**Official Title:** Two Part (Double-blind Inclisiran Versus Placebo [Year 1] Followed by Open-label Inclisiran [Year 2]) Randomized Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Inclisiran in Adolescents (12 to Less Than 18 Years) With Homozygous Familial Hypercholesterolemia and Elevated LDL-cholesterol (ORION-13)

**NCT Number:** NCT04659863

**Document Date:** Statistical Analysis Plan (Amendment 4): 20-Nov-2024

# Appendix 16.1.9 Documentation of statistical methods

| History of changes | |
|---|---|
| **Version** | **Summary of changes** |
| 1.0 | Original version |

## 1 Statistical methods

The most recent version of Statistical Analysis Plan (SAP) is included below.

NOVARTIS

Clinical Development

KJX839/inclisiran

CKJX839C12302 / NCT04659863

# Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-13)

Statistical Analysis Plan (SAP)

| | |
|---|---|
| Author: | Trial statistician |
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| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
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| [redacted] | | | | |

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| **20-Nov-2024 Amendment 4** | **Prior to final DB lock** | **Reason for update** | **Outcome for update** | **Section impacted** |

[redacted]

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| [redacted] | | | | |

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## List of abbreviations

| | |
|---|---|
| ADA | Anti-drug antibodies |
| AE(s) | Adverse event(s) |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| Apo A1 | Apolipoprotein A1 |
| Apo B | Apolipoprotein B |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| [redacted] | [redacted] |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| DBP | Diastolic Blood Pressure |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| eGFR | Estimated glomerular filtration rate |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | Full Analysis Set |
| FH | Familial Hypercholesterolemia |
| HbA1c | Hemoglobin A1c |
| HDL-C | High density lipoprotein cholesterol |
| HoFH | Homozygous Familial Hypercholesterolemia |
| ISR | Injection site reaction |
| LDL | Low density lipoprotein |
| LDL-C | Low density lipoprotein cholesterol |
| LFT(s) | Liver function test(s) |
| LLOQ | Lower limit of quantification |
| Lp(a) | Lipoprotein (a) |
| MMRM | Mixed-effect model for repeated measures |
| OAS | Open-label Phase Analysis Set |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PT | Preferred term |
| s.c. | Subcutaneous |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SCR | Screened set |
| SD | Standard deviation |
| SOC | System Organ Class |

| | |
|---|---|
| TEAE | Treatment emergent adverse event |
| ULN | Upper limit of normal |
| WBC | White blood cell(s) |

# 1 Introduction

This document contains details of the statistical methods that will be used in the Phase 3 clinical trial CKJX839C12302 (ORION-13). The purpose of this Phase 3 study is to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (aged 12 to <18 years) with homozygous familial hypercholesterolemia HoFH and elevated LDL-C (LDL-C >130 mg/dL (3.4 mmol/L)). The use of inclisiran (as an adjunct to stable, optimal background lipid-lowering therapy) for the treatment of HoFH in adolescent patients who require additional lipid-lowering will be investigated to obtain needed pediatric information on inclisiran. Percentage change in LDL-C from baseline to Day 330 (Year 1) is the primary endpoint of this study.

The analysis plan has been prepared based on the ORION-13 study protocol version V02 (protocol amendment 2), content final dated 17-Feb-2023.

Important information is given in the following sections and details are provided, as applicable, in Section 5.

## 1.1 Study design

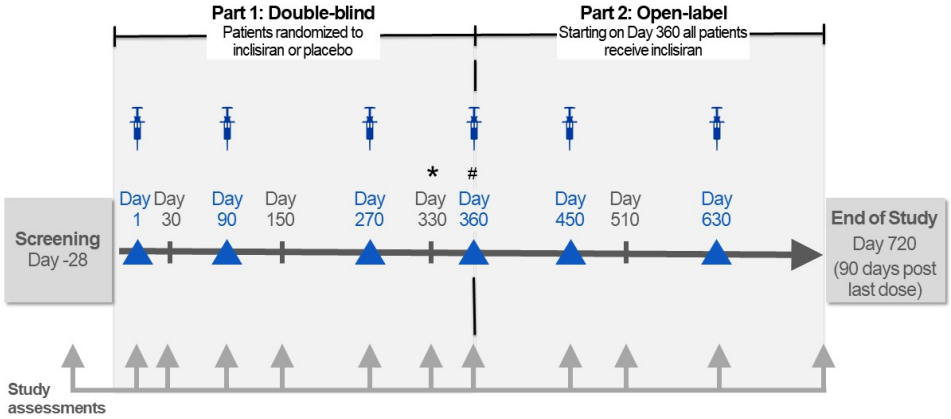
This study is a two-part (double-blind, placebo-controlled / open-label) multicenter study in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C (>130 mg/dL / 3.4 mmol/L) on stable, individualized, optimal SoC background lipid-lowering therapy (including maximally tolerated statin treatment). The overall study duration is 748 days.

Following an approximately 4 weeks screening/run-in period, the study has two sequential parts (Figure 1-1).

- **Part 1 (Year 1):** 12 months double-blind, parallel group period in which participants will be randomized to receive either inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) s.c. or placebo (given at Days 1, 90 and 270).
- **Part 2 (Year 2):** 12 months single arm, open-label follow-up period with all participants receiving inclisiran sodium 300 mg s.c. Participants randomized to placebo in Part 1 will receive inclisiran starting on Day 360 (“Switch” Day 360). Participants randomized to inclisiran in Part 1 will receive placebo on Day 360. This dose of inclisiran/placebo on Day 360 will remain blinded to maintain the blind for Part 1 of the study. All participants will receive subsequent doses of open label inclisiran on Days 450 and 630.

