NOVARTIS

Clinical Development

KJX839/Inclisiran/Leqvio®

CKJX839D12305 / NCT05888103

A 6 month randomized, double-blind, placebo-controlled study followed by a 6 month open-label extension to assess the efficacy and safety of inclisiran as monotherapy in Chinese adults with low or moderate ASCVD risk and elevated low-density lipoprotein cholesterol

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final
Release date:	29-Oct-2024
Number of pages:	43

Template Version 6.0, Effective from 23-Nov-2022

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
19-June-2023	Prior to core part DB lock	[redacted]	N/A - First version	NA
22-April-2024	Prior to core part DB lock		SAP Amendment 1	Section 2.2.1 Section 2.5.6
				Section 2.3.2
				Section 2.4.2
				Section 2.7.1
				Section 2.7.1.1
				[redacted]
				Appendix 5.1.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-August-2024	Prior to final DB lock	[redacted]	SAP Amendment 2	Section 2.2 Section 2.3.1 Section 2.4.1 Section 2.4.2 Section 2.7 Section 2.8 Appendix 5.5
				Section 2.4 Section 2.7.1 Section 2.8
				Section 2.7.3
				Section 2.4.1
				Section 2.7.1 Section 2.7.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		[redacted]		
				Section 2.7.1
				Section 2.3.1
				Section 5.4.2

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AGB	ADaM Governance Board
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ApoA-1	Apolipoprotein A-1
ApoB	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
EOC	End of Core Part
FAS	Full Analysis Set
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin (hemoglobin A1c)
HDL-C	High-Density Lipoprotein Cholesterol
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)
MACE	Major Adverse Cardiovascular Event
MAR	Missing-at-Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
non-HDL-C	non-High-Density Lipoprotein Cholesterol
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PD	Pharmacodynamics
PDS	Programming Datasets Specifications

PK	Pharmacokinetics
PMM	Pattern-Mixture Model
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RAS	Randomized Analysis Set
RDO	Retrieved Drop Out
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 to describe the implementation of the statistical analysis planned in Section 9 of the CKJX839D12305 study protocol version 00 and to support the completion of both the core part clinical study report (CSR) and the Final CSR for the study CKJX839D12305.

The core part analyses will be conducted after the core part database lock (DBL), when all randomized participants have completed the Day 180 visit (or have discontinued from the study). The results from the core part analyses will be summarized in the core part CSR.

The final analyses will be conducted when the trial ended. The results from final analyses will be summarized in the final CSR.

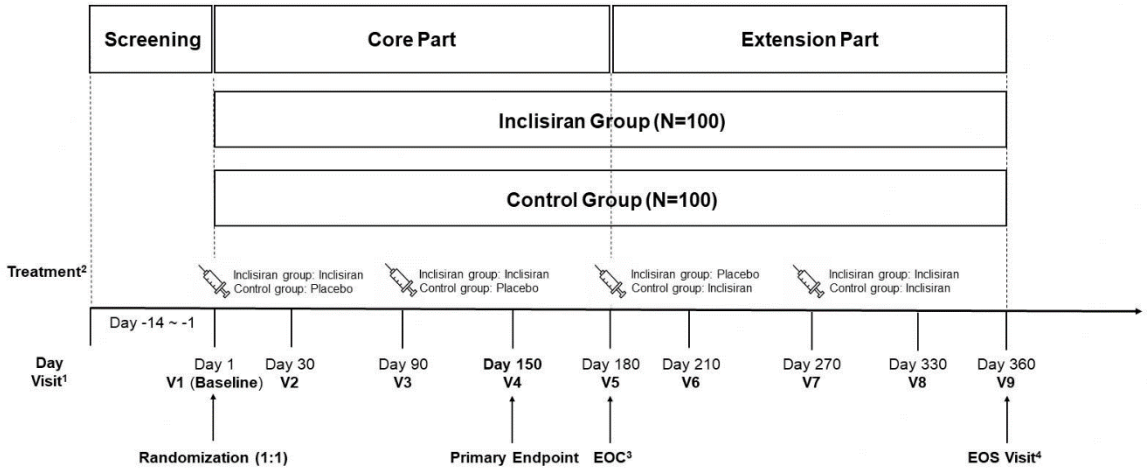
1.1 Study design

This study is designed as a randomized, double-blind, multi-center phase 3 trial, with a placebo-controlled period and an open label treatment period, to evaluate the efficacy and safety of inclisiran sodium 300mg s.c. in participants aged 18~75 years with low or moderate ASCVD risk and fasting low-density lipoprotein cholesterol (LDL-C) value of ≥ 130 mg/dL but < 190 mg/dL who are not on any lipid lowering therapy.

The study design is depicted in Figure 1-1. The study consists of 3 parts:

- **Screening**: a screening period of up to 14 days for all participants
- **Core Part:** a double-blind, placebo-controlled treatment period of 180 days in which eligible participants will be randomized 1:1 to receive either inclisiran sodium 300mg s.c. (Inclisiran Group) or matching placebo s.c. (Control Group) on Day 1 and Day 90. The end of core part (EOC) visit will be conducted on Day 180. The database lock for the core part is planned to occur after all randomized participants have completed the EOC visit (or have discontinued from the study before EOC). The primary endpoint analysis will be conducted after the database lock for the core part.
- **Extension Part:** an extended treatment period of 180 days. After all "Core part" study assessments are completed on Day 180, the extension part starts. In the extension, all patients randomized to inclisiran in the core part will continue on inclisiran while patients initially randomized to placebo will transit to inclisiran therapy. The extension part starts from a dose of study treatment on Day 180 (placebo in the inclisiran group and inclisiran for patients originally randomized to the control group). Thereafter, all participants will receive inclisiran sodium 300mg s.c. on Day 270. Treatment on Day 270 will be open-label. Participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (inclisiran vs placebo) until final database lock. The EOS visit (Day 360) will be the last visit of the study.

Figure 1-1 Study design



1. Participants who discontinue from study treatment should continue to attend the rest of the scheduled visits.
2. Participants randomized to Inclisiran Group will be treated with inclisiran sodium 300mg s.c. on Day 1 and Day 90 and Day 270, and with matching placebo s.c. on Day 180. Participants randomized to Control Group will be treated with matching placebo s.c. on Day 1 and Day 90, and with inclisiran sodium 300mg on Day 180 and Day 270.
3. The end of core part visit. The database lock for the core part is planned to occur after all randomized participants have completed the EOC visit (or have discontinued from the study before EOC). The primary endpoint analysis will be conducted after the database lock for the core part.
4. Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable.

On Day 1 (Baseline), approximated 200 eligible participants who meet all inclusion and not meet any exclusion criteria will be randomized 1:1 to Inclisiran Group and Control Group. Study visits of core part will occur on Day 1 (baseline visit), Day 30, Day 90, Day 150, and Day 180. On Day 1 and Day 90 visits, inclisiran s.c. or placebo s.c. will be administered at the site by a healthcare professional. The primary endpoint will be assessed at Day 150. The EOC visit will be conducted on Day 180.

