NOVARTIS

Clinical Development

KJX839/inclisiran/Leqvio®

CKJX839D12304 / NCT05763875

A Double-blind, Randomized, Placebo- and Active-Comparator Controlled Study to Evaluate the Efficacy of Inclisiran as Monotherapy in Patients with Primary Hypercholesterolemia Not Receiving Lipid-Lowering Therapy (VictORION-Mono)

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-Mar-2023	Prior to DB lock	Creation of final version	N/A - First version	NA
21-Jun-2024	Prior to DB lock	Creation of amendment 1	Clarified the details about how the treatment group in SAF will be determined based on the study treatment actually received.	Section 2.2 Analysis sets
			Updated the subgroup definitions and the scope of subgroup analyses.	Section 2.2.1 Subgroup of interest
			Clarified that for subjects who discontinued study treatment prematurely, the compliance will only be summarized up to last p.o. treatment date + 1 day. Added details about handling of missing compliance data in cumulative compliance calculation.	Section 2.4.1 Study treatment / compliance
			Specified that the exposure to p.o. and s.c. study treatment will be summarized separately.	Section 2.4.1 Study treatment / compliance
			Updated the missing value imputation method for Treatment-policy Estimand.	Section 2.5.3 Handling of intercurrent events
			Added the details about tipping point analyses.	Section 2.5.5 Sensitivity analyses
			Instead of using models with interaction terms with subgroup variables, subgroup analyses will be	Section 2.5.6 Supplementary analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			performed by running the primary analysis model within each subgroup.	
			Sensitivity analysis will be conducted for the primary endpoint only.	Section 2.6 Analysis supporting secondary objectives
			eGFR will be summarized by categories: Severe, Moderate, Normal or Mild.	Section 2.7.3 Laboratory data
			Added summary of COVID-related AEs	Section 2.8 Impact of COVID-19
			Added derivation rule of last p.o. treatment date for subjects with missing end date in the last dosing record.	Appendix 5.1.1 Study treatment
			Added implementation details of MCP	Appendix 5.4 Implementation of MCP

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AE	Adverse Event
AESI	Adverse Event of Special Interest
AGB	ADaM Governance Board
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BILI	Total Bilirubin
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
DBL	Database Lock
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin (hemoglobin A1c)
HDL-C	High-Density Lipoprotein Cholesterol
IA	Interim Analyses
ICF	Informed Consent Form
IRT	Interactive Response Technology
ITT	Intent-To-Treat
LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
LLQ	Lower Limit of Quantification
LLT	Lipid Lowering Therapy
Lp(a)	Lipoprotein (a)
MAR	Missing-at-Random
MCP	Multiple Comparison Procedure

MedDRA	Medical Dictionary for Drug Regulatory Affairs
non-HDL-C	non-High-Density Lipoprotein Cholesterol
NYHA	New York Heart Association
PCE	Pooled Cohort Equations
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PD	Pharmacodynamics
PDS	Programming Datasets Specifications
PK	Pharmacokinetics
p.o.	oral(ly)
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RAS	Randomized Analysis Set
RDO	Retrieved Dropout
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
s.c.	subcutaneous(ly)
SCR	Screened Set
SD	Standard Deviation
SOC	System Organ Class
TC	Total Cholesterol
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal

1 Introduction

This document contains a detailed statistical analysis plan that will be performed to support the completion of the Clinical Study Report (CSR) for the CKJX839D12304 study protocol (version 01 – amended protocol) dated 08-Feb-2023.

1.1 Study design

CKJX839D12304 (VictORION-Mono) is a randomized, double-blind, placebo- and active comparator-controlled, multicenter study in adult participants with primary hypercholesterolemia not receiving any lipid-lowering therapy (LLT) and who have a 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk of less than 7.5%, estimated using the pooled cohort equations (PCE) (Grundy et al 2019). This study will evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as a monotherapy in comparison to ezetimibe and placebo.

As depicted in Figure 1-1, the study consists of:

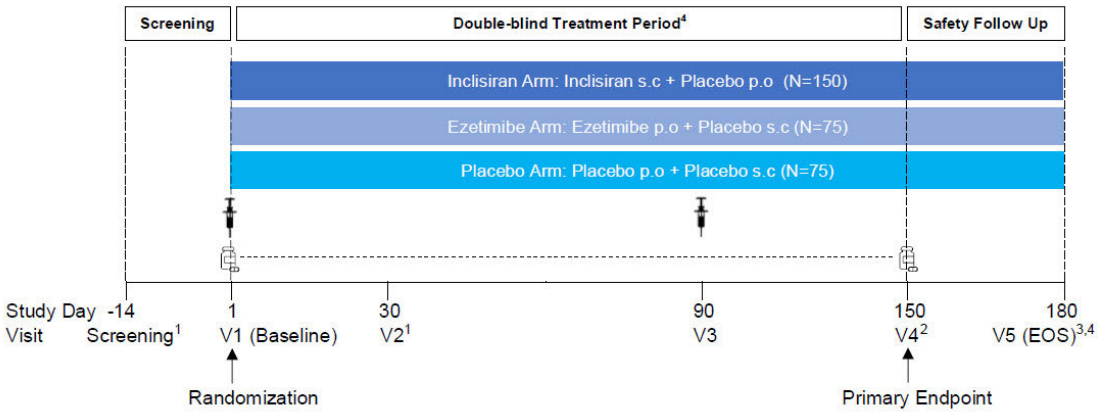
- A screening period up to 14 days
- A double-blind treatment period of 150 ± 5 days based on the Day 1 randomization date; and
- A Safety Follow-up / End of Study (EOS) visit (Day 180) conducted 30 +5 days after the Day 150 visit

At screening, participants will sign the Informed Consent Form (ICF) and their eligibility will be assessed through the review of study inclusion/exclusion criteria. If at the time of ICF signature the participant is not fasting, he/she will have to return for the blood draw in a fasting state. Key inclusion criteria assessed at the screening visit include:

- Adults ≥ 18 to ≤ 75 years of age
- Fasting low-density lipoprotein cholesterol (LDL-C) value of ≥ 100 mg/dL (equivalent to 2.59 mmol/L) but < 190 mg/dL (equivalent to 4.92 mmol/L)
- Fasting triglycerides ≤ 400 mg/dL (equivalent to 4.52 mmol/L)
- With a 10-year ASCVD risk score of less than 7.5%, estimated using the PCE
- Have not been on any lipid-lowering therapy within 90 days

The detailed inclusion/exclusion criteria are in Section 5 of the protocol. The screening period can be up to 14 days to allow adequate time for the completion of all qualifying screening and eligibility evaluations.

Figure 1-1 Study Design



[1] Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations.