Approximately 12 participants who meet the inclusion/exclusion criteria were to be randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg s.c. or placebo on Day 1 (baseline). Information regarding sample size calculation is provided in Section 3.

**Figure 1-1 Study design**




* Primary endpoint assessed at Day 330. # "Switch Day": Participants randomized to placebo in Part 1 will start to receive inclisiran on Day 360. Participants randomized to inclisiran in Part 1 will receive placebo on Day 360 only to maintain the blind for Part 1.

The primary endpoint will be measured at Day 330.

## 1.2 Study objectives and endpoints

Section 2 of the study protocol lists the following primary, secondary, [redacted] objectives.

**Table 1-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • The primary objective is to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C | • Percentage change in LDL-C from baseline to Day 330 (Year 1) |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • Evaluate the effect of inclisiran compared to placebo on reducing LDL-C [time-adjusted percent change] over Year 1 | • Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1) |
| • Evaluate the effect of inclisiran compared to placebo (for Year 1) and | • Percent change and absolute change in LDL-C, Apo B, lipoprotein (a) [Lp(a)], non-high density |

| Objective(s) | Endpoint(s) |
|---|---|
| long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and PCSK9 over time | lipoprotein cholesterol (non-HDL-C), total cholesterol, triglycerides, HDL-C, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo A1) and PCSK9 from baseline to each assessment time up to Day 720 (Year 2) |
| • Evaluate the safety and tolerability of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HoFH | • Incidence, severity and relationship to study drug of treatment-emergent AEs and SAEs; vital signs; laboratory parameters; anti-drug antibodies (ADA) measurement; growth (height, weight, BMI); pubertal development (steroid hormones and Tanner staging) |

[redacted]

# 2 Statistical methods

## 2.1 Data analysis general information

All analyses will be performed by Novartis. The most recent version of SAS available in the statistical programming environment of Novartis will be used for the analysis.
Part 1 data are defined as all data collected starting from screening visit up to the day 360 visit date prior to dosing day/date. Part 1 data will be presented by two separate groups (inclisiran

and placebo). The total column will be presented in all outputs of Part 1 as needed and will be specified in TFL shell document.

Part 2 data are defined as all data collected starting from after dosing on day 360. Part 2 data will be presented in two separate groups, (1) inclisiran since Day 1 and (2) placebo-to-inclisiran, unless otherwise specified. The column labels for these two groups will be inclisiran-inclisiran and placebo-inclisiran. The total column will be presented in all outputs of Part 2 as needed and will be specified in TFL shell document.

For instances, where it will not be possible to distinguish whether data belong to Part 1 or Part 2, based on the dosing time on the day 360 visit, all data collected from screening up to the day 360 visit will be considered as Part 1 data and all data captured after the day 360 visit (starting from day 360 visit + 1 day) will be considered as Part 2.

Part 1 data analysis will be performed after all participants completed the day 360 visit (Part 1) or discontinued the study prior to the Day 360 visit. For each participant data, collected in the database till the end of study Part 1 (up-to Day 360 visit as mentioned above) will be included in this analysis. Hence Day 360 visit of a participant will serve as data cut-off date for that participant. All events with start date before or on the cut-off date and for which the end date has not been reached yet or they are ongoing at final visit will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having a documented end date. The assessment of study primary objective and key secondary objectives will be based on this analysis.

Part 2 analysis will be conducted after all participants either completed the study or discontinued early.

Both Part 1 and Part 2 analyses will be reported in CSR. For summary of the analyses that will be performed for Part 1 analysis and Part 2 analysis see Appendix 5.3.

Detailed information regarding DMC analysis will be provided in the DMC charter and a separate DMC SAP/TFL shells.

### 2.1.1 General definitions

#### Study Day

Study day will be defined as the number of days since the date of first dose of double-blind treatment. The date of first dose of double-blind treatment will be defined as Day 1 and the day before the first dose of study drug will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

For dates on or after the first date of double-blind treatment,

Study day = Assessment date – Date of first dose of double-blind treatment + 1;

For dates prior to the first date of double-blind treatment,

Study day = Assessment date – Date of first dose of double-blind treatment.

In case, participant has been randomized but has not received double-blind treatment then randomization visit day will be considered as Day 1.

### Baseline definition

In general, for both Part 1 and Part 2, baseline value is defined as the last measurement collected on or prior to the first dose of double-blind treatment.

### Post-baseline measurement

Post-baseline values are defined as those measurements that were collected after the first dose of double-blind treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Absolute change from baseline = post-baseline value – baseline value.

Percent change from baseline = (post-baseline value – baseline value) / baseline value*100.

### LDL-C to be used in analysis

The endpoints involving LDL-C will use the beta quantification (ultracentrifugation) LDL-C for all subjects. In cases where beta quantification (ultracentrifugation) LDL-C values are missing and calculated LDL-C is available, the calculated LDL-C will be used for analysis purposes.

### VLDL-C

The endpoints involving VLDL-C will use the beta quantification (ultracentrifugation) VLDL-C for all subjects. In cases where beta quantification (ultracentrifugation) VLDL-C values are missing and calculated VLDL-C is available, the calculated VLDL-C will be used for analysis purposes.

