NOVARTIS

Clinical Development

KJX839/inclisiran

Clinical Trial Protocol CKJX839A11201 / NCT04666298

A placebo-controlled, double-blind, randomized trial to evaluate the effect of different doses of inclisiran given as subcutaneous injections in Japanese participants with high cardiovascular risk and elevated low-density lipoprotein cholesterol (LDL-C) (ORION-15)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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14-Feb-2022	Prior to DB lock		• Updated primary analysis cut-off at Day 180 • Added data analysis approach for LDL-C and VLDL-C • Added forest plots for the subgroup analyses. Corrected inequality sign (Baseline LDL-C and PCSK9) • Updated the analyses of screened participants • Updated demographic and baseline characteristics and added new categories and medical histories. • Removed new or changed concomitant medications summary • Added figures of primary and key secondary endpoints. • Added LDL-C testing handling • Added overview summary and removed summaries up to Day 90 • Updated AESI and added reported Injection Site reaction TEAEs and removed summary up to Day 90. • Removed summary of Creatine Kinase/Creatine criteria. • Added categories for the time to new-onset diabetes.	• 2.1 Data analysis general information • 2.1.1 General definitions • 2.2.1 Subgroup of interest • 2.3 Disposition • 2.3.1 Demographic and other baseline characteristics • 2.4.2 Prior, concomitant and post therapies • 2.5.3 Handling of missing values • 2.6.2 Statistical hypothesis, model, and method of analysis • 2.8.1 Adverse events. • 2.8.1.1 Adverse events of special interest • 2.8.3 Laboratory data

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			• Added list for the ADA evaluations.	• 2.8.4 Diabetes assessment
			• Updated according to the eCRS	• 2.10 Immunogenicity • 5.2.1 Search criteria for AESI
			• Added the analysis window for each scheduled visit.	• 5.1.1 Analysis Windows
			• Added responder definition as per the JAS 2017 guideline and 80% of the baseline value at Day 180	• 5.5. Responder definition
17-May-2022	Prior to DB lock		• Removed the analysis window, • Updated the DM subgroup. • Updated the LDL-C group and added Screening LDL-C. • Removed on-treatment for individual responsiveness • Added 5% cut-off for the TEAE table. • Updated adverse events of special interest and added other safety topics • Updated the HbA1c category • Added the average in the listing. • Updated CM data imputation. • Updated AE of special interest.	• 2.1.1 General definitions, 5.1 Imputation rules • 2.2.1 Subgroup of interest • 2.3.1 Demographics and other baseline characteristics • 2.7.1 Secondary endpoints [redacted] • 2.8.1 Adverse events • 2.8.1.1 Adverse events of special interest/grouping of AEs • 2.8.3 Laboratory data • 2.8.6 Vital signs • 5.1.2 Concomitant medication date imputation. • 5.2.1 Search criteria for AE of special interest

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
17-Oct-2022	Prior to final DB Lock (after primary analysis)	JAS guideline was updated in July, 2022	Added analyses according to JAS-2022 guideline.	• Table 1.2 • 2.7.1 Secondary endpoints • [redacted] • 4 Change to protocol specified analyses • 5.5 Responder definition
18-Oct-2022	Prior to final DB Lock (after primary analysis)	No need for EudraCT registry	Deleted analyses for EudraCT only	• 2.8.1 Adverse events (AEs)

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List of abbreviations

ADA	Anti-drug Antibodies
AE	Adverse event
ATC	Anatomical Therapeutic Classification
[redacted]	[redacted]
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CRS	Case Retrieval Sheet
CSR	Clinical Study report
CV	Coefficient of Variation
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	End of Study
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HeFH	Heterozygous Familial Hypercholesterolemia
JAS	Japan Atherosclerosis Society
LFT	Liver Function Test
LMT	Lipid-Modifying Therapies
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model with Repeated Measurement
MNAR	Missing Not at Random
PAD	Peripheral Artery Disease
[redacted]	[redacted]
PMM	Pattern Mixture Model
RAN	Randomized Set
RAP	Report and Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA Query
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol. The analysis planned in the SAP will be conducted on all participant data at the time the primary analysis happens and the result will be described in the Clinical Study Report (CSR). Analyses that will only be implemented at the end of the study will be described in the Day 360 CSR. Protocol version 01 has been referenced at the time of finalization of the SAP.