The extension part starts with a dose on Day 180 after all core part assessment are completed. In order to maintain the blind for the treatment group assignment, participants randomized to Control Group will receive inclisiran, while participants randomized to Inclisiran Group will receive placebo on Day 180. All participants will then receive inclisiran sodium 300 mg on Day 270, which will be the third dose of inclisiran for Inclisiran Group, and the second dose of inclisiran for Control Group. All injections will be administered at the site by a healthcare professional. The EOS visit (Day 360) will be the last visit of the study.

The randomization will not be stratified.

The core part analyses will be conducted when all randomized participants have completed the visit at Day 180 (or have discontinued from the study). The final analyses will be conducted when the trial ended. No interim analyses are planned.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate the superiority of inclisiran as monotherapy, compared to placebo, on mean percentage change from baseline in LDL-C at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid lowering therapy.	● Percentage change in LDL-C from baseline at Day 150
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on absolute change from baseline in LDL-C at Day 150.	● Absolute change in LDL-C from baseline at Day 150
● To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on percentage and absolute change from baseline in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), total cholesterol (TC), high-density lipoprotein (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), apolipoprotein A-1 (ApoA-1), lipoprotein (a) (Lp(a)) and triglycerides (TG) at Day 150.	● Percentage change from baseline at Day 150 in PCSK9 ● Absolute change from baseline at Day 150 in PCSK9 ● Percentage change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG ● Absolute change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG
● To evaluate the effect of inclisiran as monotherapy on percentage and absolute change in LDL-C from baseline at Day 330.	● Percentage change in LDL-C from baseline at Day 330 for inclisiran group ● Absolute change in LDL-C from baseline at Day 330 for inclisiran group
● To evaluate the safety and tolerability of inclisiran as monotherapy compared to placebo during core part.	● Adverse Events (AEs), vital signs and safety laboratory values
● To evaluate the safety and tolerability of inclisiran as monotherapy during extension part.	● Adverse Events (AEs), vital signs and safety laboratory values
[redacted]	

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).

The clinical question of primary interest is: what is the reduction in LDL-C, quantified by difference of mean percentage change from baseline at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy, who receive inclisiran as monotherapy, compared to placebo, regardless of discontinuation from study treatment, if other lipid-lowering therapy were not taken, and where death due to CV or non-CV causes is considered an unfavorable outcome.

The primary estimand is described by the following attributes:

Population: Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy.

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

Treatments of interest: Inclisiran as monotherapy compared to the use of placebo, regardless of study treatment discontinuation.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be handled with a treatment policy strategy, keeping treatment labels as assigned at randomization.

- Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 150 visit assessment or other LLT taken within 30 days before Day 150 visit assessment) will be treated with a hypothetical strategy of what would happen had those LLT not been taken and those participants behaved like other participants in the same treatment group.
- Participants who died will be handled with a composite strategy; death is considered an unfavorable outcome.

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

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)

1.2.2.1 Secondary estimands for core part

The secondary estimands for core part address the same clinical question as the primary estimand, albeit for different endpoints. They share the same population, intercurrent events, summary measure, as well as the same treatments as the primary estimand. They differ by the definition of the endpoints, these being:

- Absolute change in LDL-C from baseline at Day 150
- Percentage and absolute change in PCSK9, TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG from baseline at Day 150

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 2.6.

1.2.2.2 Secondary estimands for extension part

The clinical question of interest in extension part is: what is the reduction in LDL-C, quantified by mean percentage or absolute change from baseline at Day 330, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy, who receive inclisiran as monotherapy, regardless of discontinuation from study treatment, if other lipid-lowering therapy were not taken, and where death due to CV or non-CV causes is considered an unfavorable outcome.

The secondary estimand for extension part is described by the following attributes:

Population: Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy.

Endpoint: Percentage or absolute change from baseline at Day 330 in LDL-C for inclisiran group.

Treatments of interest: Inclisiran as monotherapy, regardless of study treatment discontinuation.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be handled with a treatment policy strategy, keeping treatment labels as assigned at randomization.

- Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 330 visit assessment or other LLT taken within 30 days before Day 330 visit assessment) will be treated with a hypothetical strategy of what would happen had those LLT not been taken, and those participants behaved like other participants in the same treatment group.
- Participants who died will be handled with a composite strategy; death is considered an unfavorable outcome.

Summary measure: the summary measure to be used is the mean percentage or absolute change.

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 2.6.

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis or a designated CRO. The most recent version of SAS available in the statistical programming environment of Novartis or the designated CRO will be used for the analyses.

The core part analyses will be conducted after the core part database lock, when all randomized participants have completed the Day 180 visit (or have discontinued from the study). The data snapshot at the time of the core part database lock will be used for these analyses. The analysis cutoff date will be determined and documented prior to the core part database lock, and will be chosen based on the operational feasibility, as a calendar date on or after the last core part visit date from all participants and prior to the core part database lock date. The analysis cutoff date will be applied to include relevant extension part assessments / events in the core part analyses. All events with start date before or on the cut-off date, and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. The results from the core part analyses will be summarized in the core part CSR.

The final analyses will be conducted after the final database lock at the end of the study, when all randomized participants have completed the Day 360 visit (or have discontinued from the study). The data snapshot at the time of the final database lock will be used for the final analyses. The analysis cutoff date for the final analyses will be the final database lock date, such that, all collected data will be included in the final analyses. The results from the final analyses will be summarized in the final CSR.

For overall study analyses in core part analyses, available data on or prior to the analysis cutoff date will be used, unless otherwise specified. For by-part analyses, analyses using core part data and extension part data will be performed in core part analyses and final analyses, respectively, unless otherwise specified. If there were any major changes in core part data after the core part DBL, some analyses including only core part data may be repeated in final analyses. This will be recorded in the TFL shell before the final DBL.

In general, continuous data will be summarized using number of non-missing observations (n), mean, standard deviation, median, minimum, the 25th percentile (Q1), the 75th percentile (Q3), and maximum; categorical data will be summarized using frequencies and percentages.

2.1.1 General definitions

Study treatment

The term "study drug" or "study treatment" refers to the study drug (inclisiran sodium 300 mg s.c. or inclisiran-matching placebo) dispensed during the study.

For each participant and each dosing visit, the participant will be considered to have received the study treatment if the date of dose is non-missing and the answer to 'was dose administered' is yes.

For each participant, the first dose date and the last dose date of the study treatment are defined as the earliest date and the latest date on which the participant received the study treatment.

Study day

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

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

For dates on or after the date of first dose of study treatment,

Study day = Assessment date – Date of first dose of study treatment + 1;

For dates prior to the date of first dose of study treatment,

Study day = Assessment date – Date of first dose of study treatment.

In case a participant has been randomized but has not received any study treatment then randomization visit day will be considered as Day 1.

Baseline assessment

For each variable, the baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) collected on or prior to the first dose of study treatment, unless otherwise specified. If a participant has never started any study treatment, then the last non-missing assessment (scheduled or unscheduled) collected on or prior to the study Day 1 will be used as baseline assessment.