### Discontinuation visit mapping

For patients who discontinued the study and come to site for an early exit (EE) visit, the EE visit will be mapped to the next scheduled visit. The mapping details can be found as below:

**Table 2-1 Visit mapping**

| Status | Last attended scheduled visit prior to EE | | Mapped visit for EE | |
|---|---|---|---|---|
| Visit day | Visit name | Visit day | Visit name | Visit day |
| Discontinued (Early exit) | 1 | Day 1 | 90 | Day 90 |
| Discontinued (Early exit) | 90 | Day 90 | 150 | Day 150 |
| Discontinued (Early exit) | 150 | Day 150 | 270 | Day 270 |

| | | | | |
|---|---|---|---|---|
| Discontinued (Early exit) | 270 | Day 270 | 330 | Day 330 |
| Discontinued (Early exit) | 330 | Day 330 | 360 | Day 360 |
| Discontinued (Early exit) | 360 | Day 360 | 450 | Day 450 |
| Discontinued (Early exit) | 450 | Day 450 | 510 | Day 510 |
| Discontinued (Early exit) | 510 | Day 510 | 630 | Day 630 |
| Discontinued (Early exit) | 630 | Day 630 | 720 | Day 720 |
| Completed | | | 720 | Day 720 |

## 2.2 Analysis sets

**The Screened Set (SCR)** includes all participants who provided study informed consent.

**The Randomized Set (RAN)** consists of all participants who received a randomization number, regardless of whether double blind treatment received or not.

**The Full Analysis Set (FAS)** consists of all randomized participants with the exception of those mis-randomized participants who did not receive study drug. Mis-randomized participants are defined as not qualified for randomization and were inadvertently randomized into the study. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. The FAS will be used in analyses for the primary, secondary, [redacted] efficacy objectives in Part 1.

**The Safety Set (SAF)** includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received. This will be the primary population for the safety analyses in Part 1.

Note that the Safety Set allows the inclusion of non-randomized participants who receive double-blind treatment in error.

**The Open-label Phase Analysis Set (OAS)** includes all participants who entered in study Part 2 and received at least one dose of study treatment in Part 2. The OAS will be used to analyze the data from participants who entered Part 2.

Note that in Part 1 the number of participants in FAS equals the number of participants in SAF, so only one open-label phase analysis set is defined for Part 2.

[redacted]

### 2.2.1 Subgroup of interest

No sub-group analysis will be performed.

## 2.3 Disposition, demographics and other baseline characteristics

### 2.3.1 Disposition

The overall number of participants who entered, completed, and discontinued the study will be summarized and listed, including the reasons for discontinuation for each period: screening, Study Part 1, Study Part 2. The screening disposition will be based on SCR. The RAN will be used for the summary and listing of patient disposition for Study Part 1 and 2.

The number of participants in the FAS will be summarized by country, center, and treatment group for Part1 analysis.

Number of participants with protocol deviations will be tabulated by category (e.g., selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other), deviation and Part. Listing of participants with protocol deviation will be provided.

The number of participants included in each analysis set will be tabulated using SCR.

### 2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including age, race, gender, ethnicity, country, region (North America, Europe, Other), baseline characteristics such as body height, weight, BMI, waist circumference, smoking status, number of pack years, alcohol history, baseline disease characteristics including HoFH underlying genetic mutation(s), LDL-C, TC (total cholesterol), TG (triglycerides), PCSK9, baseline use of statins or other lipid-modifying therapies (yes, no), status of statin intolerance, baseline diabetes status as determined by fasting plasma glucose and $HbA_{1C}$, baseline kidney function based on eGFR, baseline SBP, DBP, pulse will be summarized descriptively by treatment group. Listings will also be provided.

Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, non-missing observations, mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum will be presented. For Part 1 analysis, these data will be summarized using RAN.

No inferential statistics will be provided for baseline comparability among the treatment groups.

### 2.3.3 Medical history/current medical condition

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. Medical history/conditions will be summarized by primary system organ class and preferred term, treatment group. Pre-specified solicited events selected Familial Hypercholesterolemia History and other targeted family history will be summarized separately by treatment.

For Part 1 analysis, this data will be summarized using RAN.

## 2.4 Treatments (study treatment, prior and concomitant therapies)

In general, all summaries of treatments of Part 1 will be performed on the SAF and all summaries of treatments of Part 2 will be performed on the OAS.

### 2.4.1 Study treatment

The number of study doses administered, duration on study, duration of exposure, patient year of exposure will be summarized by treatment group and Part. The analysis of exposure will also be provided for overall i.e., Part 1 and 2 data combined. Listings will be provided.

The number of participants dosed, and the injection site location will also be summarized by the study visit and treatment group.

Duration of exposure will be calculated as: minimum of (Date of last dose of treatment – Date of first dose of treatment + 180 + 1, Date of last known visit – Date of first dose of treatment + 1). For Part 1 data analysis, duration of exposure will be truncated at data cut-off date.

Patient-year of exposure will be calculated as duration of exposure/365.25.

Duration on study is defined as: date of last known visit on study – date of first dose of treatment + 1. For Part 1 data analysis, duration on study will be truncated at data cut-off date.

The patients who will discontinue the treatment prematurely before discontinuing the treatment period will be summarized by treatment group and Part, including the reason for treatment discontinuation. Listing will also be provided.