1.1 Study design

This study will be a Phase II, placebo-controlled, double-blind, randomized trial in Japanese participants with history of coronary artery disease (CAD) or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD) or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or Japanese participants with HeFH and elevated LDL-C despite maximum tolerated dose of statin(s) to evaluate the efficacy, safety, tolerability, [redacted] of subcutaneous inclisiran injection(s). The study will be a Japanese multi-center study with approximately 50 study sites. Informed consent will be obtained from participants before the initiation of any study-specific procedures.

Approximately 400 participants will be screened, and approximately 308 eligible participants will be randomized into 4 treatment groups:

1. 300 mg inclisiran sodium (equivalent to 284 mg inclisiran), n=100
2. 200 mg inclisiran sodium (equivalent to 189 mg inclisiran), n=100
3. 100 mg inclisiran sodium (equivalent to 94.5 mg inclisiran), n=54
4. placebo, n=54

[redacted]

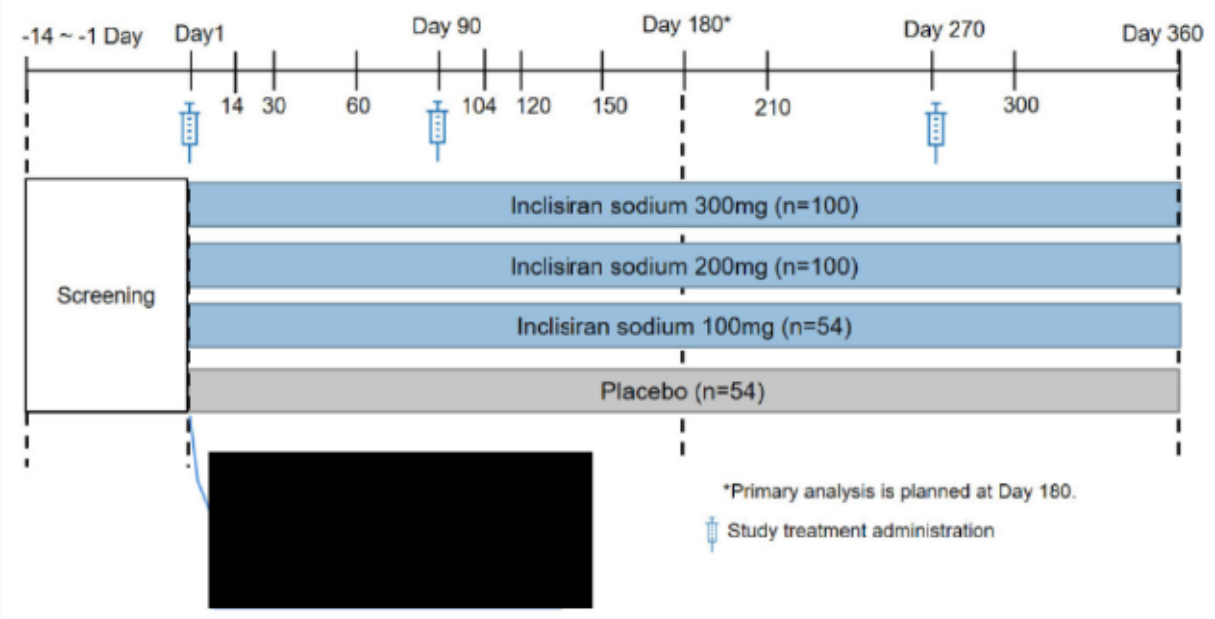
Randomization will be stratified by LDL-C at screening visit (≥130 mg/dL or <130 mg/dL), current use of statins or other lipid-modifying therapies (Yes or No), [redacted] otherwise the randomization ratio will be 2:2:1:1.

The expected duration of the participants' involvement in the study will be approximately 374 days which includes screening (up to 14 days), Day 1 study drug administration, two additional injections on Day 90 and Day 270, and the follow-up period to Day 360.

The primary analysis will be conducted after all participants have finished Day 180 visit assessments or discontinued before Day 180 visit.

After the primary analysis, double-blind treatment period is maintained to Day 360, although sponsor members (except for blinded monitors) will be unblinded for the planned regulatory submission in Japan.

Figure 1-1 Study design



Placebo volume will be matched to test product volume within each dose and injection. For example, the placebo group for the 200 mg dose will receive 1.0 mL of placebo whereas the placebo group for the 300 mg dose will receive 1.5 mL of placebo. Study treatment will be administered by the unblinded investigator or nurse to blind the arm and dose strengths. Each participant will receive a total of three injections of inclisiran or placebo (Table 1-1).