[2] Visit 4 is also the EOT visit if the participant completes the study treatment as per protocol.

[3] Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations or over the telephone if an on-site visit is not possible. During a telephone call, only AEs/SAEs and concomitant medications will be followed.

[4] When study treatment is discontinued early, participants should continue with all of their planned study visits and be retained until Day 180.

s.c inclisiran/placebo injection

p.o ezetimibe/placebo (one capsule daily from Day 1 until the day before the Day 150 visit)

Approximately 300 participants fulfilling the eligibility criteria will be randomized at the Baseline (Day 1) visit in a 2:1:1 double-blind fashion to one of three treatment arms:

- subcutaneous (s.c.) inclisiran and oral (p.o.) placebo (inclisiran arm)
- s.c. placebo and p.o. ezetimibe (ezetimibe arm)
- s.c. placebo and p.o. placebo (placebo arm).

Randomization of the participants will be stratified in interactive response technology (IRT) by their screening LDL-C result (LDL-C ≤ 130 mg/dL vs. LDL-C > 130 mg/dL). Following randomization, the participant will receive inclisiran sodium 300 mg or placebo by subcutaneous injection at Day 1 by a healthcare professional at the study site. The participant will also be dispensed one bottle of oral ezetimibe or placebo, and will be asked to take 1 capsule once a day, starting with the day of the Baseline visit (Day 1).

After the Baseline visit, participants will have study visits on Day 30, Day 90, and Day 150. The participant will receive a second subcutaneous injection of 300 mg inclisiran sodium or placebo on Day 90, administered by a healthcare professional at the study site. Treatment compliance to oral ezetimibe or placebo from Day 1 through the day before the Day 30 visit will be assessed at the Day 30 visit. The participant will also be dispensed two bottles of additional oral ezetimibe or placebo on Day 30 and Day 90 and will be asked to continue to take 1 capsule once a day through

the day before the Day 150 visit. Treatment compliance will be assessed again at the Day 90 and Day 150 visits.

The overall study duration is approximately 190 days but can vary depending on individual screening and the visit windows allowed for the treatment period and EOS visit.

The primary endpoint of the study is the percentage change from baseline to Day 150 in LDL-C. No formal interim analysis will be performed in this study.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate the superiority of inclisiran as monotherapy, compared with placebo, in reducing LDL-C as measured by percentage change from baseline to Day 150	● Percentage change in LDL-C from baseline to Day 150
● To demonstrate the superiority of inclisiran as monotherapy, compared with ezetimibe, in reducing LDL-C as measured by percentage change from baseline to Day 150	● Percentage change in LDL-C from baseline to Day 150
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To assess the efficacy of inclisiran as monotherapy, compared to ezetimibe and placebo, on absolute change in LDL-C, percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp (a) from baseline to Day 150	● Absolute change in LDL-C, percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp (a) from baseline to Day 150
● To assess the safety and tolerability of inclisiran as monotherapy, compared to placebo and ezetimibe	● Incidence of TEAEs and SAEs, safety laboratory values at each visit

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

There will be two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a “Monotherapy Estimand” and a “Treatment-policy Estimand”.

For the “Monotherapy Estimand,” the clinical question of primary interest is: what is the reduction in LDL-C, quantified by difference of mean percentage changes from baseline to Day 150, in trial

participants with primary hypercholesterolemia and a 10-year ASCVD risk of less than 7.5% who are not on any LLT, and receive inclisiran as monotherapy, compared to the reduction in those who are on placebo or ezetimibe, if participants had not died or discontinued study treatments, and if other lipid-lowering therapy were not available.

The justification for the Monotherapy Estimand is that it will capture the effect of inclisiran as monotherapy in reducing LDL-C, in line with the study purpose of assessing the treatment effects of inclisiran in the absence of confounding factors such as concomitant treatment with other LLTs.

The Monotherapy Estimand is described by the following attributes:

Population: Participants with primary hypercholesterolemia and a 10-year ASCVD risk of less than 7.5%, who are not on any LLT. ASCVD risk will be estimated using the Pooled Cohort Equations (PCE) (Grundy et al 2019).

Endpoint: Percentage change from baseline to Day 150 in LDL-C.

Treatments of interest: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe).

Handling of intercurrent events:

- Information following permanent discontinuation of study treatment will be handled with a hypothetical scenario of what would happen if the participants had not prematurely discontinued any study treatment (hypothetical strategy).
- Participants who died will be handled in a hypothetical scenario of what would have happened had they not died (hypothetical strategy).
- Use of other LLT will be treated in a hypothetical scenario of what would happen if other LLT were not available (hypothetical strategy).

Summary measure: The summary measure to be used is the difference of mean percentage changes.

In addition, for regulatory purposes, the “Treatment-policy Estimand” was added in parallel as a primary estimand. This estimand shares the same population, endpoint, and summary measure as the Monotherapy Estimand but considers different treatments of interest and adopts alternative strategies for handling intercurrent events:

Treatments of interest: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other LLTs added during the study.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be ignored (treatment-policy strategy).
- Death will be handled as an unfavorable outcome using a composite variable strategy.
- Use of other LLTs will be ignored (treatment-policy strategy).

The Treatment-policy Estimand answers the clinical question regarding inclisiran efficacy in LDL-C lowering as compared to placebo or ezetimibe irrespective of adherence to study treatment or addition of other LLTs, with death being an unfavorable outcome.

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 2.5.

1.2.2 Secondary estimand(s)

The secondary estimands address the same clinical question as the primary estimands, albeit for different endpoints. For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy Estimand will be defined in a similar way as for the primary endpoint. They share the same population, strategies for handling intercurrent events, summary measure, as well as the same treatments of interest as the primary estimands. They differ by the definition of the endpoints, these being:

- Absolute change in LDL-C from baseline to Day 150
- Percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp(a) from baseline to Day 150

The statistical methods and inference approaches are described in Section 2.6.

2 Statistical methods

The following sections contain important information on detailed statistical methodologies to be used in the analyses for the final CSR.

2.1 Data analysis general information

All analyses will be performed by Novartis using SAS version 9.4 (or above) and/or R version 4.1 (or above).

Study-collected data will be summarized by the treatment groups (Inclisiran, Ezetimibe, Placebo) using descriptive statistics, graphs, and/or raw data listings. Categorical variables will be summarized using counts and percentages. Continuous variables, including changes from baseline, will be summarized using descriptive statistics (n (number of non-missing observations), mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum).

Absolute change and percent change from baseline will be calculated as follows:

- Absolute change from baseline to Day X =Value at Day X – Baseline value.
- Percent change from baseline to Day X = (Absolute change/Baseline value)*100%.