### 2.4.2 Prior, concomitant and post therapies

Prior (pre- baseline, defined as any medication that was stopped ≥1 day before first dose date of study medication) medication will be summarized by treatment and concomitant (Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit, including those which were started pre-baseline and continued into the period when study treatment is administered) medications will be summarized by treatment group and Part. Listings will be provided.

Lipid-modifying therapy (LMT) use, [redacted] will be summarized separately at screening and at the baseline/Randomization visit (Day 1) by treatment group using the following categories:

- Any LMT
- No LMT
- Statins
- Statins only
- Other LMT
- Other LMT only
- Ezetimibe
- Ezetimibe only

[redacted]

New or changed lipid-modifying therapy, [redacted] after baseline will be summarized by treatment group and Part.

Significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and preferred term, by treatment group and Part. Significant non-drug therapies will be summarized similarly by primary system organ class, preferred term, treatment group and Part.

## 2.5 Analysis of the primary objective

The primary objective is to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C.

### 2.5.1 Primary endpoint

The primary endpoint i.e., primary analysis variable is the percentage change in LDL-C from the baseline measurement to the Day 330 visit.

The primary clinical question of interest is: What is the effect of the test treatment versus placebo on change in LDL-C after 330 days of treatment in adolescents with HoFH and elevated LDL-C who are on stable, optimal standard of care (SoC) lipid-lowering therapy, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid-lowering therapy.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of changes in additional medication(s) used for HoFH, if they occur, as would be the case in clinical practice.

The primary estimand is described by the following attributes:

- **Population**: Adolescents with the HoFH condition of interest and elevated LDL-C on stable optimal SoC lipid-lowering therapy. Further details about the population are provided in Section 5 of the study protocol.
- **Endpoint**: Percentage change in LDL-C from baseline to Day 330 (Year 1)
- **Treatment of interest**: The randomized treatment (the investigational treatment inclisiran or the control treatment placebo) as add-on to optimal SoC lipid-lowering therapy for HoFH. The type and dose of the concomitant lipid-lowering therapy for HoFH must remain stable during Part 1 (Year 1) of the study. Further details about the investigational treatment and control treatment are provided in Section 6 of the study protocol. Data collected regardless of treatment discontinuation for any reason, regardless of unforeseen change in the concomitant lipid-lowering therapy will be used for analysis [treatment policy].
- **The summary measure**: difference between treatments in mean percentage change at Day 330.

### 2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will summarize change from baseline using summary statistics to characterize change from baseline in LDL-C by treatment group and the difference between treatment groups along with 95% CI at the Day 330 time point. No formal hypothesis testing is

planned. The individual patients' data on the percentage change in LDL-C from baseline at Day 330 will be listed and depicted by waterfall plots.

### 2.5.3 Handling of remaining intercurrent events of primary estimands

No remaining intercurrent events are expected.

### 2.5.4 Handling of missing values not related to intercurrent event

The primary endpoint will not have missing data imputed. Only data from the Day 330 visit time point and baseline data needed to evaluate change from baseline in LDL-C will be included in the primary analysis.

### 2.5.5 Sensitivity analyses for primary endpoint/estimand

Since the sample size is small, in case of sparse data, median percentage change from baseline to Day 330 in LDL-C will be considered.

### 2.5.6 Supplementary analysis

A linear mixed-effects model for repeated measures (MMRM) analysis will be used as a covariate-adjusted analysis of the difference in percent change from baseline to Day 330 in LDL-C. The MMRM will include fixed effects for treatment, baseline age group (≥12-<15 or ≥15-<18 years of age), visits, interaction between treatment and visits, and baseline LDL-C as covariates. Day 90, 150, 270, 330 and 360 will be included as visit. The Restricted Maximum Likelihood (REML) estimation approach will be used with covariance structure set as "Unstructured". If the model does not converge with unstructured covariance matrix, the compound symmetry covariance matrix will be used in the mixed model. Two-sided 95% confidence intervals for the difference between treatment groups will be provided.

The above supplementary analysis was planned but will not be performed due to the small sample size in the placebo group.

[redacted] Summary statistics by treatment groups and treatment difference along with 95% CI will be provided.

## 2.6 Analysis of the secondary objectives

### 2.6.1 Secondary endpoints

Secondary efficacy endpoints include:

- Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1), defined as the average of percent changes from baseline to day 150, 270, and 330.
- Percent change and absolute change in LDL-C，Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, VLDL-C, Apo A1, and PCSK9 from baseline to each assessment time up to Day 720 (Year 2)

### 2.6.2 Statistical hypothesis, model, and method of analysis

Descriptive summaries by treatment group will be presented for all secondary endpoints. Additionally, mean treatment difference and associated 95% CI will be provided for time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330, for absolute change in LDL-C at Day 330 and for percentage change in Apo B, Lp(a), non-HCL-C, total cholesterol and PCSK9 at Day 330. No formal hypothesis testing will be performed. Summaries of LDL-C by treatment, visit and subject will be additionally presented. Listings will be provided.

### 2.6.3 Sensitivity analyses for secondary endpoint/estimand

Since the sample size is small, in case of sparse data, median percentage change from baseline to Day 330 will be considered.

### 2.6.4 Supplementary analysis

[redacted] Summary statistics by treatment groups and treatment difference will be provided for time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330 and for percentage change in Apo B, non-HCL-C, total cholesterol and PCSK9 at Day 330 and Day 720.

