Cover Page for Statistical Analysis Plan

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 requiring further LDL-C reduction
Document date*:	15 July 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.

16.1.9 Documentation of statistical methods

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Statistical Analysis Plan

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

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Version history

This Statistical Analysis Plan (SAP) for trial NN6435-4697 is based on the protocol: *"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",* version 2.0 dated 29APR2021 and applies the SAP template version 8.0 dated 19OCT2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	15JUL2021	not applicable	Original version

1 Introduction

This SAP describes the statistical analyses for the NN6435-4697 phase 2 trial.

This trial is conducted 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.

The trial includes efficacy data, safety data, immunogenicity data, as well as pharmacokinetic (PK) data.

This SAP describes in detail the planned analyses for the trial. There are no changes to the analyses as described in the protocol, but further details on e.g. missing data handling have been added.

Details on sample size calculation are reported in the protocol.

1.1 Objectives and endpoints

1.1.1 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.

1.1.2 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.

1.1.3 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.

1.1.4 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 Table 2.

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 2 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 in the protocol.	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'	

1.2 Primary, secondary and exploratory endpoints

1.2.1 Primary endpoint

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

1.2.2 Secondary endpoints

1.2.2.1 Confirmatory secondary endpoints

Not applicable.

1.2.2.2 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

1.2.3 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

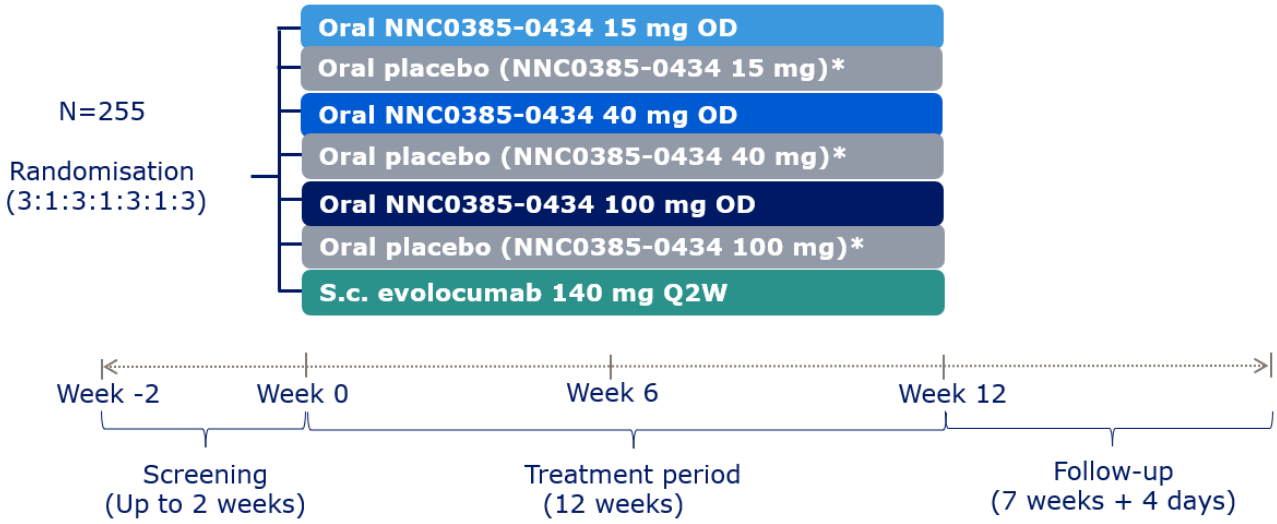
PK sub-study		
Endpoint title	**Time frame**	**Unit**
$AUC_{0\text{-}24h,0434,SS}$ (area under the steady state plasma NNC0385-0434 concentration−time curve)	From 0 to 24 hours after end of treatment at visit 9 (week 12)	h*nmol/L
$AUC_{0\text{-}\infty,0434,SS}$ (area under the steady state plasma NNC0385-0434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

1.3 Trial design

This is a randomised, multicentre, multinational, seven-armed, parallel group, dose finding trial (Figure 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.

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 in the protocol). The follow-up period for all patients is 7 weeks and 4 days. The total duration for each patient will be approximately 22 weeks.

Figure 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.

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.

We refer to section 4 in the protocol for further information concerning the trial design.