Post-baseline assessment

Post-baseline assessments are defined as those assessments that were collected after the first dose of study 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.

Percentage change from baseline = (absolute change from baseline / baseline value)*100.

Unscheduled assessment

Unscheduled assessments will not be included in by-visit summary but will be included in the derivation of over-period minimum and maximum values.

All scheduled or unscheduled assessments will be included in the listings.

Early Exist (EE) visit mapping

For participants who discontinued from the study and come to the site for the early exit (EE) visit, the EE visit will be mapped to the next scheduled visit.

Table 2-1 Early exit (EE) visit mapping

Study status	Last Attended Scheduled Visit Prior to EE		Mapped Visit for Visit EE	
	Visit Day	Visit Name	Visit Day	Visit Name
Discontinued	1	Visit 1	30	Visit 2
Discontinued	30	Visit 2	90	Visit 3
Discontinued	90	Visit 3	150	Visit 4
Discontinued	150	Visit 4	180	Visit 5/EOC
Discontinued	180	Visit 5/EOC	210	Visit 6
Discontinued	210	Visit 6	270	Visit 7
Discontinued	270	Visit 7	330	Visit 8
Discontinued	330	Visit 8	360	Visit 9/EOS
Completed	---	---	---	---

Switching date

The switching date will be defined using the following algorithm.

- For participants with non-missing Day 180 study treatment dose date, the switching date will be set to the Day 180 study treatment dose date.
- For participants with missing Day 180 study treatment dose date and non-missing Day 180 visit date, the switching date will be set to the Day 180 visit date.
- For participants with missing Day 180 study treatment dose date and missing Day 180 visit date, the switching date will be set to the study day 195 date.

If the resulting switching date locates after the study discontinuation date or the analysis cutoff date (if any), the switching date will be set to missing and the participant will be considered to have not switched until the study discontinuation or the analysis cutoff.

Assessments and events allocation

In general, assessments and events will be allocated into the screening period, the core part and the extension part using the following rules.

- For non-randomized participants, all assessments / events will be considered as screening period assessments / events.
- For randomized participants, assessments / events with assessment date / event date prior to the randomization visit date will be considered as screening period assessments / events.
- For randomized participants with missing switching date, assessments / events with assessment date / event date on or after the randomization visit date will be considered as core part assessments / events.
- For randomized participants with non-missing switching date, assessments / events with assessment date / event date on or after the randomization visit date and on or prior to the switching date will be considered as core part assessments / events.
- For randomized participants with non-missing switching date, assessments / events with assessment date / event date after the switching date will be considered as extension part assessments / events.

Study treatment allocation

In general, study treatments will be allocated using the following algorithm.

- Study treatments at the randomization visit and Day 90 will be considered as core part study treatments.
- Study treatments at Day 180 and Day 270 will be considered as extension part study treatments.

Reflexive LDL-C

The LDL-C will be collected through the central laboratory, using the Friedewald formula and the ultracentrifugation method as appropriate. The calculated LDL-C (Friedewald formula) and the directly measured LDL-C (ultracentrifugation) will be loaded from the central laboratory.

The LDL-C endpoint will be derived using a reflexive LDL-C approach: either calculated LDL-C (based on the Friedewald formula) will be used, or if the calculated LDL-C is less than 70 mg/dL or triglycerides are greater than 400 mg/dL, or calculated LDL-C is missing, directly measured (using ultracentrifugation) LDL-C will be used if it is available.

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)** consists of all randomized participants with the exception of those participants who have not been qualified for randomization and have not received study drug 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 drug. Participants will be analyzed according to the study treatment actually received. The SAF will be used for the analyses of safety variables.

The **Open-label Set (OLS)** includes all participants who entered the extension part and received at least one dose of study drug during extension part (at Day 180 or Day 270). OLS will be used to analyze the non-efficacy data in extension part, unless otherwise specified.

Participants without valid written informed consent will be excluded from all analysis sets. Further exclusions from the FAS are only justified in exceptional circumstances (e.g., site closed down for GCP reasons). The determination of which participants were excluded from the FAS is made in a blinded manner before the database lock for the Core Part.

Rules leading to exclusion from the analysis sets are given in Appendix 5.5.

Note: The last part of the definition of the FAS is what is often referred to as mis-randomized 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 study medication was not administered to the participant. These participants would subsequently not continue to take part in the study or be followed-up. Mis-randomized participants will not be included in the FAS, but they will be included in the RAS.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Core part analyses

The screening period completion status and the corresponding reason for non-completion will be collected for all participants with informed consent signed as the screening disposition and will be summarized using the number of screened participants, the number and the percentage of screened participants, who completed the screening period, and who discontinued during the screening period. In addition, the reason for discontinuation will also be summarized, using the number and the percentage of screened participants discontinued due to each reason. The SCR will be used for screening disposition.

The study completion status and the corresponding reason for non-completion will be collected for all randomized participants as the study disposition. The study disposition for core part will be summarized by treatment group separately using the number of randomized participants, the number and the percentage of participants who completed core part, and who discontinued from the study during core part. The reason for discontinuation during the core part will be summarized by treatment group separately, using the number and the percentage of participants discontinued due to each reason. The RAS will be used. Listing for study disposition will also be provided for core part.

The study treatment completion status and the corresponding reason for non-completion for core part will be summarized by treatment group, using SAF.

Duration on study is defined as: date of last known visit on study – date of study Day 1 + 1. For core part analyses, duration on study will be truncated at switching date. The duration on study will be summarized by treatment group for core part, using FAS.

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 for core part, using RAS. Listing of participants with protocol deviation will be provided for core part.

The number of participants included in each analysis set will be tabulated by treatment group using SCR. Participants exclusion from analysis sets will be summarized for all participants with reasons for exclusion (i.e. including both protocol and non-protocol deviations) and corresponding listing will be provided.

Final analyses

The study disposition for extension part will be summarized by treatment group separately using the number of randomized participants, the number of completed core part participants, the number and the percentage of participants who completed extension part, and who discontinued from the study during extension part. The reason for discontinuation during the extension part will be summarized by treatment group separately, using the number and the percentage of participants discontinued due to each reason. The RAS will be used. Listing for study disposition will also be provided for overall study.

The study treatment completion status and the corresponding reason for non-completion for extension part will be summarized by treatment group, using OLS.

Duration on study is defined as: date of last known visit on study – date of study Day 1 + 1. The duration on study will be summarized by treatment group for overall study using FAS.

Number of participants with protocol deviations will be tabulated by category, deviation for extension part and for overall study, using OLS and RAS, respectively. Listing of participants with protocol deviation will be provided for overall study.

The number of participants included in each analysis set will be tabulated by treatment group using SCR. Participants exclusion from analysis sets will be summarized for all participants with reasons for exclusion (i.e. including both protocol and non-protocol deviations) and corresponding listing will be provided.