## 2.7 Safety analyses

In general, for Part 1 safety analyses, the SAF will be used; for Part 2 safety analysis, the OAS will be used.

Safety summaries will include only treatment emergent adverse events (TEAEs) by Part. For Part 1, TEAEs are adverse events (AEs) that started on or after the first dose of double-blind treatment or adverse events (AEs) that were present prior to start of double-blind treatment but increased in severity in Part 1. For Part 2, TEAEs are defined as AEs starting after the Day 360 dosing time or AEs that were present prior to the Day 360 dosing time but increased in severity in Part 2. For Part 1, if the AE start date is the same as the date of the first dose of double-blind treatment but the time is not available for comparison, the AE will be considered as treatment emergent; for Part 2, if the AE start date is the same as the date of the Day 360 treatment but the time is not available for comparison, the AE will be considered as treatment emergent

Vital signs values that have complete data and time values will be assigned to pre- or post-dose assessment (as per protocol) based on the actual date/time. For values with missing date/time, the scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by visit/time point summary.

### 2.7.1 Adverse events (AEs)

The number (and percentage) of participants with TEAEs will be summarized by Part in the following ways:

- Overall summary.

- By treatment, primary system organ class (SOC) and preferred term (PT).
- By treatment and PT.
- By treatment and PT for most common TEAEs (For Part 1: occurring in >=15% in total; for Part 2: threshold to be determined before final database lock)
- By treatment, SOC, PT, and maximum severity.
- By treatment, SOC, and PT for TEAEs leading to study drug discontinuation.
- By treatment, SOC, and PT for TEAEs related to study drug.

The number (and percentage) of participants with treatment emergent serious adverse events (TESAEs) will be summarized by Part in the following ways:

- By treatment, SOC, and PT.
- By treatment and PT.
- By treatment, SOC, and PT for TESAEs related to study drug.

Unless otherwise specified, SOCs will be sorted alphabetically and, within each SOC, the PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one AE with the same PT, the AE will be counted only once. A participant with multiple AEs within a SOC is only counted once towards the total of the SOC. In case of summary by severity or relationship to study drug, summary will be done using the most severe or related occurrence respectively. Listing of all AEs and SAEs will be provided.

### AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than X% (X will be selected prior to database lock) and on TEAEs and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term for on the Safety Set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

These summaries will be provided after full study completion.

### Injection site reactions

The number and percentage of participants who reported injection site reaction TEAEs will be summarized in the following ways:

- SOC, PT, treatment group and Part.
- SOC, PT, severity, treatment group and Part.

Listing will be provided for participants with injection site reactions.

The time to the first injection site reaction will also be summarized by treatment and Part using the following categories: ≤4h, 4h to ≤12h, >12h. The time (hours) to the event will be calculated from the most recent administration of study drug. The duration of the first and the longest injection site reaction will be summarized by treatment and Part using descriptive statistics. The outcome of the first and the longest injection site reaction will be summarized using the following categories: Resolved (≤4h, >4h to ≤7 days, >7 days to ≤14 days >14 days), not resolved and unknown. The total number of injection site reactions per participants will be summarized in categories (e.g., 1, 2, 3, and >3 etc.). Symptoms of injection site reactions will be summarized by treatment group and Part.

### Other safety topics

The number and percentage of participants who reported TEAEs of other safety topics will be summarized by PT, treatment group and Part. PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one AE within the same PT, the AE will be counted only once. If a participant reported more than one AE within the same safety topic, the participant will be counted only once at that safety topic. Listings of participants with AEs of other safety topics will be provided.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of other safety topics.

AEs of other safety topics will include the following:

- Hepatic events
- Renal events
- Hypersensitivity events
- Neurological events
- Psychiatric events
- Musculoskeletal events
- Cardiac events
- New onset diabetes and worsening of glycemic control

For search criteria of AEs of other safety topics, refer to Appendix 5.4.

For detailed analysis of new onset diabetes and worsening of glycemic control, please see Section 2.7.4. Any immune-related events will be identified in the SOC of immune system disorders.

The percentage of participants with abnormal ECG findings reported as AEs will be summarized by treatment group and Part.

### 2.7.2 Deaths

Summary for deaths will be provided by SOC and PT of cause of death, treatment group, and Part. Listing of all deaths will be provided.

### 2.7.3 Laboratory data

Laboratory data consist of hematology, biochemistry, sexual hormones, urinalysis measurements and ADA (see Section 2.7.6 ). Absolute values and change from baseline will be summarized for continuous laboratory parameters by visit and box plots will also be provided by visit. Frequency table of results for categorical laboratory parameters will be presented by visit. This analysis will be performed by treatment group and Part.

Shift tables using the low, normal, high/low, or high classification (except for eGFR and HbA1c where the categories outlined below are applied) will be used to compare baseline to the worst on-treatment value by treatment group and Part. All data collected from scheduled, unscheduled and premature discontinuation visits in each part will be used to determine the worst on-treatment value.

The following categories will be used for eGFR and HbA1c:

- For eGFR, the categories will be = <30 mL/min/1.73m2; = ≥ 30 to <60 mL/min/1.73m2; = ≥ 60 to <90 mL/min/1.73m2; and = ≥90 mL/min/1.73m2.
- For HbA1c, the categories will be <5.7%, ≥5.7% to <6.5%, and ≥6.5%.