2 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 μ_{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.

3 Sample size determination

We refer to section 9.2 in the protocol for the sample size determination.

4 Analysis sets

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 (five half-lives plus the visit window of the last visit)
    - 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.

5 Statistical analyses

5.1 General considerations

5.1.1 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.

5.2 Subject disposition

Not applicable for this trial.

5.3 Primary endpoint analyses

5.3.1 Definition of 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:

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

5.3.2 Main analytical approach

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 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.

The multiple imputation is done in three steps:

1. Imputation:

a. Intermittent missing values are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the treatment groups separately and 1000 copies of the dataset will be generated.
b. A sequential regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit after baseline and sequentially continuing to the last planned visit at week 12. A model used to impute missing values at each planned visit will be fitted for each of the treatment groups (each NNC0385-0434 dose, evolocumab or pooled placebo) using observed data. 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.

2. Analysis: An ANCOVA with treatment and strata (population strata (inclusion criteria 3a/3b), country (Japan/non-Japan)) as factors and baseline LDL-C as a covariate will be used to analyse LDL-C % change at week 12 for each of the 1000 complete data sets generated as part of the imputation of missing values.

3. Pooling: Rubin's rule will be used to combine the analysis results in order to draw inference.

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.

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 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). 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.

The multiple imputation approach is done in three steps:

1. Imputation: 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. The estimated posterior distribution for the parameters (regression coefficients and variances) in the imputation models are then used to impute missing week 12 LDL-C values. This will be done 1000 times, resulting in 1000 complete data sets.

2. Analysis: Analysis of each of the 1000 complete data sets using the 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, resulting in 1000 estimates for each treatment.

3. Pooling: Rubin's rule will be used to combine the analysis results in order to draw inference.

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

This analysis will evaluate the treatment difference between individual oral NNC0385-0434 doses and s.c. evolocumab using the same analysis as the primary analysis for the primary estimand described above. However, the treatment differences with 95% confidence intervals between oral NNC0385-0434 doses and s.c. evolocumab will be estimated but no confirmatory testing will be carried out.

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 3 will be fit.

Table 3 Dose-response candidate models

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

E_0: the expected effect on LDL-C when treated with placebo, ED_{50}: The dose, which produces half of E_{max}, E_{max}: Maximum effect attributable to the drug, d: NNC0385-0434 dose.

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.

5.3.3 Sensitivity analysis

A sensitivity analysis will evaluate the treatment difference between individual oral NNC0385-0434 doses and placebo using the same analysis as the primary analysis for the primary estimand described above, but with baseline LDL-C not included as a covariate in the model.

5.4 Secondary endpoints analyses

5.4.1 Confirmatory secondary endpoints

Not applicable for this trial.

5.4.2 Supportive secondary endpoints

The following supportive secondary endpoints

- change in total cholesterol
- change in HDL-cholesterol
- change in VLDL-cholesterol
- change in triglycerides
- change in total Apo B
- change in total Apo CIII

are computed similar as the primary endpoint, that is for each of these six lipid/lipoprotein parameters, the percentual change from randomisation at week 0 to week 12 is defined as:

$$\%\ \text{parameter change} = \frac{(\text{parameter value at week 12} - \text{parameter value at baseline})}{\text{parameter value at baseline}} \times 100\%$$

Each of these six endpoints will be analysed separately by 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 parameter value as a covariate.

The parameter Lipoprotein a (Lp(a)) follows a log-normal distribution and will be log-transformed before analysis. The supportive secondary endpoint: Change in total Lp(a) (from baseline (week 0) to visit 9 (week 12)), will be reported as the result of the difference in log-transformed Lp(a) back-transformed to the original scale, implying that log-treatment-differences are reported as treatment ratios. Confidence intervals for the treatment ratios will be calculated as exponential upper and lower limits for log-treatment difference confidence intervals.