For laboratory measurements below the lower limit of quantification (LLQ), LLQ/2 will be used as the numeric value for the measurement. For example, if numeric result is missing in the database and character result is “< 3”, the numeric result should be treated as 3/2 = 1.5 during analysis.

Analyses for the final CSR will be conducted after the final database lock (DBL) of the study. The final DBL will be performed after all participants either complete the study or discontinued early.

The stratification factor (screening LDL-C result ≤ 130 mg/dL vs. > 130 mg/dL) will be included as a covariate in the efficacy analysis models.

2.1.1 General definitions

Study treatment

Throughout this document, the term "study treatment" refers to:

- s.c. inclisiran and p.o. placebo (for participants in the inclisiran arm)
- s.c. placebo and p.o. ezetimibe (for participants in the ezetimibe arm)
- s.c. placebo and p.o. placebo (for participants in the placebo arm)

where s.c. inclisiran refers to inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution for subcutaneous injection in prefilled syringe, and s.c. placebo refers to its matching placebo; p.o. ezetimibe refers to the 10 mg oral ezetimibe capsule and p.o. placebo refers to its matching placebo. The term "s.c. study treatment" refers to the s.c. part of the study treatment (s.c. inclisiran or s.c. placebo) and "p.o. study treatment" refers to the p.o. part of the study treatment (p.o. ezetimibe or p.o. placebo).

Date of first administration of study treatment

The term "date of first administration of study treatment" refers to the first date of administration of the s.c. or the p.o. study treatment, whichever is earlier.

Study day

Day 1 is defined as the date of first administration of study treatment. For participants who were randomized but not treated, if any, Day 1 will be defined as the randomization date.

The term "study day" of any assessment refers to the assessment date relative to Day 1.

For a particular assessment date, its study day will be calculated as follows:

For dates on or after Day 1,

Study day = Assessment date – Date of Day 1 + 1;

For dates prior to Day 1,

Study day = Assessment date – Date of Day 1.

Baseline

The term "baseline" is defined as the last available non-missing record on or prior to Day 1, unless otherwise specified.

Last contact/participation date

The last contact/participation date for a participant is the last available date across all the data collected for that participant. For a participant with a death event, the date of death will be used.

Unscheduled visit

Only for selected analyses of safety laboratory assessments will unscheduled measurements be considered. For efficacy analyses and by-visit safety analyses, measurements from unscheduled visits will generally not be used, unless otherwise specified.

Reflexive LDL-C

The endpoints involving LDL-C will use a reflexive LDL-C approach. When both calculated and beta-quantified LDL-C are available for a sample, calculated LDL-C will be used unless triglycerides are greater than 400 mg/dL or calculated LDL-C is less than 70 mg/dL. When only calculated LDL-C or beta-quantified LDL-C is available for a sample but not both, the available one will be used.

2.2 Analysis sets

The following analysis sets will be used for statistical analyses:

The **Screened Set (SCR)** consists of all participants who signed the informed consent. The SCR includes only unique screened participants, i.e., in the case of re-screened participants only the chronologically last screening data is counted.

The **Randomized Analysis Set (RAS)** consists of all participants who received a randomization number, regardless of receiving trial medication.

The **Full Analysis Set (FAS)** comprises all randomized participants with the exception of those participants who have not been qualified for randomization and have not received study treatment but have been inadvertently randomized into the study. Following the intent-to-treat (ITT) principle, participants will be analyzed according to the treatment they have been assigned to at randomization. Efficacy variables will be analyzed based on the FAS.

The **Safety Analysis Set (SAF)** includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment actually received. Participants who received at least one dose of inclisiran will be considered in the inclisiran arm of SAF. Participants who received at least one dose of ezetimibe but never received any inclisiran will be considered in the ezetimibe arm of SAF. Participants who never received any dose of inclisiran

or ezetimibe will be considered in the placebo arm of SAF. The SAF will be used for the analyses of safety variables.

Note: The last part of the definition of the FAS is what is often referred to as misrandomized participants; i.e. participants for whom IRT calls were made by the site either prematurely or inappropriately prior to confirmation of the participant's final randomization eligibility and double-blind medication was not administered to the participant. These participants would subsequently not continue to take part in the study or be followed-up. Misrandomized participants will not be included in the FAS, but they will be included in the RAS. Further exclusions from the FAS may only be justified in exceptional circumstances (e.g., serious GCP violations).

2.2.1 Subgroup of interest

Subgroup analyses will be performed to explore the consistency of treatment effects and safety profiling on selected parameters between the subgroups and the overall population. In general, subgroups will be defined based on baseline information. In Table 2-1, subgroups defined for this study and the ways to derive them have been listed. Additional subgroups may be included later as needed.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Demographics and baseline characteristics	Efficacy	Selected Safety
Age group (< Median, >= Median)	Screening	X	X	X
Sex (Male, Female)	Screening	X	X	X
Race (White, Black or African American, Other or multiracial)	Screening	X	X	X
Region*	Screening	X	X	X
Hypertension (Yes, No)	Screening		X	
ASCVD risk score (<5%, ≥5%) estimated using PCE	Screening		X	
Screening LDL-C [mg/dL] (<= 130mg/dL, > 130mg/dL)	Screening		X	
Baseline PCSK9 [ug/L] (< Median, >= Median)	Randomization		X	
Baseline Lp(a) [nmol/L] (< Median, >= Median)	Randomization		X	

* *The regions are: USA, Europe (Germany, Hungary), Latin America (Colombia, Mexico)*

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The following participant disposition at screening and randomization will be summarized by treatment group and overall, for the SCR:

- Screened (Screened Set)
    - Completed screening
    - Did not complete screening
        - Reasons for not completing screening
- Randomized (Randomized Analysis Set)
- Included in the Full Analysis Set
- Treated (Safety Analysis Set)

The following study treatment disposition will be summarized by treatment group and overall, for the SAF:

- Completed study treatment
- Discontinued study treatment prematurely
    - Primary reason for early discontinuation of study treatment

The following study disposition will be summarized by treatment group and overall, for the RAS:

- Completed study
- Discontinued prior to study completion
    - Primary reason for discontinuing study

The duration of study (number of days from Day 1 to the date of last contact/participation date) will be summarized using descriptive statistics by treatment group and overall, for the FAS.

The frequency (%) of participants with protocol deviations will be presented for the RAS. Finally, the number of randomized participants by region (Latin America, Europe, USA) and country will be presented descriptively for the RAS.

2.3.2 Demographics and other baseline characteristics

The FAS will be used for the analyses in this section.