Table 1-1 Dosing regimens

Study Drug and Dose	Number of randomized participants	Volume (mL)
Placebo for 100 mg	12	0.5
100 mg inclisiran sodium	54	0.5
Placebo for 200 mg	21	1.0
200 mg inclisiran sodium	100	1.0
Placebo for 300 mg	21	1.5
300 mg inclisiran sodium	100	1.5

After the first study drug administration, participants will be observed in the clinic for at least 4 hours to have vital signs completed before being discharged. Participants will receive a second dose of study drug at the Day 90 visit and a third dose at Day 270. Participants will be observed for 30 min after the second dose (Day 90) and the third dose (Day 270) to have vital signs collected. Participants will also undergo the scheduled visit assessments as per the Assessment Schedule [redacted]

1.2 Study objectives and endpoints

This study is designed to evaluate the efficacy, safety, tolerability [redacted] of subcutaneous inclisiran injection(s) in Japanese participants. [redacted]

Table 1-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate superiority of inclisiran treatment at different dose levels (100 mg, 200 mg, and 300 mg) to placebo on LDL-C levels at Day 180	• Percentage change in LDL-C from baseline to Day 180
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of inclisiran until Day 180 on the following:	
• PCSK9 levels over time	• Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180
• LDL-C levels over time	• Percentage change in LDL-C from baseline to Days 14, 30, 60, 90, 104, 120, and 150
	• Absolute change in LDL-C from baseline to Day 180
	• Proportion of participants in each group with LDL-C greater than 80% of the baseline value at Day 180
	• Proportion of participants in each group with greater or equal to 50% LDL-C reduction from baseline at Days 14, 30, 60, 90, 104, 120, 150, and 180
• Other lipids, lipoproteins, apolipoproteins (total cholesterol, triglycerides, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a))	• Percentage change in other lipids, lipoproteins, apolipoproteins from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180

Objective(s)	Endpoint(s)
• Proportion of participants achieving lipid control target pre-specified by JAS 2017 guidelines	• Proportion of participants in each group who attain lipid control target pre-specified by JAS 2017 and 2022 guidelines for their level of cardiovascular risk at Day 180
• Individual responsiveness to different doses	• Individual responsiveness defined as the number of participants reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 14, 30, 60, 90, 104, 120, 150, and 180
• To evaluate the safety and tolerability profile of inclisiran	• Incidence, severity and relationship to study drug of TEAEs and Serious Adverse Events (SAEs); anti-drug antibodies (ADA) measurement
[redacted]	[redacted]

1.3 Primary estimands

The primary clinical question of interest is: What is the effect of doses of 100 mg, 200 mg, and 300 mg of inclisiran versus placebo on percent change in LDL-C levels at Day 180 in

participants with high cardiovascular risk and elevated LDL-C despite maximum tolerated dose of statin, regardless of treatment discontinuations for any reason and regardless of change in the dose of allowed concomitant medication.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of additional medications, mirroring the conditions in clinical practice. Further details can be found in Section 2.5.

The primary estimand is described by the following attributes:

1. Population: Japanese participants with history of coronary artery disease (CAD) or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD) or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or Japanese participants with HeFH despite maximum tolerated dose of statin. Further details about the population are provided in the protocol.
2. Endpoint: percentage change from baseline to Day 180 in LDL-C levels
3. Treatment of interest: the randomized treatment (the investigational treatment of inclisiran at different dose levels or the control treatment placebo) with the optimal SoC lipid-lowering therapy. The type and dose of the concomitant lipid-lowering therapy must remain stable until Day 180. Further details about the investigational treatment and control treatment are provided in the protocol.
4. intercurrent events :

- Treatment discontinuations for any reason: ignore (treatment policy strategy)
- Unforeseen change in the dose of allowed concomitant medications: ignore (treatment policy strategy)

The summary measure: difference between different Inclisiran dose groups and the placebo group in percentage change in LDL-C levels from baseline to Day 180.

1.4 Secondary estimands

Secondary estimands corresponding to key secondary efficacy endpoints are defined similarly to the primary estimand. These endpoints, and the corresponding summary measures, are listed below. Population, treatment of interest and intercurrent events are defined similarly as for the primary estimand.