The shift table dealing with the fasting plasma glucose parameter will require the lab sample to be taken fasting. Samples taken while the subjects were not fasted will not be analyzed.

For selected laboratory tests, the number and percentage of patients meeting the clinically notable criteria at any time, considering all data collected after first dose of double-blind treatment, from scheduled, unscheduled and premature discontinuation visits, will be summarized by laboratory parameter and treatment group and Part. The worst post-baseline value will be used for this analysis. Notable criteria are defined in Appendix 5.5. Clinically notable criteria will be considered met when both of the following occur:

- Post-baseline value meets the clinically notable criteria.
- Baseline value does not meet the clinically notable criteria.

Furthermore, the number and percentage of participants meeting notable criteria in liver function tests (LFT) will be summarized by treatment and Part considering on-treatment data from scheduled, unscheduled and premature discontinuation visits. LFT criteria are defined in Appendix 5.5.

The baseline value is the last value prior to the first dose of double-blind treatment.

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available, abnormalities will be flagged.

### 2.7.4 Diabetes assessment

Diabetes will be assessed by the analysis of:

- TEAEs
- Change in glucose-related laboratory values over time
- Shifts from baseline in glucose control category and
- Incidence of post-baseline new onset of diabetes

Note that diabetes related tables dealing with the fasting plasma glucose parameter will require the lab sample to be taken fasting. Samples taken while the subject was not fasted will not be analyzed.

Unless otherwise specified, baseline of fasting plasma glucose will be defined as the average of Screening and Day 1 assessments. If one fasting plasma glucose value is missing (Screening or Day 1), the baseline will be based on the available data. For HbA1c, the Day 1 assessment will be considered as baseline. If missing, then the baseline will be based on the assessment at screening.

#### Diabetes TEAE

New onset/worsening of diabetes will be identified by the search criteria specified in Appendix 5.4. The analysis will be performed for all subjects and then by baseline diabetes status. A participant will be identified as being diabetic at baseline if the medical history notes that the subject is diabetic or the baseline HbA1c value is ≥ 6.5% or the baseline fasting plasma glucose is ≥126 mg/dL. This summary will be provided by treatment and Part.

#### Change in Glucose-related Laboratory Values over Time

This analysis only utilizes laboratory data (fasting plasma glucose and HbA1c). The change from baseline to the last on-treatment observation and the worst on-treatment observation will be summarized by treatment and Part, separately for fasting plasma glucose and HbA1c for all participants and then by baseline glucose control status. Baseline glucose control status will be identified separately for fasting plasma glucose and HbA1c using the values provided in the table below (note that medical history will not be considered for this analysis). Figures will also be created showing change in mean fasting plasma glucose and HbA1c values over time by baseline glucose control status.

| Parameter | Baseline Glucose Control Status (Laboratory Values) |
|---|---|
| Fasting Plasma Glucose | <100 mg/dL |
| | ≥100 to <126 mg/dL |
| | ≥126 mg/dL |
| HbA1c | <5.7% |
| | ≥5.7 to <6.5% |
| | ≥6.5% |

### Shifts from Baseline in Glucose Control Category

Shifts from baseline in glucose control category will be summarized by treatment and Part in two different ways. The change from baseline to the worst-on-treatment and the last-on-treatment laboratory values will be used to classify the on-treatment glucose control category. Medical history will not be considered for this analysis.

| Shift Category* | Baseline Category | Post-baseline Category** |
|---|---|---|
| Normal to Normal (no change) | Fasting plasma glucose <100 mg/dL<br>AND<br>HbA1c <5.7% | Fasting plasma glucose <100 mg/dL on two consecutive occasions<br>AND<br>HbA1c <5.7% |
| Normal to Impaired | Fasting plasma glucose <100 mg/dL<br>AND<br>HbA1c <5.7% | Fasting plasma glucose ≥100 and <126 mg/dL on two consecutive occasions<br>OR<br>HbA1c ≥5.7 and <6.5% |
| Normal to Diabetes | Fasting plasma glucose <100 mg/dL<br>AND<br>HbA1c <5.7% | Fasting plasma glucose ≥126 mg/dL on two consecutive occasions<br>OR<br>HbA1c ≥6.5% |
| Impaired to Normal | Fasting plasma glucose ≥100 and <126 mg/dL<br>OR<br>HbA1c ≥5.7 and <6.5% | Fasting plasma glucose <100 mg/dL on two consecutive occasions<br>AND<br>HbA1c <5.7% |
| Impaired to Impaired (no change) | Fasting plasma glucose ≥100 and <126 mg/dL<br>OR<br>HbA1c ≥5.7 and <6.5% | Fasting plasma glucose ≥100 and <126 mg/dL on two consecutive occasions<br>OR<br>HbA1c ≥5.7 and <6.5% |
| Impaired to Diabetes | Fasting plasma glucose ≥100 and <126 mg/dL<br>OR<br>HbA1c ≥5.7 and <6.5% | Fasting plasma glucose ≥126 mg/dL on two consecutive occasions<br>OR<br>HbA1c ≥6.5% |
| Diabetes to Normal | Fasting plasma glucose ≥126 mg/dL<br>OR<br>HbA1c ≥6.5% | Fasting plasma glucose <100 mg/dL on two consecutive occasions<br>AND<br>HbA1c <5.7% |

| | | |
|---|---|---|
| Diabetes to Impaired | Fasting plasma glucose ≥126 mg/dL<br>OR<br>HbA1c ≥6.5% | Fasting plasma glucose ≥100 and <126 mg/dL on two consecutive occasions<br>OR<br>HbA1c ≥5.7 and <6.5% |
| Diabetes to Diabetes (no change) | Fasting plasma glucose ≥126 mg/dL<br>OR<br>HbA1c ≥6.5% | Fasting plasma glucose ≥126 mg/dL two consecutive occasions<br>OR<br>HbA1c ≥6.5% |