Safety endpoints

The secondary endpoint Treatment-emergent adverse events (TEAE) is the number of AEs recorded during the on-treatment period (see section 4 for the definition of the on-treatment period). All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA)

Summaries of TEAEs are presented as an overview including all AEs, serious AEs, AEs leading to withdrawal, AEs by severity, AEs by relation to treatment and outcome of AEs. Furthermore, summary tables based on system organ class and preferred term is made for:

- All TEAEs
- Serious TEAEs
- TEAEs evaluated to be probably or possibly related to the trial products
- TEAEs by severity
- Serious TEAEs evaluated to be probably or possibly related to the trial products

5.5 Exploratory endpoints analysis

5.5.1 PK sub-study exploratory endpoints

Below the exploratory endpoints related to the PK sub-study are defined and the planned analyses are presented.

The following PK endpoints will be derived at steady state from 0 to 24 hours after the last dose of oral NNC0385-0434 on visit 9 (week 12):

- $AUC_{0\text{-}24h,0434,SS}$: area under the steady state plasma NNC0385-0434 concentration−time curve
- $C_{max,0434,SS}$: maximum observed plasma NNC0385-0434 concentration at steady state
- $t_{max,0434,SS}$: time to maximum observed plasma NNC0385-0434 concentration at steady state, in case this is not uniquely determined, the lowest value will be chosen.

The following exploratory endpoint will be derived at steady state after the last dose of oral NNC0385-0434 on visit 9 (week 12):

- $t_{½,0434,SS}$ terminal phase elimination half-life of NNC0385-0434 at steady state

The following exploratory endpoint will be derived from 0 hours to infinity at steady state after the last dose of oral NNC0385-0434 on visit 9 (week 12):

- $AUC_{0\text{-}\infty,0434,SS}$: area under the steady state plasma NNC0385-0434 concentration−time curve

Subjects included in the PK sub-study that discontinue treatment, but will complete visit 9X, will have derived PK endpoints after the last dose of oral NNC0385-0434 on Visit 9X.

The oral NNC0385-0434 PK endpoints will be derived as stated in the table in appendix 6.3.

Each of the PK endpoints will be summarised descriptively by dose level of oral NNC0385-0434 (15, 40 and 100 mg) and country (Japan/non-Japan).

The endpoint $AUC_{0\text{-}24h,0434,SS}$ will be analysed by a linear mixed model based on the log-transformed values. The model will include country (Japan/non-Japan) and dose level of oral NNC0385-0434 (15, 40 and 100 mg) as fixed factors, and the difference between the 2 levels in the country factor will be interpreted as a race difference. The estimated race difference will be transformed back to the original scale and presented as the race ratio with two-sided 95% confidence interval.

A sensitivity analysis using the above model including body weight at baseline as a covariate will also be done.

The same analyses as described above for $AUC_{0\text{-}24h,0434,SS}$ will be performed for $C_{max,0434,SS}$.

5.5.2 NNC0385-0434 concentration and NNC0385-0434 binding antibodies endpoints

Each of the endpoints related to the NNC0385-0434 concentration and the NNC0385-0434 binding antibodies:

- Concentration of NNC0385-0434 at steady state
- Occurrence of NNC0385-0434 binding antibodies
- Occurrence of NNC0385-0434 binding antibodies cross reacting with endogenous counterpart (EGF-A)
- Titre of NNC0385-0434 binding antibodies

will be presented in a listing.

5.6 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.

5.7 Other analyses

Not applicable for this trial.

5.7.1 Other derivations and assessments

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.

5.7.2 Subgroup analyses

Not applicable for this trial.

5.8 Interim analyses

Not applicable for this trial.

5.8.1 Data monitoring committee

Not applicable for this trial.

6 Supporting documentation

6.1 Appendix 1: List of abbreviations

AE *adverse event*

ANCOVA *analysis of covariance*

CTR *clinical trial report*

FAS *full analysis set*

MedDRA *Medical Dictionary for Regulatory Activities*

PK *pharmacokinetics*

SAP *statistical analysis plan*

SAS *safety analysis set*

TEAE *treatment emergent adverse event*

6.2 Appendix 2: Changes to protocol-planned analyses

There are no changes to the analyses as described in the protocol.