- Endpoint: Percentage change in PCSK9 from baseline to Day 180; the summary measure: difference between different inclisiran dose groups and the placebo group in percentage change in PCSK9 from baseline to Day 180
- Endpoint: Absolute change in LDL-C from baseline to Day 180; the summary measure: difference between different inclisiran dose groups and the placebo group in absolute change in LDL-C levels from baseline to Day 180

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis according to the data analysis Section 12 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

SAS will be used for generating study outputs used for clinical reports. The most recent version of SAS available in the statistical programming environment of Novartis will be used for the analysis.

Unless otherwise stated, summary tables/figures/listings will be on all participants included in the study analysis set under consideration. Data will be summarized with respect to demographic and baseline disease characteristics, efficacy, and safety assessments. Categorical variables will be presented as frequencies and percentages. For continuous variables, n (non-missing observations), mean, standard deviation, median, minimum, and maximum will be presented. The analysis will be conducted on all participant data at the time of the primary analysis and the end of the study trial.

The primary analysis will be conducted after all participants have finished the Day 180 visit assessments or discontinued before Day 180 visit. The primary analysis will be performed using all data collected in the database up to the Day 180 visit date. All data with an assessment date or event start date (e.g. start date of an adverse event) prior to or on the Day 180 visit date will be included in the analysis. Any data collected beyond the Day 180 visit date will not be included in the analysis and will not be used for any derivations. All events with start date before or on the Day 180 visit date and end date after the Day 180 visit date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the Day 180 visit date and not having a documented end date. This approach applies, in particular, to adverse event and concomitant medication and significant non-drug therapies (surgical and medical procedures) reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

At the end of the study (EOS), a final analysis of all data collected will be performed when all participants have completed their last visit in the study.

The stratification factors LDL-C category at screening and current use of statins or other lipid-modifying therapies [redacted] will be included in subgroup analysis where appropriate.

Additional analysis may be conducted to evaluate the impact of COVID-19 pandemic on participants finishing or discontinuing the Day 180 visit assessments and completing or discontinuing the End of Study visit..

2.1.1 General definitions

The screening period will be up to 14 days. The treatment period will be 360 days.

Study drug refers to the investigational drug inclisiran sodium and placebo.

Date of first administration of study drug, or first date of study drug, refers to the date when the first dose of assigned treatment is administered. Date of last administration of study drug/treatment, or last date of study drug, refers to the date when the last dose of assigned treatment is administered.

Study day is defined as: if after first date of study drug, then Study Day = Date – first date of study drug + 1; if before first date of study drug, then Study Day = Date – first date of study drug; Study Day 1 is defined as the first date of study drug; there is no Study Day 0.

The visits in all analyses are based on the eCRF data.

Baseline is defined as the last non-missing result prior to the initial treatment.

Both LDL-C and VLDL-C for the analysis will be based on the reflexive approach: the calculated LDL-C based on the Friedewald formula will be used; however, if the calculated LDL-C <40 mg/dL or Triglyceride >400 mg/dL, then the non-missing LDL-C using the Beta Quantification (BQ) method will be used instead. Safety data until last visit (EOS) will be summarized.

2.2 Analysis sets

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

The Randomized Set (RAN) comprises all participants who receive a randomization number, regardless of receiving double blind study medication or not.

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

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

[redacted]

2.2.1 Subgroup of interest

Subgroup analyses of primary efficacy endpoint and key secondary efficacy endpoints will be performed on the FAS only.

For tables presenting results from statistical models, the treatment effects in the subgroup will be derived using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary. For displaying the results of subgroup analyses, a forest plot will be used.

The subgroups are listed in Table 2.2.

Table 2.2 Subgroup analysis and categories

Number	Subgroup	Categories
1	Sex	Female, Male
2	Age	<65, ≥65
3	BMI	<25, ≥25
4	Baseline (Day 1) statin use	Yes or No
5	Baseline Lipid modifying therapy	Any statin or Other LMT but no statin or None
6	Baseline LDL-C	≤ or > baseline median
7	Baseline PCSK9	≤ or > baseline median
8	eGFR	<60, ≥60
9	CAD history	Yes or No
10	HeFH	Yes or No
11	DM history	Yes or No
12	Hypertension history	Yes or No
13	Current smoker	Yes or No

Subgroup analysis of all treatment emergent adverse events (TEAE) will also be performed by treatment, SOC and PT on Safety set. The number (and percentage) of participants with TEAEs will be provided for each categories of subgroups which is the same as Table 2.2.