*No change (Normal to Normal, Impaired to Impaired, and Diabetes to Diabetes), worsened

(Normal to Impaired, Normal to Diabetes, and Impaired to Diabetes), and Improved (Impaired to Normal, Diabetes to Impaired, and Diabetes to Normal) categories will also be summarized.

***For post-baseline categories, if the post-baseline two consecutive fasting plasma glucose measurements fall in separate categories, or if only one post-baseline fasting plasma glucose measurement is available, then the post-baseline glucose control category will be defined based on the HbA1c measurement only. If HbA1c value is missing and two consecutive fasting plasma glucose measurements fall in separate categories, the lower category will be used to determine the post-baseline category.

### Incidence of Post-baseline New-Onset of Diabetes

The number of participants who shift from no diabetes at baseline to post-baseline new onset of diabetes will be summarized.

The participants with no diabetes at baseline are those who had no medical history of diabetes in the medical history CRFs, had baseline HbA1c <6.5%, and had baseline fasting plasma glucose <126 mg/dL prior to the start of study treatment.

A 4-component analysis will be utilized to detect post-baseline new onset of diabetes. The 4 components are provided below:

- Diabetic TEAEs identified by the SMQ search (see Section 5.4), or
- Post-baseline fasting plasma glucose ≥126 mg/dL on two consecutive occasions, or
- Initiation of anti-diabetic medication at any time post-baseline, or
- At least one post-baseline HbA1c ≥6.5%.

The number of participants who have any of the 4 components will be summarized (post-baseline new onset of diabetes) by treatment and Part.

This analysis will be performed separately for participants who had normal and impaired glucose control categories at baseline.

- Subjects with normal glucose control status at baseline are those with all the following:
  - No medical history of diabetes.
  - HbA1c < 5.7% AND fasting plasma glucose < 100 mg/dL at baseline.

- Subjects with impaired glucose control status at baseline are those with all the following:
  - No medical history of diabetes.
  - HbA1c ≥5.7% and <6.5% (and fasting plasma glucose <126 mg/dL) OR fasting plasma glucose ≥100 mg/dL and <126 mg/dL (and HbA1c <6.5%) at baseline.

The time to new-onset diabetes will also be summarized by treatment and Part. Only participants without diabetes at baseline will be included in the analysis. The time (weeks) to new-onset diabetes will be calculated from the date of the first administration of study drug.

### 2.7.5 Vital signs

Absolute values and change from baseline will be summarized for vital sign parameters by visit, time-point, treatment group and Part. For SBP and DBP, average of 3 readings will be used for analysis while all 3 readings will be provided in the listing. Baseline and change from baseline in height, weight, and BMI will be assessed with/without using age- and sex-adjusted z-scores and summarized by visit, treatment group and Part.

The number and percentage of patients meeting clinically notable criteria at any time, considering all data collected after first dose of double-blind treatment, from scheduled, unscheduled and premature discontinuation visits will be summarized by treatment group and Part. The worst post-baseline value in each part will be used for this analysis. Notable criteria are defined in Appendix 5.6. Clinically notable criteria will be met when both of the following occur:

- Post-baseline value meets the clinically notable criteria.
- Baseline value does not meet the clinically notable criteria.

The baseline value is the last value prior to and up to Day 1 of the double-blind treatment.

All vital signs data will be listed by treatment group, participant, and visit/time and if clinically notable criteria are met, abnormalities will be flagged.

### 2.7.6 Immunogenicity

Number and percentage of subjects with treatment-induced transient and persistent ADA and no treatment-induced ADA will be summarized. Listing will be provided.

Treatment induced ADA will be defined as a negative ADA sample at baseline and at least one positive ADA sample post-baseline. Persistent will be defined as negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample. Transient will be defined as treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

In addition, further ADA details will be assessed and will be listed in a separate ADA report. If applicable, additional analyses may be conducted.

### 2.7.7 Other safety evaluation

Shift from baseline in Tanner stage will be summarized by sex, treatment, visit and Part. Additionally, shift in menarche status from baseline will be summarized by visit and treatment group and Part. Mean and SD of age of the participants in each of category of shift table will be provided. Listing will be provided.

In cases where following a Tanner stage 5 assessment the data of the next visit are missing, they will be imputed as Tanner stage 5 (as the protocol does not mandate to repeat the Tanner stage assessment once Tanner stage 5 has been reached). Similarly, missing menarche data will be imputed to yes if the previous assessment was yes for menarche.

[redacted]

## 2.9 Biomarkers

Analyses of PCSK9 and lipids/lipoproteins are discussed in Section 2.6. No additional biomarkers will be evaluated in this study.

[redacted]

[redacted]

## 2.11 Interim analysis

Interim analyses are planned for the monitoring of participants' safety and will be performed as determined by the DMC (see DMC charter). Interim safety analyses before the unblinding for the analysis of Part 1 of the study will be performed by an independent statistician/programmer who will not be involved in the trial conduct. The interim results will be reviewed by the independent DMC.