The following demographics and baseline characteristics will be summarized descriptively by treatment group and overall:

- Age [years]
- Age group 1 (< 55, ≥ 55 to < 65, and ≥ 65 years)
- Age group 2 (< Median, >= Median)
- Sex
- Race
- Race group (White, Black or African American, Other or multiracial)
- Ethnicity
- Region (Latin America, Europe, USA)
- Height [cm]
- Weight [kg]
- Body mass index (BMI) [kg/m^2] calculated as weight [kg] / height^2 [m^2]
- Baseline BMI groups (< 30, ≥ 30 to < 35, and ≥ 35 kg/m^2)
- Pulse
- Systolic and diastolic blood pressure (SBP and DBP) [mmHg]
- Alcohol history
- Smoking and vaping history
- Baseline estimated glomerular filtration rate (eGFR) groups (< 30, ≥ 30 to < 60, and ≥ 60 $mL/min/1.73m^2$)
- Baseline HbA1c [%]
- Baseline plasma glucose [mg/dL, mmol/L]
- Screening LDL-C stratum (≤ 130, > 130 mg/dL)
- Baseline lipid profile
    - LDL-C [mg/dL; mmol/L]
    - High-density lipoprotein cholesterol (HDL-C) [mg/dL; mmol/L]
    - Non-HDL-C [mg/dL; mmol/L]
    - Total cholesterol (TC) [mg/dL; mmol/L]
    - TC/HDL-C ratio
    - Apolipoprotein (Apo) A-1 [mg/dL]

- Apo B [mg/dL]
- Apo B/Apo A-1 ratio
- Lipoprotein A (Lp(a)) [nmol/L; mg/dL]
- Triglycerides [mg/dL; mmol/L]

- Baseline PCSK9 [ug/L]

The number and percentage of participants with protocol solicited medical history, such as primary hypercholesterolemia, hypertension, NYHA class I and II, will be presented by treatment group and overall.

Other relevant medical histories will be summarized by primary system organ class (SOC) and preferred term (PT), for each treatment group and overall.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SAF will be used for the analyses in this section.

2.4.1 Study treatment / compliance

The number and percentage of participants receiving the s.c. injection, the injection site location, and the reason for not receiving the injection will be summarized for each study visit, by treatment group and overall. The total number of s.c. injections will also be summarized.

Compliance [%] to the p.o. treatment will be summarized for the period from Day 1 to Day 30 visit, from Day 30 to Day 90 visit, and from Day 90 to Day 150 visit, by treatment group and overall. Cumulative compliance will also be summarized. For participants who completed the planned duration of study treatment, the cumulative compliance will be calculated from Day 1 to Day 150 visit. For participants who discontinued study treatment prematurely, both the by-visit compliance summary and the cumulative compliance will only consider the compliance data up to the treatment disposition date + 1 day (or last p.o. treatment date + 1 day, if the treatment disposition date is missing). For example, consider a subject who discontinued study treatment early and had the treatment disposition date on Day 123 and had the Day 150 visit on Day 152. Because 152 > 123 + 1, only the subject's Day 30 and Day 90 compliance data will contribute to the by-visit summary, and the cumulative compliance for that subject will also be calculated from Day 1 to Day 90 visit instead of from Day 1 to Day 150 visit. The formulae to calculate cumulative compliance are

- Cumulative compliance from Day 1 to Day 90 visit = [Compliance from Day 1 to Day 30 visit * (Day 30 date – Day 1 date) + Compliance from Day 30 visit to Day 90 visit * (Day 90 date – Day 30 date)] / [Day 90 date – Day 1 date]
- Cumulative compliance from Day 1 to Day 150 visit = [Compliance from Day 1 to Day 30 visit * (Day 30 date – Day 1 date) + Compliance from Day 30 visit to Day 90 visit * (Day

90 date – Day 30 date) + Compliance from Day 90 visit to Day 150 visit * (Day 150 date – Day 90 date)] / [Day 150 date – Day 1 date]

The calculations above are essentially the weighted average of treatment compliance at each visit interval (for subjects who discontinued treatment early, only consider visits no later than one day after treatment disposition date), where the weights are proportional to the duration of the interval. If there is any visit interval for which the treatment compliance is missing, the interval with missing treatment compliance will be excluded from the calculation of cumulative compliance. For example, if a subject who completed study treatment missed a compliance assessment at Day 90 for the interval from Day 30 visit to Day 90 visit, this subject's cumulative compliance will be the weighted average of Day 30 and Day 150 visit compliance assessments.

The duration of exposure to s.c. study treatment (inclisiran or its matching placebo) will be computed as the time from the first administration of s.c. study treatment to the first of the following two events to occur:

- The last administration of s.c. injection plus 180 days, or
- The participant's last contact/participation date. For subjects who died, the death date will be considered.

The duration of exposure to p.o. study treatment (ezetimibe or its matching placebo) will be computed as the time from the first administration of p.o. study treatment to the first of the following two events to occur:

- The last administration of p.o. study treatment plus 1 day, or
- The participant's last contact/participation date. For subjects who died, the death date will be considered.

These algorithms reflect the planned treatment schedule and the exposure attributable period of the s.c. and p.o. study treatments respectively. The duration of exposure to s.c. and p.o. study treatment (in days) will be summarized separately by treatment group and overall using descriptive statistics. The total participant years of exposure will be computed as the sum of duration of exposure (in days) across all participants, then divided by 365.25.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized by the treatment group and overall, in separate tabulations based on the coding dictionary used. Medications will be presented using the preferred drug names and grouped by anatomical main group. Tables will show the number and percentage of participants receiving at least one drug of a particular preferred drug name and at least one drug in a particular anatomical main group. Significant non-drug therapies will be summarized in a similar way, using the PTs and grouped by primary SOC.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken and stopped prior to the first administration of study treatment (Day 1). Concomitant medications and significant non-drug therapies are defined as those used during the

double-blind period, including those that started before or on Day 1 and are either ongoing or stopped on Day 1 or later, as well as those that started after Day 1.

In addition, LLTs added after Day 1 will be presented using the preferred drug names and summarized by the treatment group and overall. LLTs added after Day 1 are defined as concomitant medications with 2nd level ATC classification being C10 (lipid modifying agents) and start date after Day 1 date.

2.5 Analysis supporting primary objective(s)

The primary aim of the study is to demonstrate the superiority of inclisiran to either placebo or ezetimibe in reducing LDL-C.

The FAS will be used for the primary efficacy analysis.

2.5.1 Primary endpoint(s)

The primary endpoint of the study is the percentage change from baseline to Day 150 in LDL-C. .