2.3 Disposition, demographics and other baseline characteristics

The number of screened participants who completed screening and the number of screened participants who discontinued prior to screening phase completion will be given in the SCR. The number and percentage of participants in the RAN who are completed/discontinued before the Day 180 visit, and the reason for discontinuation will be presented by treatment group. The duration (days) of the participants' involvement in the study before Day 180 visit will be summarized in the RAN. For the final analysis at the end of the study, the number and percentage of participants in the RAN who completed/discontinued before the Day 360 visit, and the reason for discontinuation will also be presented by treatment group. The duration (days) of the participants' involvement in the study before Day 360 visit will be summarized in the RAN. Patient disposition will be listed, including the reasons for discontinuation.

The number of participants with protocol deviations will be tabulated by category (e.g., selection criteria not met, participants not withdrawn as per protocol, treatment deviation,

prohibited concomitant medication, other) for the FAS set. Protocol deviation will be listed for the SCR.

2.3.1 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS set.

Categorical data of the following variables will be presented as frequencies and percentages.

- Sex: Female or Male
- Race: Asian, Subcategory (Asian):Japanese
- Smoking status: No or Yes, Subcategory (Yes):Usage of Tobacco: Current or Former

For the following continuous variables, n (non-missing observations), mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

- Age
- Age group: <65 years or ≥65 years
- Height
- Weight
- BMI
- BMI group: <25 kg/m^2 or ≥25 kg/m^2
- Baseline lipid parameters (LDL-C, PCSK9, TC, TG, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a))
- Screening LDL-C
- Baseline vital (SBP, DBP, Pulse)
- Baseline eGFR

In addition, the following categorizations of continuous variables will be done as frequencies and percentages.

- Screening LDL-C group: <130 mg/dL or ≥130 mg/dL
- Baseline eGFR group: <60 mL/min/1.73m^2 or ≥60 mL/min/1.73m^2
- LDL-C target by JAS 2017: <70 mg/dL, <100 mg/dL, <120 mg/dL

Note: The categories of LDL-C target by JAS 2017 are as follows.

<70 mg/dL: Participant with history of CAD with additional risk factors such as HeFH, ACS or diabetes complicated by other risk factors.

<100 mg/dL: Participant with history of CAD without additional risk factors or HeFH participant without CAD history.

<120 mg/dL: Participant categorized in high risk.

And the following hypercholesterolemia related medical histories and current medical conditions at baseline and other medical histories and current conditions will be summarized.

- Heterozygous familial hypercholesterolemia, Coronary artery disease, Diabetes mellitus, Arterial hypertension, Family history of Coronary artery disease,

  Dyslipidemia/Hyperlipidemia/Hypercholesterolemia (Non-familial hypercholesterolemia): Yes or No
- Background lipid-lowering therapy at Screening/Day 1: Yes or No
- Background statin at Day 1: Yes or No
- Statin intolerance (partial or complete): Yes or No

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

The Safety Set will be used for the analyses below.

2.4.1 Study treatment / compliance

The number of participants dosed at each dosing visit, number of participants by number of injections, duration of exposure will be summarized by treatment group using the safety set. Listing will be provided.

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

Patient-year of exposure will be calculated as the sum of the durations of exposure for all subjects in each treatment group divided by 365.25..

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

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Lipid-modifying therapy use and the baseline/Randomization visit (Day 1) will be summarized by treatment group. The categories of lipid-modifying therapy use are as follows.

- LMT and No LMT
- Statins (Yes, No)

- Ezetimibe (Yes, No)
- Statins only and no other LMT, other LMT, other LMT only (No statin).

For Statin (Yes), it is further sub-categorized by the intensity (high, moderate, low) defined in the table below.

Table 2-4 High/Moderate/Low intensity statin therapy

	High intensity	Moderate intensity	Low intensity
Statin name and dose/day	Atorvastatin 40 mg Rosuvastatin 20 mg	Atorvastatin ≥10 and < 40 mg Rosuvastatin ≥5 and < 20 mg Simvastatin 20 mg Pitavastatin 1-4 mg	Atorvastatin < 10 mg Rosuvastatin < 5 mg Simvastatin ≤ 10 mg Pravastatin ≤ 20 mg Fluvastatin ≤ 60 mg

Respecting reference 2018 AHA/ACA classification but taking into account the eventuality that some study subjects may be on doses falling between the consensus categories.