2.3.2 Demographics and other baseline characteristics

Summary statistics will be provided by treatment group for demographics and for other baseline characteristics, including age (years), age group (< 65 years, >= 65 years), sex, race, ethnicity, smoking history, alcohol history, protocol solicited medical history, ASCVD risk level, height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, eGFR, eGFR group (>=30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, >= 60 mL/min/1.73 m^2), LDL-C, PCSK9, TG, TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a), where the BMI will be calculated as weight (kg) / [height (m)]^2 from the height and the weight at screening. For variables only scheduled at screening, the scheduled assessment at screening will be summarized. For other variables, the baseline assessment will be summarized. Listings will also be provided.

The FAS will be used for the above summaries.

The above summaries for demographics and baseline characteristics will be conducted only in the core part analyses.

Medical histories will be collected using the medical history case report form (CRF) and coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA). The collected medical histories will be summarized by treatment group, primary system organ class (SOC), and preferred term (PT), using the number and the percentage of participants with each medical history.

The FAS will be used for the above summaries.

The above summaries for medical histories will be conducted only in the core part analyses.

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

The SAF will be used for the analyses below, unless otherwise specified.

2.4.1 Study treatment / compliance

The number and percentage of participants receiving study dose and the injection site location will be summarized by study visit and treatment group for both core part analyses and final analyses. For core part analyses, the summary tables including Day 1 and Day 90 visit and for overall study will be provided. For final analyses, the summary table will include Day 180, and Day 270 visit using OLS.

The number of doses received during the core part (at Day 1 and Day 90), duration of exposure, patient year of exposure will be summarized by treatment group for core part analyses. Such summary table of exposure to study treatment and listing for overall study will also be provided in core part analyses. The number of doses received during the whole study, duration of exposure for overall study and patient year of exposure will be summarized by treatment group for final analyses. Listings for overall study will also be provided in final analyses.

Duration of exposure for overall study will be calculated as: minimum of (Date of last dose of treatment – Date of first dose of treatment + 1 + 180, Date of last known visit – Date of first dose of treatment + 1). Duration of exposure to study treatment for overall study will be truncated at the analysis cutoff date for core part analyses.

The number of doses received during the extension part (at Day 180 and Day 270), duration of exposure in extension part and patient year of exposure will also be summarized by treatment group using OLS for final analyses. Duration of exposure for extension part will be calculated as: minimum of (Date of last dose of treatment in extension part – Date of treatment at Day 180 + 1 + 180, Date of last known visit in extension part – Date of treatment at Day 180 + 1). If the Day 180 treatment was not taken, then the date of Day 180 visit will be used.

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

2.4.2 Prior and concomitant therapies

Prior / concomitant medications / non-drug therapies will be collected in the corresponding CRF and will be coded using the WHO dictionary and the MedDRA dictionary accordingly. The medications / non-drug therapies will be classified into prior, core part concomitant, and extension part concomitant.

- The prior (pre-baseline) medications / non-drug therapies will be defined as medications / non-drug therapies with the end date prior to the first dose date of study treatment.
- The core part concomitant medications / non-drug therapies will be defined as medications / non-drug therapies with the end date on or after the first dose date of study treatment (or no documented end date) and the start date on or prior to the switching date.
- The extension part concomitant medications / non-drug therapies will be defined as medications / non-drug therapies with the end date after the switching date (or no documented end date).

The prior medications will be summarized by treatment group, anatomical therapeutic chemical (ATC) class and PT for core part analyses only. The concomitant medications will be summarized by study part, treatment group, ATC class and PT. For the extension part, the summary will be provided using OLS.

The prior non-drug therapies will be summarized by treatment group, SOC and PT for core part analyses only. The concomitant non-drug therapies will be summarized by study part, treatment group, SOC and PT. For the extension part, the summary will be provide using OLS.

The following lipid-lowering therapies will be identified from the medications, using the ATC class and the PT. Detailed specifications will be provided separately.

- Statins
- Cholesterol absorption inhibitor
- PCSK9 inhibitor monoclonal antibody
- Inclisiran
- Other lipid lowering therapy

Any above lipid-lowering therapy added after study Day 1 will be summarized by treatment group and medication, using the numbers and the percentages of participants who received the corresponding medication on or prior to the following select time points.

- Study day 1
- Study day 90
- Study day 150
- Study day 180
- Study day 270
- Study day 330
- Study day 360

In core part analyses, the above new added LLT summary table will include time points up to study Day 180 only. In final analyses, summary table of new added LLT will be provided including the time points from study Day 180 up to study Day 360 using OLS.

2.5 Analysis supporting primary objective(s)

The FAS will be used for the primary efficacy analysis.

2.5.1 Primary endpoint(s)

The primary objective of this study is to demonstrate the superiority of inclisiran as monotherapy, compared to placebo, on mean percentage change from baseline in LDL-C at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid lowering therapy.

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

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint will be analyzed using an Analysis of Covariance (ANCOVA) model, in which the response variable will be the percentage change from baseline at Day 150 in LDL-C, treatment will be included as fixed-effect factor and baseline LDL-C will be included as a covariate.

The primary statistical hypothesis is stated as below.

- H_0: the mean difference (inclisiran minus placebo) in percentage change from baseline at Day 150 in LDL-C is no less than zero.
- H_1: the mean difference (inclisiran minus placebo) in percentage change from baseline at Day 150 in LDL-C is less than zero.

The study can be claimed a success if the null hypothesis (H_0) is rejected at the one-sided significance level of 0.025.

The statistical test will be performed at the one-sided significance level of 0.025 based on the ANCOVA model. The estimate and the 95% confidence interval will be provided for the adjusted mean difference between inclisiran and placebo, and for the adjusted mean for both inclisiran and control groups, based on the ANCOVA model. The one-sided p-value will be provided for the primary null hypothesis.

2.5.3 Handling of intercurrent events

The primary efficacy analysis will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment:** Retrieved drop out (RDO) data collected after discontinuation from study treatment will be used for the analysis (treatment policy). Missing data after discontinuation from study treatment will be multiply imputed based on RDO data within each treatment group, and when there are no sufficient RDO data, a control-based Pattern-Mixture Model (PMM) will be used for multiple imputation. In the PMM, missing not at random (MNAR) assumption will be used for inclisiran group. The detailed information is specified in Appendix 5.4.1.1.
- **Use of prohibited LLT:** Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 150 visit assessment or other LLT taken within 30 days before Day 150 visit assessment) will be treated in a hypothetical scenario of what would happen had those LLT not been taken, and those participants behaved like other participants in the same treatment group (hypothetical strategy). Data after those intercurrent events will be

excluded for the analysis and will be multiply imputed within each treatment group under MAR assumption.

- **Death:** Death due to CV or non-CV causes is considered as an unfavorable outcome (composite strategy). The LDL-C values at Day 150 after death will be set using the participant's baseline values.