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objectives are to demonstrate the superiority of inclisiran as monotherapy compared to the use of placebo or ezetimibe separately, in reducing LDL-C as measured by percentage change from baseline to Day 150. To this end, the Monotherapy Estimand assesses the treatment effect of inclisiran alone in the absence of confounding factors such as additional LLT.

As described in Section 1.2.1, in addition to the primary Monotherapy Estimand, the Treatment-policy Estimand was added for regulatory purposes. Both estimands will be considered in parallel as primary analysis.

The primary statistical hypotheses to be tested are:

- H_{IP0}: $\mu_i - \mu_p \geq 0$ vs. H_{IPa}: $\mu_i - \mu_p < 0$
- H_{IE0}: $\mu_i - \mu_e \geq 0$ vs. H_{IEa}: $\mu_i - \mu_e < 0$

where μ_i, μ_p and μ_e are the mean percentage changes in LDL-C from baseline to Day 150 in the inclisiran group, placebo group, and ezetimibe group respectively. The study can be claimed a success if at least one of the above two individual hypotheses is rejected.

The primary efficacy endpoint will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment, stratification factor, and baseline value as fixed effects. Due to probable heterogeneity of variances between treatment groups, an ANCOVA model that assumes unequal variances between treatment groups will be used. The two primary endpoint hypotheses will be tested using an equally weighted Dunnett test (Dunnett 1955).

A multiple comparison procedure (MCP) will be used in statistical hypothesis testing for primary and secondary endpoints to control the overall type I error rate at 0.025 (one-sided test). For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy

Estimand will be defined in a similar way as for the primary endpoint, and the MCP will be applied to Monotherapy Estimands and Treatment-policy Estimands separately, to control the overall type I error rate within each set of estimands. Since the Treatment-policy Estimands are intended for regulatory purposes, while the Monotherapy Estimands are intended for all other purposes, no multiplicity adjustment will be made across those two sets of estimands. The testing procedure to be followed is graphically presented in Figure 2-1, and outlined in the following steps:

- First, a weighted Dunnett test with equal weights assigned to each of the two individual primary hypotheses (H_{IP0} and H_{IE0}) is performed. This test will exploit the correlation of the primary endpoint between the two comparisons, with the test statistics derived from the ANCOVA model described as above.
- If one primary hypothesis is rejected, a fraction of its significance level will be passed to the other primary hypothesis while the remaining alpha will be propagated to the family of secondary hypotheses under the same treatment comparison, according to the pre-specified weights as indicated in the graph. The choice of weights for passing alpha to the other primary hypothesis (0.4 and 0.6 respectively) reflects the importance of demonstrating efficacy in the comparison between inclisiran and placebo.
- Within a family of secondary hypotheses (H_{IPk} or H_{IEk}), the hierarchical testing procedure will be used. Refer to Section 2.6.2 for details.
- If one secondary hypothesis in the comparison between inclisiran and placebo H_{IPk} is rejected, a fraction of its significance level will be passed to the next hierarchy of secondary hypotheses under the same treatment comparison, while the remaining alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. If there is no next hierarchy of secondary hypotheses, then the whole alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. Vice versa for the alpha passing from H_{IEk}.

The nodes H_{IP} and H_{IPk} represent the null hypotheses related to the primary and secondary endpoints compared between inclisiran and placebo, while the nodes H_{IE} and H_{IEk} represent the null hypotheses related to the primary and secondary endpoints compared between inclisiran and ezetimibe. The correlations between endpoints and between the two comparisons for each endpoint will also be considered.

The least squares means for the difference between inclisiran and two comparators and corresponding unadjusted two-sided confidence intervals (CI) will be provided separately. The raw p-value for testing the individual hypothesis will also be provided. The superiority of inclisiran to a comparator can be claimed when the corresponding individual null hypothesis is rejected or the raw p-value is statistically significant at corresponding alpha level of current stage.

Details of MCP implementation are described in SAP Appendix 5.4.

2.5.3 Handling of intercurrent events

The Monotherapy Estimand will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment:** Discontinuation of study treatments will be treated in a hypothetical scenario of what would happen if the participants had not discontinued study treatments (hypothetical strategy).
- **Death:** Participants who die will be treated in a hypothetical scenario of what would happen if participants had not died (hypothetical strategy).
- **Use of lipid-lowering therapy:** Use of LLT will be treated in a hypothetical scenario of what would happen if other LLT were not available (hypothetical strategy).

The efficacy endpoints after the intercurrent events will be multiply imputed under the missing-at-random (MAR) assumption. In other words, it is assumed that a subject who experienced intercurrent events would have had similar efficacy compared to subjects with the same observed covariates in the same treatment group but did not experience any intercurrent event, in a hypothetical scenario that the subject had not experienced any intercurrent event. The imputation model will include stratification factor, baseline value, and available post-baseline values as covariates.

The Treatment-policy Estimand will account for intercurrent events as follows:

- **Discontinuation of study treatment:** Retrieved dropout (RDO) data collected after discontinuation from study treatments will be used for the analysis (treatment-policy strategy). Missing data after discontinuation from study treatments will be multiply imputed based on RDO data, and when there are no sufficient RDO data, a placebo-based Pattern-Mixture Model (PMM) will be used for multiple imputation, which includes stratification factor, baseline value, and available post-baseline values as covariates.
- **Death:** A composite variable strategy will be utilized to handle the intercurrent event of death, and efficacy parameter measurements after death will be imputed using the participant's baseline values.
- **Use of lipid-lowering therapy:** The data collected after use of other LLTs will be used for analyses (treatment-policy strategy). Missing data will be multiply imputed using a placebo-based PMM, which includes stratification factor, baseline value, and available post-baseline values as covariates.

The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's method (Rubin 1987).

2.5.4 Handling of missing values not related to intercurrent event

In the Monotherapy Estimand, missing values not related to intercurrent events will be multiply imputed under the MAR assumption. The imputation model will include stratification factor, baseline value, and available post-baseline values as covariates.

In the Treatment-policy Estimand, missing values not related to intercurrent events will be multiply imputed using a placebo-based PMM, which includes stratification factor, baseline value, and available post-baseline values as covariates.

The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's method (Rubin 1987).

2.5.5 Sensitivity analyses

The following sensitivity analyses will be conducted to assess the robustness of the inferences to various assumptions about the missing data:

- Conduct the primary analyses under the alternative missing value imputation model where the post-baseline (Day 30 and Day 90 visit) measurements are not included as covariates.
- Tipping point analyses: a tipping point analysis will be performed to search for the tipping point that reverses the study conclusion regarding the primary endpoint. In the tipping point analysis, scale-adjustments will be applied to the imputed values in the inclisiran arm. The multiplicity adjustment between the inclisiran vs. placebo and inclisiran vs. ezetimibe comparisons will be performed using the same graphical approach as outlined in Section 2.5.2, but the graph in Figure 2-1 is reduced using Algorithm 1 in Bretz et al 2011 to only include the two hypotheses regarding the primary endpoint. In the reduced graph, the initial weights are 1/2 for each of the two hypotheses, with transition weight = 1 between them.