New or changed lipid-modifying therapy after baseline using the same categories as above will be summarized by treatment group.

Prior medications and other concomitant medications will be summarized by treatment group according to the Anatomical Therapeutic Chemical (ATC) classification system. Significant non-drug therapies (surgical and medical procedures) will be summarized by treatment group, according to the SOC and PT in the MedDRA dictionary.

2.5 Analysis of the primary objective

The analysis for the primary objective will be performed when all participants completed the Day 180 visit.

2.5.1 Primary endpoint

The analysis set used for the primary efficacy analysis will be the FAS.

The primary estimand is defined in Section 1.3. The corresponding endpoint, i.e. primary analysis variable, is the percentage change in LDL-C from baseline to Day 180. The treatment effect (summary measure) of the primary estimand is the difference in mean percentage change from baseline to Day 180 between different inclisiran sodium dose groups and the placebo group.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective of this study is to evaluate the effect of inclisiran compared to placebo in terms of percentage change from baseline in LDL-C to Day 180. The global statistical hypotheses that will be tested are as follows:

- H0: $\mu i-\mu 0 = 0$ for i=1,2,3 versus Ha: $\mu i-\mu 0 < 0$ for at least i=1,2,3

Where $\mu 0$ is the mean percentage change in LDL-C from baseline to Day 180 in placebo group, and $\mu 1$, $\mu 2$, $\mu 3$ are the mean percentage changes in LDL-C from baseline to Day 180 in inclisiran sodium 100mg, 200mg and 300mg group respectively.

An MMRM (Mixed-effect Model with Repeated Measurement) will be used as the primary analysis model, with treatment group, visits, interaction between visits and treatment groups and current use of statins or other lipid-modifying therapies as fixed effects and baseline LDL-C as a continuous covariate. Further details can be found in Section 5.4.1.

The significance level of the hypothesis test is 0.025 using one-sided test. To control the overall type-one error rate, Dunnett's test (one step) will be used on the above statistical model to provide adjusted p-values. In addition, point estimate and 95% confidence interval will be presented for the difference between inclisiran and placebo groups. Also the p-value (before and after multiplicity adjustment) will also be provided.

The primary objective will be achieved if the null hypothesis is rejected.

2.5.3 Handling of missing values/censoring/discontinuations

The MMRM model implicitly imputes missing data under a missing at random (MAR) assumption and results are valid under this MAR assumption. Patients who have at least one post-baseline are included in the MMRM analysis. This includes not only the patients who have completed Day 180 visit, but also those who discontinue from study treatment early (although only able to contribute to a partial time profile). This is under the assumption that dropouts would follow the similar data pattern like other patients who complete the treatment period in the same treatment group, as if they had not discontinued from the study treatment.

Patients who discontinue from study treatment early will remain in the study and follow the procedures described in protocol Section 9.1. All collected data after discontinuation from study treatment will be used in the analysis based on the treatment policy strategy in Section 1.3.

The other potential intercurrent events could be death, which considering its expected small number of occurrences with the short follow-up period planned and being consistent with the approach in the other phase II and III studies, will be treated the same way as for the other missing data.

2.5.4 Supportive/Sensitivity analyses

The following sensitivity analysis will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis:

- MMRM analysis with multiple imputation using a control-based pattern mixture model (PMM)

The control-based pattern mixture model (PMM) will be used to explore the possibility of missing data being missing not at random. This approach will utilize placebo data for monotone missing inclisiran treatment data. The details are described in Section 5.4.2.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary efficacy endpoints of this study are the following:

- Percentage change in PCSK9 from baseline to Day 180

- Absolute change in LDL-C from baseline to Day 180

2.6.2 Statistical hypothesis, model, and method of analysis

The key secondary efficacy endpoints will be analyzed using the same methods as for the primary efficacy endpoint.

Descriptive statistics on percentage change from baseline in LDL-C and PCSK9 and absolute change from baseline in LDL-C will include number of participants (n), mean, standard deviation, median and interquartile range [first and third quartiles], minimum and maximum.

The two-sided 95% confidence interval for difference will be provided for continuous variables. Nominal p-values will be provided when applicable.

For displaying the results, figures of LDL-C and PCSK9 (absolute mean by visit, percentage change from baseline by visit, absolute mean change from baseline by visit) and waterfall plot of LDL-C (percentage change and absolute change from Baseline to Day 180) will be used.