In the case of multiple intercurrent events, death will be the dominant one in the analysis (if present). If a participant experiences only two other intercurrent events and usage of prohibited LLT occurs first, s/he will be handled by the event of usage of LLT (hypothetical strategy). If treatment discontinuation occurs prior to usage of prohibited LLT, then data after usage of LLT will be set missing and s/he will be handled by the event of treatment discontinuation (treatment policy). The detailed imputation model and algorithm are specified in Appendix 5.4.1.1. Number and percentage of participants by each intercurrent event will be summarized by treatment group in core part analyses. Listing will also be provided.

2.5.4 Handling of missing values not related to intercurrent event

Missing values not related to intercurrent event will be multiply imputed within each treatment group under MAR assumption. The detailed imputation model and algorithm are specified in Appendix 5.4.1.1. The primary efficacy 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 rule.

2.5.5 Sensitivity analyses

The following sensitivity analysis will be conducted to assess the robustness of the inferences to various assumptions about the hypothetical strategy for handling usage of prohibited LLT.

- **Tipping point analyses:** a tipping point analysis will be performed to search for the tipping point that reverses the study conclusion. In the tipping point analysis, scale-adjustment to the MAR assumptions will be applied multiplicatively to the imputed values, where the multiplicative factor is allowed to vary for inclisiran group only.

2.5.6 Supplementary analyses

A plot displaying descriptive mean percentage change in LDL-C from baseline up to Day 180 visit for both treatment groups will be provided, using the observed data.

Subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline characteristics will be performed in subgroups as specified in Section 2.2.1. The subgroup analyses will use the same ANCOVA model as specified above. The difference in the adjusted means between treatment groups, corresponding two-sided 95% CI and one-sided p-value will also be provided for each of the subgroups. The adjusted means in both treatment groups, corresponding two-sided 95% CI will also be provided for each of the subgroups. The subgroup analysis results will be left blank if the subgroup analysis model did not converge. Forest plot will be provided for subgroup analyses. The multiply imputed datasets created from primary analysis will be used in the subgroup analyses. The results from the subgroup analysis models will be combined using the Rubin's rule.

Two sets of supplementary analyses under different estimand will also be conducted.

For the first one, all three intercurrent events, including discontinuation of study treatment, use of prohibited LLT under certain conditions and death due to CV or non-CV causes, will be handled with a hypothetical strategy. Data after all these intercurrent events will be multiply imputed under missing at random assumption. Missing values not related to intercurrent events will also be multiply imputed under missing at random assumption. Details are specified in Appendix 5.4.1.2.

For the second one, the intercurrent events of discontinuation of study treatment and death due to CV or non-CV causes will be handled in the same way as in the primary analysis. Use of prohibited LLT under certain conditions will be treated with a treatment policy strategy, keeping treatment labels as assigned at randomization. Retrieved drop out (RDO) data collected after use of prohibited LLT under certain conditions will be used for the analysis. Missing data after usage of prohibited LLT will be multiply imputed using a control-based PMM. Missing values not related to intercurrent events will also be multiply imputed using a control-based PMM. Details are specified in Appendix 5.4.1.3.

2.6 Analysis supporting secondary efficacy objectives

The FAS will be used for all below efficacy analyses.

2.6.1 Secondary endpoint(s).

2.6.1.1 Secondary efficacy endpoints for core part

The secondary efficacy endpoints for core part are listed as follows:

- Absolute change in LDL-C from baseline at Day 150
- Percentage and absolute change in PCSK9, TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG from baseline at Day 150

All secondary efficacy endpoints for core part will be analyzed using the same ANCOVA model as for the primary efficacy endpoint. Lp(a) will be log-transformed before modeling. The model will include treatment as fixed effect, and baseline value as a covariate. The adjusted mean difference between inclisiran and placebo and corresponding two-sided 95% CIs will be provided separately. Nominal two-sided p-values will also be provided.

2.6.1.2 Secondary efficacy endpoints for extension part

The secondary efficacy endpoints for extension part are listed as follows:

- Percentage change in LDL-C from baseline at Day 330 for inclisiran group
- Absolute change in LDL-C from baseline at Day 330 for inclisiran group

The secondary efficacy endpoints for extension part will be analyzed descriptively. Mean percentage and absolute change from baseline at Day 330 in inclisiran group will be provided, respectively, as well as the 95% confidence intervals.

2.6.2 Statistical hypothesis, model, and method of analysis

No multiple comparisons including primary and secondary efficacy endpoints will be made.

2.6.3 Handling of intercurrent events

2.6.3.1 Estimands for core part

The same methods as specified in Section 2.5.3 will be applied to all secondary efficacy endpoints for core part. Multiple imputation will be conducted for log-transformed Lp(a) values. The details are specified in Appendix 5.4.2.

2.6.3.2 Estimands for extension part

The secondary efficacy analysis for extension part will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment:** Retrieved drop out (RDO) data collected after discontinuation from study treatment will be used for the analysis (treatment policy). Missing data after discontinuation from study treatment will be multiply imputed based on RDO data, and when there are no sufficient RDO data, a control-based PMM (using the Core Part data) will be used for multiple imputation. The detailed information is specified in Appendix 5.4.2.
- **Use of prohibited LLT:** Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 330 visit assessment or other LLT taken within 30 days before Day 330 visit assessment) will be treated in a hypothetical scenario of what would happen had those LLT not been taken, and those participants behaved like other participants in the same treatment group (hypothetical strategy). Data after those intercurrent events will be excluded for the analysis and will be multiply imputed under MAR assumption.
- **Death:** Death due to CV or non-CV causes is considered as an unfavorable outcome (composite strategy). The LDL-C values at Day 330 after death will be set using the participant's baseline values.

In the case of multiple intercurrent events, death will be the dominant one in the analysis (if present). If a participant experiences only two other intercurrent events and usage of prohibited LLT occurs first, s/he will be handled by the event of usage of LLT (hypothetical strategy). If treatment discontinuation occurs prior to usage of prohibited LLT, then data after usage of LLT will be set missing and s/he will be handled by the event of treatment discontinuation (treatment policy). The detailed imputation model and algorithm are specified in Appendix 5.4.2. Number and percentage of participants by each intercurrent event will be summarized by treatment group in final analyses. Listing will also be provided.

2.6.4 Handling of missing values not related to intercurrent event

2.6.4.1 Estimands for core part

The same methods as specified in Section 2.5.4 will be applied to all secondary efficacy endpoints for core part. Multiple imputation will be conducted for log-transformed Lp(a) values. The details are specified in Appendix 5.4.2.

2.6.4.2 Estimands for extension part

Missing values not related to intercurrent event will be multiply imputed under MAR assumption. The detailed imputation model and algorithm are specified in Appendix 5.4.2. The secondary efficacy analysis for extension part will be conducted on each multiply imputed dataset, and the results from each of those imputed datasets will be combined using Rubin's rule.

2.6.5 Sensitivity analyses

The same sensitivity analysis as specified in Section 2.5.5 will be conducted for LDL-C endpoint at Day 150.

2.6.6 Supplementary analyses

The same subgroup analyses as specified in Section 2.5.6 will be performed for absolute change in LDL-C at Day 150 and percentage change in PCSK9, TC, non-HDL-C and ApoB at Day 150. The difference in the adjusted means between treatment groups, corresponding two-sided 95% CI and two-sided p-value will be provided for each of the subgroups. The adjusted means in both treatment groups, corresponding two-sided 95% CI will also be provided for each of the subgroups.