2.5.6 Supplementary analyses

Subgroup analyses

Subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline characteristics will be performed. The subgroup variables are defined in Table 2-1.

The subgroup analyses will be based on the multiply imputed datasets created for the primary analysis. Within each subgroup, the same ANCOVA model as described in Section 2.5.2 will be used. For the analysis of subgroups which are also stratification factors, the corresponding stratification factor term will be removed from the model. The least squares means for the difference between inclisiran and two comparators and corresponding unadjusted two-sided confidence intervals (CI) will be provided separately. The unadjusted p-value for testing the individual hypothesis will also be provided. No adjustment for multiple comparisons will be made. Forest plot will be provided for subgroup analyses. If the model did not converge for a subgroup, the results for that subgroup will be left blank or indicated as not estimable.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

There are seven secondary efficacy endpoints defined, and fourteen secondary hypotheses to be tested for these seven secondary endpoints in the comparison between inclisiran and each comparator (placebo or ezetimibe) respectively:

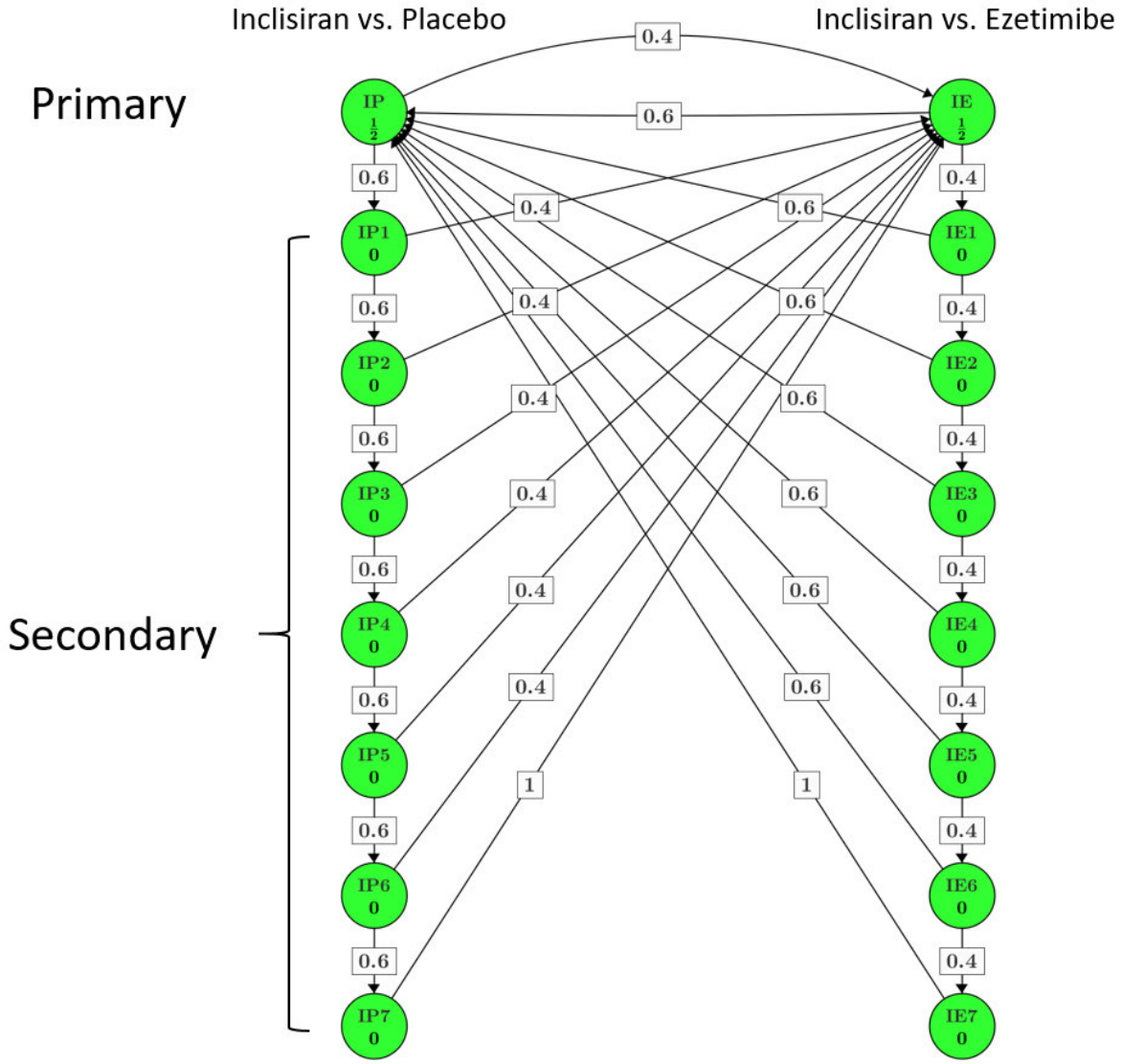
1. Percentage change in PCSK9 from baseline to Day 150
2. Absolute change in LDL-C from baseline to Day 150
3. Percentage change in non-HDL-C from baseline to Day 150
4. Percentage change in TC/HDL-C ratio from baseline to Day 150
5. Percentage change in Apo B from baseline to Day 150
6. Percentage change in Apo B/Apo A-1 ratio from baseline to Day 150
7. Percentage change in Lp (a) from baseline to Day 150

2.6.2 Statistical hypothesis, model, and method of analysis

For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy Estimand will be defined in a similar way as for the primary endpoint. All secondary efficacy endpoints will be analyzed on FAS using the same ANCOVA model as for the primary efficacy endpoint as described in Section 2.5.2. Lipoprotein (a) will be log-transformed before modeling. The model will include treatment, stratification factor, and baseline value as fixed effects, and assume unequal variances between treatment groups. The least squares means for the difference between inclisiran and two comparators and corresponding unadjusted two-sided CIs will be provided separately.

As stated in Section 2.5.2, the two families of secondary hypotheses H_{IPk} and H_{IEk} (k = 1, 2, ..., 7, following the order of the seven secondary endpoints as above) are included in the multiple testing procedure as presented in Figure 2-1. The hierarchical testing procedure will be used to test the seven secondary hypotheses within each family of the secondary endpoints (H_{IPk} or H_{IEk}). If one secondary hypothesis in the comparison between inclisiran and placebo H_{IPk} is rejected, a fraction of its significance level will be passed to the next hierarchy of secondary hypotheses under the same treatment comparison, while the remaining alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe, according to the pre-specified weights as indicated in the graph. If there is no next hierarchy of secondary hypotheses, then the whole alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. Vice versa for the alpha passing from H_{IEk}.