2.6.3 Handling of missing values/censoring/discontinuations

Same approach as for primary analysis will be applied.

2.7 Analysis of other secondary efficacy objective(s)

2.7.1 Secondary endpoints

The other secondary efficacy objectives of this study are to evaluate the effect of inclisiran on the following:

- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, and 150
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 90, 104, 120, and 150
- Proportion of participants in each group with LDL-C greater than 80% of the baseline value at Day 180 (Appendix 5.5)
- Percentage change in other lipids, lipoproteins, apolipoproteins from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180
- Proportion of participants in each group with greater or equal to 50% LDL-C reduction from baseline at Days 14, 30, 60, 90, 104, 120, 150, and 180
- Individual responsiveness defined as the number of participants reaching LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 14, 30, 60, 90, 104, 120, 150, and 180
- Proportion of participants in each group who attain Japanese lipid modification targets specified by JAS-2017 and JAS-2022 guidelines (Appendix 5.5) for their level of cardiovascular risk at Day 180

2.7.2 Statistical hypothesis, model, and method of analysis

- For other secondary endpoints, only the descriptive statistics by treatment group will be presented. The two-sided 95% confidence interval for the proportion will be provided using the exact method of Clopper and Pearson.

2.7.3 Handling of missing values/censoring/discontinuations

Missing values for other parameters will not be imputed. Discontinuations are treated the same as for the primary analysis.

2.8 Safety analyses

The safety objectives of this study are to evaluate the safety and tolerability profile of inclisiran. For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only treatment-emergent events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only treatment emergent AEs.

The primary analysis after all participants discontinued before Day 180 visit or have finished Day 180 visit assessments will be conducted.

2.8.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment group and participant.

The MedDRA dictionary will be used for coding AEs. An AE (classified as preferred term) occurring during the double-blind treatment period will be counted as a TEAE either if it is not present at baseline or if it is present at baseline but increased in severity during the treatment period.

The number (and percentage) of participants with TEAEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity
- by treatment, primary system organ class and preferred term for treatment emergent AEs leading to study drug discontinuation
- by treatment, primary system organ class and preferred term for treatment emergent AEs related to study drug.

Separate summaries will be provided for death and serious adverse events (SAEs). The overview summary table (TEAEs, Severe AEs, SAEs, Fatal SAEs, AEs leading to discontinuation and respective treatment-related) will be provided.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Listings will also be generated for deaths, SAEs, TEAEs and AEs leading to discontinuation.

AE reporting for CT.gov

For the legal requirement of ClinicalTrials.gov, two required tables on TEAEs which are not serious adverse events with an incidence greater than 5% (5% was selected prior to database lock) and on serious TEAEs will be provided by system organ class and preferred term 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

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

These summaries will be provided only after full study completion.

2.8.1.1 Adverse events of special interest / grouping of AEs

In order to support the additional assessment of adverse events, adverse events of special interest and other safety topics will be summarized by treatment group, including the number (and proportion) of participants. In addition, the adverse events of special interest will also be summarized by seriousness and severity, and other safety topics will be summarized by seriousness. Adverse events of special interest and other safety topics used in this analysis are specified as follows. The search criteria including subcategoires will be defined in detail in an external file according to the latest version of eCRS at the DBL. This includes MedDRA version and Novartis MedDRA Query (NMQ) dictionary date. However, for major cardiovascular events (MACE), the outcome data (fatal/non-fatal) will also be used, the details is provided in Appendix 5.2.

Adverse events of Special Interest

- Injection Site Reaction
- Hepatotoxicity_Hepatic events
- New onset diabetes or worsening of diabetes mellitus

Other safety topics

- Renal events
- Hypersensitivity reactions
- Neurological events
- Neurocognitive disorders
- Ophthalmological events
- Major cardiovascular events (MACE)

The eCRS safety definitions used to identify AEs of special interest and other safety topics will be provided as a listing.

The number and percentage of participants who had injection site reactions (sign and symptom) will be summarized and listed.

Listing of participants with adverse event of special interest and other safety topics will be provided.

2.8.2 Deaths

Overall deaths will be summarized and listed.

2.8.3 Laboratory data

Laboratory values will be summarized by treatment group, including changes from baseline at each time point. Frequency table of results for categorical laboratory parameters will be presented by visit and time point.