A plot displaying descriptive mean percentage change in LDL-C from baseline up to Day 360 visit for both treatment groups will be provided, using the observed data.

2.7 Safety analyses

For all safety analyses, the SAF will be used, unless otherwise specified. All listings and tables will be presented by treatment group. Baseline data will be summarized where appropriate (for change from baseline summaries).

2.7.1 Adverse events (AEs)

An AE will be counted as a treatment emergent AE (TEAE) if the AE started after the first dose of study treatment or the AE present prior to start of study treatment but increased in severity based on preferred term. 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 date of first dose of study treatment. All TEAEs will be classified into core part TEAEs and extension part TEAEs.

- The core part TEAEs will be defined as TEAEs with the start date on or prior to the switching date.

- The extension TEAEs will be defined as TEAEs with the start date after the switching date.

Overall summary of TEAE will be displayed by treatment group and study part. The number (and percentage) of participants with TEAEs will be summarized:

- By study part, treatment group, primary system organ class (SOC) and preferred term (PT).
- By study part, treatment group, SOC, PT and maximum severity.
- By study part, treatment group, PT.
- By study part, treatment group, SOC and PT for TEAEs leading to study drug discontinuation.
- By study part, treatment group, SOC and PT for TEAEs related to study drug.

The number (and percentage) of participants with treatment emergent serious adverse events (TESAE) will be summarized:

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

In core part analyses, the number (and percentage) of participants with TESAE will also be summarized for overall study:

- By treatment group, SOC and PT.
- By treatment group, 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. If a participant reported more than one adverse event with the same PT, the AE will be counted only once. A participant with multiple adverse events 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 in both core part analyses and final analyses, regardless of whether they are treatment emergent.

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 study part, treatment group, SOC and PT.

For above by-part summary tables, OLS will be used for extension part data in final analyses. Besides, above summary tables for overall study will also be provided using SAF in final analyses. Subgroup analyses for safety will be performed in subgroups as specified in Section 2.2.1. Overall summary of TEAE by subgroup will be provided by treatment group in core part analyses. Subgroup analyses of all treatment emergent adverse events (TEAE) will also be displayed by treatment group, SOC and PT in core part analyses. The number (and percentage) of participants with TEAEs will be provided for each category of subgroup.

AE reporting for CT.gov

For the legal requirements of clinicaltrials.gov, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than X% (X will

be selected prior to final database lock)* 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 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 AE's 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 only after full study completion.

*Note: the X% has been chosen as 5% before the final database lock.

2.7.1.1 Adverse events of special interest / grouping of AEs

The number and percentage of participants with adverse event of special interest (AESI) will be summarized for each topic for:

- TEAE by study part, treatment group and PT

In final analyses, OLS will be used for the summary tables of extension part data. Besides, summary tables for overall study will also be provided using SAF. In core part analyses, summary of TEAE by treatment group, PT and maximum severity and of TESAE by treatment group and PT will also be provided. PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one adverse event with the same PT, the AE will be counted only once. If a participant reported more than one AE within the same AESI, the participant will be counted only once at that AESI.

Adverse event of special interest will include the following:

- Hepatotoxicity
- Injection site reaction

For injection site reaction, separate listing will be provided for participants with injection site reaction AE in both core part analyses and final analyses. The time to the first injection site reaction TEAE will also be summarized by treatment group and study part using the following categories: No ISR, ≤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 injection site reaction TEAE will also be summarized by treatment group and study part using the following categories: No ISR, ≤4h, >4h to ≤7 days, >7 days to ≤14 days, >14 days. Total number of TEAE at the injection site per participants will be summarized in categories (e.g. 1, 2, 3, and >3 etc.)

by treatment group and study part. In final analyses, OLS will be used for the summary tables of extension part data. Besides, all summary tables of injection site reaction will also be provided for overall study using SAF.

Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify the AESI. The CRS listing will be provided.

2.7.2 Deaths

As stated in Section 2.7.1, summary for deaths will be provided by SOC, PT of death cause and treatment. Specifically, the summary tables for core part and for overall study will be provided in core part analyses using SAF. Besides, the summary tables for extension part (using OLS) and for overall study (using SAF) will also be provided in final analyses. Listing of all deaths will be provided in both core part analyses and final analyses.

2.7.3 Laboratory data

Laboratory data consists of hematology, biochemistry, and urinalysis measurements. Observed value, absolute change, and percent change from baseline in continuous laboratory parameters will be summarized descriptively by visit and by treatment group. Frequency table of results for categorical laboratory parameters will be presented by visit. For some parameters, only screen tests are planned. Thus, summaries of post-baseline values will not be provided. For core part analyses, the summary tables will include Day 1 visit up to Day 180 visit. For final analyses, the summary table will include Day 1 visit up to Day 360 visit.

Shift tables using the low, normal, or high classification based on the normal range will be used to compare baseline to the worst post-baseline value by treatment group and study part for hematology and biochemistry measurements. All data collected after first dose of study treatment, from scheduled, unscheduled, and premature discontinuation visits will be used. For some parameters, if only screen tests are planned and there are no scheduled post-baseline values, then the shift table will not be provided. In final analyses, OLS will be used for the shift tables of extension part data. Besides, shift tables for overall study will also be provided using SAF.

The following ranges will be used for shift tables of eGFR, fasting glucose and HbA1c

- For eGFR, the categories will be:
  Severe = <30 mL/min/1.73m^2;
  Moderate = ≥ 30 to <60 mL/min/1.73m^2;
  Mild = ≥ 60 to <90 mL/min/1.73m^2;
  Normal = ≥90 mL/min/1.73m^2.
- For fasting glucose, the categories will be < 100 mg/dL, ≥ 100 mg/dL to < 126 mg/dL, and ≥ 126 mg/dL.
- For HbA1c, the categories will be <5.7%, ≥5.7% to <6.5%, and ≥6.5%.

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 study treatment, from scheduled, unscheduled, and premature discontinuation visits, will be summarized by

laboratory parameter and treatment group and study part. The worst post-baseline value will be used for this analysis. In final analyses, OLS will be used for the summary of worst post-baseline value from extension part. Besides, such summary of worst post-baseline from overall study will also be provided using SAF. Notable criteria are defined in Appendix 5.3. Clinically notable criteria will be considered to be met when both of the following occur:

- Post-baseline value meets the thresholds listed in Appendix 5.3.
- Baseline value and any prior post-baseline values do not meet the thresholds listed in Appendix 5.3.

Furthermore, the number and percentage of participants meeting notable criteria in liver function tests (LFT) will be summarized by treatment group and study part considering post-baseline data from scheduled, unscheduled, and premature discontinuation visit. LFT criteria are defined in Appendix 5.3. In final analyses, OLS will be used for the summary of post-baseline value from extension part. Besides, such summary of post-baseline from overall study will also be provided using SAF.