[redacted]

# 3 Sample size calculation

The sample size for this study was selected based on feasibility.

# 4 Change to protocol specified analyses

No change from protocol specified analysis was made.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Missing/partial start date or end date of treatment will not be imputed.

### 5.1.2 AE date imputation

Partial AE start and end dates will be imputed. If there is uncertainty whether an AE occurred on-treatment or not, imputation will be performed, such that AE will be considered as on-treatment. Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

### 5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

## 5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

## 5.3 Analyses to be performed in Part 1 analysis (ANA1) and Part 2 analysis (ANA2)

| | Data to be included (ANA1 and ANA2 analysis) | | | Comment |
|---|---|---|---|---|
| | Part 1 | Part 2 | Overall: Part 1 & Part 2 combined | |
| Disposition | ANA1 | ANA2 | | |
| Protocol Deviations | ANA1 | ANA2 | | |
| Demography and baseline characteristics | ANA1 | | | |
| Medical History | ANA1 | | | |
| Prior therapies (Including lipid modifying therapy [redacted] | ANA1 | | | |
| Concomitant therapies** | ANA1 | ANA2 | | SAF for ANA1; |

| | | | | |
|---|---|---|---|---|
| (Including lipid modifying therapy [redacted] | | | | OAS for ANA2. CM will be counted in both parts when starting from part 1 and continuing to part 2 |
| [redacted] | | | | |
| Doses, Duration on study, Exposure | ANA1 | ANA2 | For exposure | |
| Efficacy (Primary endpoint & secondary endpoints) | ANA1 | | | |
| Efficacy (secondary endpoints) | ANA1 | ANA2 | For some selected efficacy parameters | |
| AEs** | ANA1 | ANA2 | | SAF for ANA1; OAS for ANA2. |
| Diabetes assessment | ANA1 | ANA2 | | SAF for ANA1 ; OAS for ANA2. |
| Lab and Vital signs | ANA1 | ANA2 | | SAF for ANA1 ; OAS for ANA2. |

## 5.4 Search criteria for other safety topics

The most recent eCRS available during database lock will be used.

## 5.5 Laboratory parameters derivations

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined:

**Table 5-1 Clinical notable criteria for selected laboratory tests**

| | Notable post-baseline value |
|---|---|
| Hematology | |
| Hemoglobin | ≤10 g/dL |
| Hematocrit | ≤ 0.8 x LLN |
| WBC count / Leukocytes | ≤ 2.8 x 10^9/L or ≥16 x 10^9/L |
| Platelet count | ≤ 75 x 10^9/L or ≥700 x 10^9/L |
| Clinical chemistry | |
| C(P)K | >5 x ULN<br>>5 and ≤10 x ULN<br>>10 and ≤20 x ULN<br>>20 x ULN |
| Creatinine | ≥50% increase from baseline (not >2 mg/dL)<br>>2 mg/dL<br>≥50% increase from baseline or >2 mg/dL |
| eGFR | <30 mL/min/1.73m2<br>≥ 30 to <60 mL/min/1.73m2<br>≥ 60 to <90 mL/min/1.73m2 |
| Glucose | ≥100 to <126 mg/dL<br>≥126 mg/dL |
| HbA1C | ≥5.7% to <6.5%<br>≥6.5% |

**Table 5-2 Notable liver function test values**

| Criterion |
|---|
| ALT > 3 x the upper limit of normal range (ULN)<br>ALT > 5 x ULN<br>ALT > 8 x ULN<br>ALT > 10 x ULN<br>ALT > 20 x ULN |
| AST > 3 x ULN<br>AST > 5 x ULN<br>AST > 8 x ULN<br>AST > 10 x ULN<br>AST > 20 x ULN |

| |
|---|
| ALT or AST > 3 x ULN<br>ALT or AST > 5 x ULN<br>ALT or AST > 8 x ULN<br>ALT or AST > 10 x ULN<br>ALT or AST > 20 x ULN |
| Total bilirubin > 2 x ULN |
| TBL >2xULN & DBL >ULN<br>TBL >2xULN & DBL >2xULN |
| ALP > 2 x ULN |
| ALT or AST > 3 x ULN and total bilirubin > 2 x ULN<br>ALT or AST > 5 x ULN and total bilirubin > 2 x ULN<br>ALT or AST > 8 x ULN and total bilirubin > 2 x ULN<br>ALT or AST > 10 x ULN and total bilirubin > 2 x ULN<br>ALT or AST > 20 x ULN and total bilirubin > 2 x ULN |
| ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law) |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window.

## 5.6 Vital signs – definition of clinically notable values

The following table show the clinical notable criteria for vital signs.

**Table 5-3 Clinical notable criteria for vital signs**

| Age | SBP [mmHg] | DBP [mmHg] | HR [$min^{-1}$] |
|---|---|---|---|
| ≥12 years | < 90, > 145 | < 55, > 90 | < 45, > 95 |

## 5.7 Statistical models

No additional details to be discussed.

## 5.8 Rule of exclusion criteria of analysis sets

The protocol deviations (PD) and other criteria leading to complete exclusion from analyses sets will be included in this section and will be finalized before study DBL.

# 6 Reference

Cuchel M, Raal FJ, Hegele RA, et al (2023) 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J; 44: 2277-2291.