Figure 2-1 Testing procedure for primary and secondary endpoints



The intercurrent events and missing values will be handled following the same approach as described for the primary endpoint.

2.6.3 Handling of intercurrent events

Intercurrent events will be handled using the strategies described in Section 2.5.3.

2.6.4 Handling of missing values not related to intercurrent event

Missing values not related to intercurrent events will be imputed as described in Section 2.5.4.

2.7 Safety analyses

For all safety analyses, the SAF will be used. All tables and listings will be presented by treatment group and overall.

2.7.1 Adverse events (AEs)

The most recent version of MedDRA before DBL will be used for coding AEs. An AE will be counted as a treatment emergent AE (TEAE) if the AE started on or after Day 1 or the AE was present prior to Day 1 but increased in severity on or after Day 1. Since the investigators are required to enter any worsened AE as a separate record, implementation-wise an AE is a TEAE as long as its start date is on or after Day 1.

The following summaries will be presented for TEAEs using number and percentage of participants with the event:

- Overall Summary of TEAEs
- TEAEs by primary SOC and PT
- TEAEs by primary SOC
- TEAEs by PT
- TEAEs by primary SOC, PT, and maximum severity
- TEAEs possibly related to inclisiran/placebo by primary SOC and PT
- TEAEs possibly related to ezetimibe/placebo by primary SOC and PT
- TEAEs possibly related to inclisiran/placebo by PT
- TEAEs possibly related to ezetimibe/placebo by PT
- Treatment Emergent Serious AEs (TESAEs) by primary SOC and PT
- TESAEs by primary SOC
- TESAEs by PT
- TESAEs possibly related to inclisiran/placebo by primary SOC and PT
- TESAEs possibly related to ezetimibe/placebo by primary SOC and PT
- TEAEs leading to discontinuation of inclisiran/placebo by primary SOC and PT
- TEAEs leading to discontinuation of ezetimibe/placebo by primary SOC and PT
- TEAEs leading to discontinuation of inclisiran/placebo by PT
- TEAEs leading to discontinuation of ezetimibe/placebo by PT

- TEAEs with a fatal outcome by primary SOC and PT

If more than one event occurred with the same SOC/PT for the same participant, the participant will be counted only once for that SOC/PT.

Participant data listings will be presented for AEs with a fatal outcome, SAEs, AEs leading to discontinuation of inclisiran/placebo, and AEs leading to discontinuation of ezetimibe/placebo. Those listings will include all AEs in database, regardless of whether they are TEAE.

Additional Analysis of Adverse Events for ClinicalTrials.gov and EudraCT:

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than certain percentage in any treatment group and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by SOC and PT on the SAF.

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.

2.7.1.1 Adverse events of special interest / grouping of AEs

Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify adverse events of special interest (AESI). The number and percentage of participants with treatment emergent AESIs will be presented by treatment group, for each topic of AESI. The AESIs in this study are specified as follows:

- New Onset Diabetes Mellitus
- Hepatotoxicity

The following summary tables will be generated for the AESIs:

- Overall Summary of TEAEs
- TEAEs by PT
- TEAEs possibly related to inclisiran/placebo by PT

- TEAEs possibly related to ezetimibe/placebo by PT
- TEAEs by primary SOC, PT, and maximum severity
- TESAEs by PT
- TEAEs leading to discontinuation of inclisiran/placebo by PT
- TEAEs leading to discontinuation of ezetimibe/placebo by PT

Participant data listings will be provided for each topic of AESI, which will include all AEs in the database, regardless of whether they are TEAE. The CRS definitions for the AESIs will also be provided in a listing.

2.7.2 Deaths

As stated in Section 2.7.1, TEAEs with fatal outcome will be summarized by primary SOC and PT. All deaths (regardless of treatment emergent or not) will be listed at the individual participant level as well.

2.7.3 Laboratory data

Observed value, absolute change, and percent change from baseline in safety laboratory parameters will be summarized descriptively at baseline (for observed value only) and at each post-baseline visit. eGFR will be summarized by categories (< 30, ≥ 30 to < 60, and ≥ 60 mL/min/1.73m^2) at baseline and at each post-baseline visit. For each parameter, only the visits at which the parameter is scheduled to be assessed per protocol will be presented for such visit-based summary.

For glucose, only measurements taken in a fasting state will be used. Baseline glucose is defined as the average of the last two non-missing fasting glucose values on or prior to Day 1. If only one non-missing fasting glucose value is available on or prior to Day 1, the available value will be used as baseline.

In addition, shift tables using the low, normal, or high classification based on the standard ranges for each laboratory parameter will be used to present incidence of transitions from baseline to the worst post-baseline value. For eGFR, HbA1c, and fasting glucose, the following ranges will be used:

- For eGFR, the categories will be Severe: < 30 mL/min/1.73m^2; Moderate: ≥ 30 to < 60 mL/min/1.73m^2; Normal or Mild: ≥ 60 mL/min/1.73m^2.
- For HbA1c, the categories will be $< 5.7\%$, $\geq 5.7\%$ to $< 6.5\%$, and $\geq 6.5\%$.
- For fasting glucose, the categories will be < 100 mg/dL, ≥ 100 mg/dL to < 126 mg/dL, and ≥ 126 mg/dL

The number and percentage of participants with abnormalities in liver function tests (LFT) will also be summarized, according to the criteria defined in Table 2-2.

The shift tables and the analyses of abnormalities in LFT will use all the available post-baseline laboratory assessments, including unscheduled visits and early exit.

Table 2-2 Notable liver function test criteria

Peak post-baseline value
ALT >3x ULN
ALT >5x ULN
ALT >10x ULN
ALT >20x ULN
AST >3x ULN
AST >5x ULN
AST >10x ULN
AST >20x ULN
ALT or AST >3x ULN
ALT or AST >5x ULN
ALT or AST >8x ULN
ALT or AST >10x ULN
ALT or AST >20x ULN
ALP > 2x ULN
Total bilirubin (BILI) >2x ULN
Total bilirubin (BILI) >3x ULN
Combined elevations post-baseline
For participants with AST and ALT =< ULN at baseline
Elevated ALT or AST ($) & BILI >2x ULN
Elevated ALT or AST ($) & BILI >2x ULN & ALP >=2x ULN
Elevated ALT or AST ($) & BILI >2x ULN & ALP <2x ULN
For participants with ALT or AST > ULN at baseline
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP >=2x ULN
Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase
Combined elevations based on the peak post-baseline values (considering all post-baseline data from scheduled, unscheduled and premature discontinuation visit) for each parameter for each participant.
* Elevated AST or ALT for participants with > ULN at baseline is defined as >3x Baseline or 8x ULN.
$ Elevated AST or ALT for participants with =< ULN at baseline is defined as >3x ULN.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

New or worsened clinically significant ECG findings occurring after informed consent will be reported as AEs and included in the applicable AE summaries.

