | | | | | | | | |
| Childbearing Potential | 10.4 | | X | | | | | | | | | | | | | | |
| Pregnancy Test | 10.4 | | X | X | | | | | X | | X | X | | | | | X |
| PK Sampling | 8.6 | | | X | | X | | X | X | X | X | X | X | X | X | X | X |
| Pre-dosing | | | | | | X | | X | X | X | X[e] | X | | | | | |
| Post-dosing[b] | | | | X | | X | | | X | | | | | | | | |
| Attend Visit Fasting[c] | 5.3.1 | | X | X | | X | | X | X | X | X | X | | | | | X |
| Adverse Event | 8.4 | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication Error, Misuse and Abuse | 8.4 | | | X | | X | | X | X | X | X | X | | | | | |
| Technical Complaint | 8.4.7 | | | X | | X | | X | X | X | X | X | | | | | |
| Laboratory Assessments | 10.2 | | | | | | | | | | | | | | | | |
| Anti-NNC0385-0434 antibodies[d] | | | | X | | X | | X | | X | X | X | | | | | X |
| Biochemistry | | | X | | | X | | X | X | X | X | X | | | | | X |
| Haematology | | | X | | | X | | X | X | X | X | X | | | | | X |
| Lipids | | | X | X | | X | | X | X | X | X | X | | | | | X |
| ECG | 8.3.4 | | | X | | | | | X | | X | X | | | | | X |
| Physical Examination | 8.3.1 | | | X | | | | | | | X | X | | | | | X |

| | Protocol Sections | Information visit | Screening | Randomisation | Treatment | | | | | | End of treatment | Treatment Discontinuation[f] | PK sub-study[g] | | | | End of trial |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | V0 | V1 | V2 | P3 | V4 | P5 | V6 | V7 | V8 | V9 | V9X | V9A | V9B | V9C | V9D | V10 |
| Timing of Visit | | Minimum 1 day prior to V1 | -2W | 0W | 1W | 2W | 3W | 4W | 6W | 9W | 12W | | V9/V9X +1D[h] | V9/V9X +1W | V9/V9X +2W | V9/V9X +3W | 138D |
| Visit Window | | -7/0D | 0/13D | ±0D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | ±3D | | ±4H | ±3D | ±3D | ±3D | 0/5D |
| Vital Signs | 8.3.3 | | X | | | X | | X | | X | X | X | | | | | X |
| Administration of Trial Product | | | | X | | X | | X | X | X | X[e] | X | | | | | |
| IWRS Session | | | X | X | | X | | X | X | X | X | X | | | | | |
| Drug Dispensing | | | | X | | X | | X | X | X | X[e] | X | | | | | |
| Hand Out ID Card | | | X | | | | | | | | | | | | | | |
| Hand Out Direction for Use | | | | X | | X | | | | | | | | | | | |
| End of Trial | | | | | | | | | | | | | | | | | X |

**Notes:**

[a] Date of birth, age, sex, race and ethnicity (according to local regulation). Germany, The Netherlands: For country-specific requirements, please refer to Appendix 9 (Section 10.9).

[b] Patients will receive a meal 30-60 min post dosing, and the PK sampling should be performed 60-90 minutes post dosing.
Date and exact time point for trial product ingestion at site, including start of meal must be collected in the laboratory requisition form.

[c] Fasting for blood sampling is defined as no food or liquid within the last 8 hours prior to blood sampling, however water is allowed up until 2 hours prior to blood sampling.

[d] Pre-dosing

[e] Only applicable for patients in the PK sub-study to cover one dose given at site. Sampling scheme for PK sub-study is outlined in Table 1-2.

[f] V9X is only applicable for patients in the PK sub-study who have discontinued trial product prematurely. Visit 9X has to be performed as soon as site has been informed of prematurely trial product discontinuation by the patient.

[g] Patients part of the PK sub-study who discontinue treatment will be requested to take their last trial product dose at site and attend visit 9X followed by visit 9A, 9B, 9C and 9D.