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

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

NA

2.7.4.2 Vital signs

Observed values, absolute change from baseline and percentage change from baseline will be summarized descriptively for vital sign parameters (SBP, DBP and pulse) by visit and treatment group. At each assessment, average of 3 readings will be used for analysis while all 3 readings will be provided in listing. For core part analyses, the summary tables will include Day 1 visit up to Day 180 visit. For final analyses, the summary table will include Day 1 visit up to Day 360 visit.

2.8 Impact of COVID-19

Below analysis about impact of COVID-19 may be performed, if needed.

The number and percentage of participants with any and each of the following COVID-19 impacted criteria will be provided for all randomized participants by treatment group and study part: (1) missed visit due to COVID-19; (2) treatment not given due to COVID-19; (3) study treatment discontinuation due to COVID-19; (4) premature study discontinuation related to COVID-19; (5) death related to COVID-19. OLS will be used for summary of extension part data in final analyses.

2.9 Pharmacokinetic endpoints

NA

2.10 PD and PK/PD analyses

NA

2.11 Patient-reported outcomes

NA

[redacted]

[redacted]

2.14 Interim analysis

NA

3 Sample size calculation

This study is designed to randomize approximately 200 Participants (with randomization ratio of 1:1 to inclisiran and placebo arms) in order to provide adequate information to characterize the safety profile of inclisiran as well as to have sufficient power for the primary efficacy endpoint.

[redacted]

4 Change to protocol specified analyses

NA

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

NA

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

For LLT, the end date will be imputed using below rules.

Year missing	Set the earliest of (last visit date, date of death, analysis cutoff date)
Month missing	Set the earliest of (last visit date, 31DecYYYY, date of death, analysis cutoff date)
Day missing	Set the earliest of (last visit date, last date of reported month, date of death, analysis cutoff date)

If imputed end date is prior to start date, set the end date using start date.

For other medications, 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

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 Laboratory parameters derivations

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

For fasting 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.

Notable laboratory values are defined in Table 5-1:

Table 5-1 Clinically notable laboratory abnormalities for selected tests

HbA1c criteria is explicitly stated in the table below.

All other criteria are met when both of the following occur:

- Post-baseline values meet the thresholds below
- Baseline values or any previous post-baseline values do not meet the thresholds below

Parameters	Criteria
Hemoglobin	≤ 10 g/dL
Hematocrit	≤ 0.8 × LLN
WBC(total)	≤ 2.8 $\times 10^3$ / μL, ≥ 16 $\times 10^3$ / μL

Parameters	**Criteria**
Platelet count	≤ 75 $\times 10^3$ / µL, ≥ 700 $\times 10^3$ / µL
HbA1c	≥ 6.5% and ≥0.5% increase from baseline
Creatinine	> 2 mg/dL
CK	> 1 and ≤ 3 × ULN
CK	> 3 and ≤ 5 × ULN
CK	> 5 and ≤ 10 × ULN
CK	> 10 × ULN

Notable liver function test criteria are defined in Table 5-2.

Table 5-2 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.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

5.4.1.1 Primary efficacy analysis

In handling of intercurrent events and missing data not related to intercurrent events, multiple imputation will be used to account for uncertainty in the imputation process and there will be 100 multiply imputed datasets. The results from these 100 imputed datasets will be combined using Rubin's method. Further details are provided below.

For control-based PMM, the missing data after specific intercurrent events in inclisiran group will be imputed using data from control group. The covariates and baseline characteristics which can be predictive of the response will be included in a multiple imputation procedure (SAS PROC MI) and will include the following:

- Baseline value of efficacy measurement (continuous)
- Observed/imputed value of efficacy measurement at Day 30 (continuous)
- Observed/imputed value of efficacy measurement at Day 90 (continuous)
- Observed/imputed value of efficacy measurement at Day 150 (continuous)
- Observed/imputed value of efficacy measurement at Day 180 (continuous)

For RDO based imputation model, the missing data after treatment discontinuation will be imputed based on RDO data within each group. The covariates, baseline characteristics and on- or off- treatment status at the same visit with the response which can be predictive of the response will be included in a multiple imputation procedure (SAS PROC MI) and will include the following:

- Baseline value of efficacy measurement (continuous)
- Observed/imputed value of efficacy measurement at Day 30 (continuous)
- Observed/imputed value of efficacy measurement at Day 90 (continuous)
- Observed/imputed value of efficacy measurement at Day 150 (continuous)
- Indicator of on- or off- treatment status at Day 180 (binary)
- Observed/imputed value of efficacy measurement at Day 180 (continuous)

The indicator variable will vary with the imputed response from visit to visit.

1. For those participants who experienced the intercurrent event of using prohibited LLT, set the LDL-C values on or after the usage of LLT missing (out_step1).
2. Missing data will be imputed under MAR assumption in this step. The same imputation model as specified for control-based PMM will be used except that the missing data will be multiply imputed using data within each treatment group. SAS PROC MI will be utilized using the FCS REG statement, where only previous measurements will be included for each imputed variable. A total of 100 datasets (out_step2) will be created. These fully imputed datasets will be utilized in step 3.

3. For participants handled by intercurrent events of treatment discontinuation, if the measurement is missing in (out_step1) and after treatment discontinuation, set this value back to missing (out_step3). These datasets (out_step3) will be utilized in step 4.
4. If there are enough RDO data, the RDO based imputation model will be used in this step. SAS PROC MI will be utilized using the FCS REG statement, where previous measurements and an indicator of on- or off-treatment status at the same visit with the response will be included for each imputed variable. This imputation will be implemented based on data within each group. If there are not enough RDO data, the control-based PMM will be used in this step. With this imputation model, the missing value in the inclisiran group will not be constructed from the observed data in the inclisiran group but rather from the observed and imputed data in the control group. SAS PROC MI will be utilized using the FCS REG statement, where only previous measurements will be included for each imputed variable. The MNAR statement in SAS PROC MI will also be used under MNAR assumption for inclisiran group. After this step, the 100 datasets(out_step4) will be fully imputed. These datasets will be utilized in step 5. (Which model will be used in this step will be determined before Core Part database lock)
5. For participants who died, set the values after death using his/hers baseline value. (out_step5)
6. Datasets (out_step5) will be used in this step. The absolute change and the percentage change values will be calculated in each of the imputed datasets.
7. These 100 datasets will be analyzed using the ANCOVA model for the LDL-C endpoints.
8. The results from the 100 datasets will be combined using Rubin's method via SAS PROC MIANALYZE procedure.

5.4.1.2 Supplementary analysis under estimand 1

The same imputation model as specified in Appendix 5.4.1.1 will be used in supplementary analysis 1. Again, multiple imputation will be used to account for uncertainty in the imputation process and there will be 100 multiply imputed datasets. The results from these 100 imputed datasets will be combined using Rubin's method. Further details are provided below.