2.7.4.2 Vital signs

Observed value, absolute change, and percent change from baseline in vital signs (SBP, DBP, and pulse) will be summarized descriptively at baseline (for observed value only) and at each post-baseline visit. At each assessment, the average of 3 repeated readings will be used for analysis.

2.8 Impact of COVID-19

AEs related to COVID-19 by preferred term will be summarized by treatment group and overall. All AEs in clinical database will be considered regardless of whether the AE is treatment emergent or not.

The number and percentage of participants with any and each of the following COVID-19 impacted criteria will be provided for all randomized participants: (1) missed visit due to COVID-19; (2) assessment/procedure changed due to COVID-19; (3) treatment not given due to COVID-19; (4) study treatment discontinuation due to COVID-19; (5) premature study discontinuation due to COVID-19; (6) death related to COVID-19.

2.9 Pharmacokinetic endpoints

Not applicable for this study.

2.10 PD and PK/PD analyses

Not applicable for this study.

2.11 Patient-reported outcomes

Not applicable for this study.

[redacted]

2.14 Interim analysis

No formal interim analysis will be performed in this study.

3 Sample size calculation

3.1 Primary endpoints

The sample size calculation was based on a two sample t-test for the hypothesis that inclisiran is superior to either placebo or ezetimibe in terms of mean percentage change from baseline to Day 150 in LDL-C, at a one-sided significance level of 0.0125 (assuming a more conservative Bonferroni alpha split between the two primary hypotheses).

The sample size of 280 completers in total (with randomization ratio of 2:1:1 to inclisiran, placebo, and ezetimibe arms) will provide at least 99% power to detect a 40% difference between inclisiran and placebo or a 20% difference between inclisiran and ezetimibe at significance level of 0.0125 (one-sided test) assuming 30% for the standard deviation. Adjusted for 6% potential dropouts, approximately 300 participants in total will be randomized with a 2:1:1 ratio, i.e., 150 participants in the inclisiran arm, and 75 participants in both the placebo and ezetimibe arm.

3.2 Secondary endpoints

Statistical power will not be assessed for secondary endpoints.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

For subjects whose end date of last dosing summary record with p.o. study treatment dose > 0 is missing, the date of last p.o. study treatment will be derived as the start date of that dosing summary record or the last IRT date of p.o. study treatment dispensing record, whichever is later.

5.1.2 AE date imputation

The partially missing AE start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study programming datasets specifications (PDS).

5.1.3 Concomitant medication date imputation

The partially missing concomitant medication start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study PDS.

5.2 AEs coding/grading

Coding of AE will be done per MedDRA dictionary.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Implementation of MCP

The graphical MCP outlined in Section 2.5.2 and Section 2.6.2 will be implemented using a closed test procedure. Let $U = \{IP, IE, IP1, IE1, \ldots, IP7, IE7\}$ denote the index set for the 16 hypotheses H_{IP}, H_{IE}, H_{IP1}, H_{IE1}, …, H_{IP7}, H_{IE7} that correspond to the nodes in Figure 2-1. The closed test procedure rejects H_i, $i \in U$, at overall significance level alpha, if all non-empty intersection hypotheses containing H_i, i.e. $H_J = \cap_{j \in J} H_j$, $i \in J \subseteq U$, are rejected by their corresponding alpha-level tests. The weights $w_j(J)$ assigned to each individual hypothesis $j \in J$ for each non-empty intersection hypothesis H_J, $J \subseteq U$, are derived by Algorithm 1 in Bretz et al 2011 based on the graph in Figure 2-1. Because of the hierarchical structure of the graph, $2^{16} - 1$ non-empty intersection hypotheses can be categorized into two types based on the number of intersected individual hypotheses that are given positive weights:

> Type 1: Only one individual hypothesis has positive weight $w_j(J) = 1$, $j \in J$. All the other individual hypotheses (if any) included in the intersection have zero weight.
>
> Type 2: Exactly two individual hypotheses H_i, H_j, i and $j \in J$, $i \neq j$ have positive weights $w_i(J)$ and $w_j(J)$ that sum up to one. All the other individual hypotheses (if any) included in the intersection have zero weight.

Type 2 can be further categorized based on whether the two positive-weight individual hypotheses are for the same endpoint (i.e. a pair of nodes in the same layer in Figure 2-1):

> Type 2-1: The two hypotheses are for different endpoints.
>
> Type 2-2: The two hypotheses are for the same endpoint.

A Type 1 intersection hypothesis will be rejected at level alpha if the only positive-weight individual hypothesis is rejected at local level alpha. A Type 2-1 intersection hypothesis will be tested using a weighted Bonferroni test, i.e. the intersection hypothesis is rejected if $p_i \leq w_i(J)$ * alpha or $p_j \leq w_j(J)$ * alpha, where p_i and p_j are the unadjusted p-values for the two positive-weight individual hypotheses.

Although the Type 2-2 intersection hypotheses can also possibly be tested using a weighted Bonferroni test, a weighted Dunnett test will be used to benefit from the correlation between the inclisiran-placebo and inclisiran-ezetimibe comparisons for the same endpoint. The correlation will be based on the total covariance matrix derived by combining within-imputation covariance matrix and between-imputation covariance matrix using Rubin's method (Rubin 1987). Within-imputation covariance matrix is the average of the covariance matrices of least squares means, each estimated from the ANCOVA model applied to a multiply imputed dataset. Between-imputation covariance matrix is the sample covariance matrix of least squares means across multiply imputed datasets. Let Φ^{-1} denote the inverse cumulative distribution function (a.k.a. quantile function) of standard univariate normal distribution, and (Z_1, Z_2) denote a bivariate normal random vector with marginal variance = 1 and correlation as estimated above. The weighted Dunnett test rejects a Type 2-2 intersection hypothesis if $p_i \leq c_J * w_i(J) * alpha$ or $p_j \leq c_J * w_j(J) * alpha$, where c_J is a constant between 1 and 2 that satisfies Prob $[Z_1 \geq \Phi^{-1}(1- c_J * w_i(J) * alpha)$ or $Z_2 \geq \Phi^{-1}(1- c_J * w_j(J) * alpha)] = alpha$.

6 Reference

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