[h] Visit 9 + 1 day (24 hours)

**Abbreviations:** ECG: Electrocardiogram; IWRS: Interactive web response system; P: Phone visit; PCSK9: proprotein convertase subtilisin/kexin type 9; PK: pharmacokinetics; V: Clinic visit

## 10.9 Appendix 9: Country-specific requirements

### Belgium

- Appendix 1, 10.1.13. Indemnity statement: Novo Nordisk accepts liability in accordance with: Law concerning experiments on the human person of 07 May 2004 - Article 29: §1. Even if without fault, the sponsor is liable for the damage which the subject and/or his rightful claimants sustain, and which shows either a direct or an indirect connection with the trial.

### Germany

- Section 1.2 and 8.1. Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.
- Appendix 4, 10.4. Contraception requirements as per Clinical Trial Facilitation Group (CTFG)[31]

### Japan

- Section 6.2. Preparation/Handling/Storage/Accountability: The head of the trial site or the
- trial product storage manager assigned by the head of the trial site (a pharmacist in
- principle) is responsible for control and accountability of the trial products.
- Appendix 1, 10.1.1: Regulatory and ethical considerations: A name or a seal is accepted as a signature.

### The Netherlands

- Section 1.2 and 8.1. Patient's full Date of Birth is not allowed to be collected and must be shortened to Year of Birth.

### United States of America

- Section 10.1.10: Retention of clinical trial documentation: 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- Section 10.4: Male patients in the trial with partners of childbearing potential should use condoms during treatment and until 53 days after the last dose of the trial product.

## 10.10 Appendix 10: Abbreviations

| | |
|---|---|
| AE | adverse event |
| AIC | akaike information criterion |
| ANCOVA | analysis of covariance |
| ASCVD | atherosclerotic cardiovascular disease |
| AUC | area under the curve |
| CI | confidence interval |
| CFR | Code of Federal Regulations |
| CKD | moderate chronic kidney disease |
| CT | computed tomography |
| CTR | clinical trial report |
| CV | cardiovascular |
| DFU | directions for use |
| DNA | Deoxyribonucleic acid |
| DUN | dispensing unit number |
| EAS | European Atherosclerosis Society |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EGF-A | epidermal growth factor-like repeat A |
| eGFR | estimated Glomerular Filtration Rate |
| EMA | European Medicines Agency |
| ESC | European Society of Cardiology |
| EU | European |
| FAS | full analysis set |
| FDA | U.S. Food and Drug Administration |
| FDAAA | U.S. Food and Drug Administration Amendments Act |
| FHD | first human dose |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| HDL | high density lipoprotein |
| HDPE | high density polyethylene |
| HRT | hormone replacement therapy |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |

| | |
|---|---|
| IRB | institutional review board |
| IWRS | interactive web response system |
| LAR | legally acceptable representative |
| LDL-C | low-density lipoprotein-cholesterol |
| LPFT | last patient first treatment |
| LPLV | last patient last visit |
| MAR | missing at random |
| MR | magnetic resonance |
| NOAEL | no-observed-adverse-effect level |
| NYHA | New York Heart Association |
| PCD | primary completion date |
| PCSK9 | proprotein convertase subtilisin/kexin type 9 |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PYE | patient years of exposure |
| PYO | patient years of observation |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| s.c. | subcutaneous |
| SD | standard deviation |
| SNAC | Salcaprozate sodium |
| SUSAR | suspected unexpected serious adverse reaction |
| TBI | toe-brachial index |
| TMM | trial materials manual |
| UNL | upper normal limit |
| VLDL | very low density lipoprotein |

## 10.11 Appendix 11: Protocol amendment history

The protocol amendment summary of changes in table for the current protocol version is located directly before the table of contents.

### Protocol version 2.0 (29 April 2021), global

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it neither significantly impacts the safety nor physical/mental integrity of participants nor the scientific value of the study.

### Overall rationale for preparing protocol, version 2.0:

| Section # and name | Description of change | Brief rationale |
|---|---|---|
| Section 1.2 Flowchart | Errors in flowchart<br>(misplaced and missing assessments have been corrected) | To align protocol text and flowchart |
| Section 6.1 Treatments administered | Incomplete protocol text description | To align protocol text and flowchart |
| Section 8.3.3 Vital signs | Wording has been slightly changed | To clarfiy text |

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## 16.1.01 Protocol Attachment

Protocol Attachment I is located in the Trial Master File.

If applicable, Protocol Attachment II is also located in the Trial Master File.

Content: Global key staff and Country key staff.