1. For those participants handled by any intercurrent event, set the LDL-C values on or after the intercurrent event missing (out_step1).
2. Missing data will be imputed under MAR assumption in this step. The same imputation model as specified for control-based PMM will be used except that the missing data will be multiply imputed using data within each treatment group. SAS PROC MI will be utilized using the FCS REG statement, where only previous measurements will be

included for each imputed variable. A total of 100 datasets (out_step2) will be created. These fully imputed datasets will be utilized in step 3.

3. The absolute change and the percentage change values will be calculated in each of the imputed datasets.
4. These 100 datasets will be analyzed using the ANCOVA model for the LDL-C endpoints.
5. The results from the 100 datasets will be combined using Rubin's method via SAS PROC MIANALYZE procedure.

5.4.1.3 Supplementary analysis under estimand 2

The same imputation model as specified in Appendix 5.4.1.1 will be used in supplementary analysis 1. Again, multiple imputation will be used to account for uncertainty in the imputation process and there will be 100 multiply imputed datasets. The results from these 100 imputed datasets will be combined using Rubin's method. Further details are provided below.

1. In this step, the control-based PMM will be used. With this imputation model, the missing value in the inclisiran group will not be constructed from the observed data in the inclisiran group but rather from the observed and imputed data in the control group. SAS PROC MI will be utilized using the FCS REG statement, where only previous measurements will be included for each imputed variable. The MNAR statement in SAS PROC MI will also be used under MNAR assumption for inclisiran group. After this step, the 100 datasets(out_step1) will be fully imputed.
2. Datasets (out_step1) will be used in this step. If there are enough RDO data, the RDO based imputation model will be utilized in this step. Thus, for participants handled by intercurrent events of treatment discontinuation, if the LDL-C value is missing before step 1 and after treatment discontinuation, set this value back to missing. Then, SAS PROC MI will be utilized using the FCS REG statement, where previous measurements and an indicator of on- or off-treatment status at the same visit with the response will be included for each imputed variable. This imputation will be implemented based on data within each group. After this step, the 100 datasets (out_step2) will be fully imputed.
3. If step 2 is conducted, then datasets (out_step2) will be used in this step. Otherwise, datasets (out_step1) will be used. For participants who died, set the values after death using his/hers baseline value. (out_step3)
4. Datasets (out_step3) will be used in this step. The absolute change and the percentage change values will be calculated in each of the imputed datasets.
5. These 100 datasets will be analyzed using the ANCOVA model for the LDL-C endpoints.
6. The results from the 100 datasets will be combined using Rubin's method via SAS PROC MIANALYZE procedure.

5.4.2 Analysis supporting secondary objective(s)

Objectives for core part

The same imputation models and procedure as specified in Appendix 5.4.1.1 will be applied to all secondary efficacy endpoints for core part. For Lp(a), log-transformation will be taken before the imputation and the imputation model will exclude variables at Day 30 and Day 90 visits.

Objectives for extension part

The RDO based imputation model is the same as specified in Appendix 5.4.1.1 except that the model here is extended to include more measurements at Day 210, Day 270, Day 330 and Day 360.

For the control-based PMM, the same model as specified in Appendix 5.4.1.1 will be used for fitting the imputation model based on data from control group (i.e., the measurements at baseline, Day 30, 90, 150 and 180 from control group will be used to fit the imputation model). Based on the fitted regression model, the imputation model for missing measurements at Day 330 after specific intercurrent events in inclisiran group will only include following as covariates:

- Baseline value of efficacy measurement (continuous)
- Observed/imputed value of efficacy measurement at Day 30 (continuous)
- Observed/imputed value of efficacy measurement at Day 90 (continuous)
- Observed/imputed value of efficacy measurement at Day 150 (continuous)

In other words, the imputed Day 180 values in inclisiran group under the control-based PMM will be carried forward as imputations for missing measurements at Day 330 in inclisiran group.

1. Only inclisiran group data will be included. For those participants who experienced the intercurrent event of using prohibited LLT, set the LDL-C values on or after the usage of LLT missing (out_step1).
2. Missing data will be imputed under MAR assumption in this step. The same imputation model as specified for fitting purpose in the control-based PMM will be used. SAS PROC MI will be utilized using the FCS REG statement, where only previous measurements will be included for each imputed variable. A total of 100 datasets (out_step2) will be created. These fully imputed datasets will be utilized in step 3.
3. For participants handled by intercurrent events of treatment discontinuation, if the measurement is missing in (out_step1) and after treatment discontinuation, set this value back to missing (out_step3). These datasets (out_step3) will be utilized in step 4.
4. If there are enough RDO data, the RDO based imputation model as specified will be used in this step. SAS PROC MI will be utilized using the FCS REG statement, where previous measurements and an indicator of on- or off-treatment status at the same visit with the response will be included for each imputed variable. This imputation will be implemented based on data in inclisiran group. If there are not enough RDO data, the control-based

PMM will be used in this step. With this imputation model, the missing value in the inclisiran group will not be constructed from the observed data in the inclisiran group but rather from the observed (excluding data after usage of LLT) and imputed data in the control group. SAS PROC MI will be utilized using the FCS REG statement. The MNAR statement in SAS PROC MI will also be used under MNAR assumption for inclisiran group. These datasets(out_step4) will be utilized in step 5.

5. For participants who died, set the values after death using his/hers baseline value. (out_step5)
6. Datasets (out_step5) will be used in this step. The absolute change and the percentage change values will be calculated in each of the imputed datasets.
7. These 100 datasets will be analyzed descriptively for the LDL-C endpoints.
8. The results from the 100 datasets will be combined using Rubin's method via SAS PROC MIANALYZE procedure.

5.5 Rule of exclusion criteria of analysis sets

The protocol deviation criteria are listed in the sheet "Protocol Deviations" in the data review plan. The protocol deviation criteria leading to exclusion from the analysis sets are provided in below table, which may be updated prospectively and will be finalized before database lock.

Table 5-3 Protocol deviation criteria leading to exclusion from the analysis sets

Protocol Deviation		Excluding from Analysis Set				
ID	**Description**	**SCR**	**RAS**	**FAS**	**SAF**	**OLS**
INCL01A	Written informed consent not obtained.	X	X	X	X	X
TRT03	Subject was not randomized but took study drug		X	X	X	X
OTH07	Participant was randomized in error but did not receive IMP			X	X	X
OTH01A	Site closed down for GCP reasons during Core part.			X		
OTH01B	Site closed down for GCP reasons during Extension.			X		

Below table presents patient classification criteria including protocol deviation criteria and non-protocol-deviation criteria leading to exclusion from analysis sets.

Table 5-4 Patient classification

Analysis Set	Protocol Deviation ID leading to exclusion of patients	Non-protocol deviation criteria leading to exclusion from analysis sets
SCR	INCL01A	Not applicable
RAS	INCL01A, TRT03	• Patient without a randomization number
FAS	INCL01A, TRT03, OTH07, OTH01A,OTH01B	• Patient without a randomization number
SAF	INCL01A, TRT03, OTH07	• Patient without a randomization number
OLS	INCL01A, TRT03, OTH07	• Patient without a randomization number

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.