6.3 Appendix 3: Definition and calculation of endpoints, assessments and derivations

Type	***Title***	***Time frame***	***Unit***	***Details***
Primary endpoint	Change in LDL-cholesterol	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(LDL-C at week 12 – LDL-C at baseline)}}{\text{LDL-C at baseline}} \times 100\%$
Supportive secondary endpoint	Change in total cholesterol	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(total-C at week 12 – total- C at baseline)}}{\text{total- C at baseline}} \times 100\%$
Supportive secondary endpoint	Change in HDL-cholesterol	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(HDL-C at week 12 – HDL-C at baseline)}}{\text{HDL-C at baseline}} \times 100\%$
Supportive secondary endpoint	Change in VLDL-cholesterol	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(VLDL-C at week 12 –VLDL-C at baseline)}}{\text{VLDL-C at baseline}} \times 100\%$
Supportive secondary endpoint	Change in triglycerides	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(triglycerides week 12 – triglycerides baseline)}}{\text{triglycerides baseline}} \times 100\%$
Supportive secondary endpoint	Change in total Apo B	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(Apo-B at week 12 – Apo-B at baseline)}}{\text{Apo-B-C at baseline}} \times 100\%$
Supportive secondary endpoint	Change in total Apo CIII	From baseline (week 0) to visit 9 (week 12)	%	$\frac{\text{(Apo-CIII at week 12 – Apo-CIII at baseline)}}{\text{Apo-CIII at baseline}} \times 100\%$
Supportive secondary endpoint	Change in total Lp(a)	From baseline (week 0) to visit 9 (week 12)	Ratio	$\frac{\text{Lp(a) at week 12}}{\text{Lp(a) at baseline}}$

Type	*Title*	*Time frame*	*Unit*	*Details*
Supportive secondary endpoint	Treatment-emergent adverse events	From baseline (week 0) to visit 10 (19 weeks + 4 days)	Number of events	The secondary endpoint Treatment-emergent adverse events (TEAE) is the number of AEs recorded during the on-treatment period.

Type	*Title*	*Time frame*	*Unit*	*Details*
Explorative endpoint	Concentration of NNC0385-0434 at steady state	From visit 7 (week 6) to visit 9 (week 12)	nmol/L	Not applicable.
Explorative endpoint	Occurrence of NNC0385-0434 binding antibodies	From baseline (week 0) to visit 10 (19 weeks + 4 days)	Yes/no	Not applicable.
Explorative endpoint	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	Not applicable.
Explorative endpoint	Titre of NNC0385-0434 binding antibodies	From baseline (week 0) to visit 10 (19 weeks + 4 days)	No unit	Not applicable.

PK sub-study endpoints

Type	*Title*	*Time frame*	*Unit*	*Details*
Explorative endpoint	$AUC_{0\text{-}24h,0434,SS}$ (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	Calculated using the linear trapezoidal method based on observed values and actual measurement times. If the last quantifiable sample occurs before 24 hours, then the first value after this last quantifiable sample will be set to lower limit of quantification (LLOQ)/2 and the following to 0.
Explorative endpoint	$AUC_{0\text{-}\infty,0434,SS}$ (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	Derived as the sum of two areas; namely the area under the curve from time zero (time of dosing) to the time of the last quantifiable concentration measurement of NNC0385-0434 and the area under the curve from the time of the last quantifiable concentration measurement to infinity. The first area will be approximated using the linear trapezoidal technique on the observed concentrations of NNC0385-0434 using actual time points. The second area will be estimated as the ratio of the predicted concentration at the time of the last quantifiable observation to the estimated elimination rate constant λ_z, with the elimination rate constant λ_z estimated as defined below in relation to calculating $t_{½,0434,SS}$
Explorative endpoint	$C_{max,0434,SS}$ (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	The maximum of all valid concentrations of NNC0385-0434 at steady state, from nominal time 0 to 24 hours.

Type	***Title***	***Time frame***	***Unit***	***Details***
Explorative endpoint	$t_{max,0434,SS}$ (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	The actual time to $C_{max,0434,SS}$, in case this is not uniquely determined, the lowest value will be chosen.
Explorative endpoint	$t_{½,0434,SS}$ (terminal phase elimination half-life of NNC0385-0434 at steady state)	After end of treatment at visit 9 (week 12)	Hours	Calculated as $t_{½,0434,SS}=\log(2)/\lambda_z$ where λ_z is the elimination rate constant estimated as the negative of the slope of a log-linear regression on the terminal part of the NNC0385-0434 concentration-time curve using at least three observations above LLOQ. If deemed relevant the estimation of λ_z will take observations below LLOQ into account and use them as interval censored observations