Shift tables using the low, normal, or high classification (except for eGFR and HbA1c) will be used to compare baseline to the worst on-treatment value by treatment group. All data collected after first dose of double-blind treatment, from scheduled, unscheduled and premature discontinuation visits will be used.

The following ranges will be used for eGFR and HbA1c

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

The shift table dealing with the fasting glucose parameter will require the lab sample to be taken while fasting. Samples taken while the participant was not fasting will not be analyzed.

For selected laboratory tests, the number and percentage of patients meeting the clinically notable criteria at any time, considering all data collected after first dose of double-blind treatment, from scheduled, unscheduled and premature discontinuation visits, will be summarized by laboratory parameter and treatment group. Notable criteria are defined in Appendix 5.3. Clinically notable criteria and notable liver criteria will be considered to be met when both of the following occur:

- Post-baseline values meet the thresholds listed in Appendix 5.3
- Baseline values or 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 test (LFT) will be summarized by treatment group considering on-treatment data from scheduled, unscheduled and premature discontinuation visits. LFT criteria are defined in Appendix 5.3.

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

2.8.4 Diabetes assessment

Diabetes will be assessed by the analysis of:

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

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

Diabetes TEAE

New onset/worsening of diabetes will be identified by the search criteria specified in Appendix 5.2. The analysis will be performed for all participants and then by baseline diabetes status. A participant will be identified as being diabetic at baseline if the targeted medical history notes that the participant is diabetic or the baseline HbA1c value is ≥ 6.5%. This summary will be provided by treatment group.

Change in Glucose-related Laboratory Values over Time

This analysis only utilizes laboratory data (fasting glucose and HbA1c). The change from baseline to the last on-treatment observation and the worst on-treatment observation will be summarized by treatment group, separately for fasting glucose and HbA1c for all participants and then by baseline glucose control status. Baseline glucose control status will be identified separately for fasting glucose and HbA1c using the values provided in the table below (note that medical history will not be taken into account for this analysis).

Parameter	Baseline Glucose Control Status	Baseline Laboratory Values
Fasting Glucose*	Normal	<100 mg/dL
	Impaired	≥100 to <126 mg/dL
	Diabetes	≥126 mg/dL
HbA1c**	Normal	<5.7%
	Impaired	≥5.7 to <6.5%
	Diabetes	≥6.5%

*Average of Screening and Day 1 fasting glucose values will be considered as baseline. If one fasting glucose value is missing (Screening or Day 1), the assessment will be based on the available data.

**Day 1 assessment will be considered as baseline. If missing, then the baseline will be based on assessment at screening visit.

Shifts from Baseline in Glucose Control Category

Shifts from baseline in glucose control category will be summarized by treatment group in two different ways. The change from baseline to the worst-on-treatment and the last-on-treatment laboratory values (up to min (last visit, last dose +180 day)) will be used to classify the on-treatment glucose control category. Medical history will not be taken into account for this analysis.

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

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

*No change (Normal to Normal, Impaired to Impaired, and Diabetes to Diabetes), worsened (Normal to Impaired, Normal to Diabetes, and Impaired to Diabetes), and Improved (Impaired to Normal, Diabetes to Impaired, and Diabetes to Normal) categories will also be summarized.

** Baseline of fasting glucose is defined as average of Screening and Day 1 assessment. If one fasting glucose value is missing (Screening or Day 1), the baseline will be based on the available data. For HbA1c, Day 1 assessment will be considered as baseline.

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

Incidence of Post-baseline New-Onset of Diabetes

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

The participant with no diabetes at baseline are those who had no medical history of diabetes in the targeted medical history CRF, had HbA1c <6.5%, and had fasting glucose <126 mg/dL prior to the study treatment (the baseline fasting glucose is defined as the average of fasting glucose values at Screening and Day 1. If one of the baseline fasting glucose values is missing, the assessment will be based on the available data).

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

1. Diabetic TEAEs identified by the SMQ search (see Appendix 5.2), or
2. Post-baseline fasting glucose ≥126 mg/dL on two consecutive occasions, or
3. Initiation of anti-diabetic medication at any time post-baseline, or
4. At least one post-baseline HbA1c ≥6.5%.

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

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

The time to new-onset diabetes will also be summarized by treatment group. The number and percentage of participants meeting the 4 week interval category (<4 weeks, 4 to <8 weeks, 8 to <12 weeks, 12 to <16 weeks, >=16 weeks) will also be summarized. Only participants without diabetes at baseline will be included in the analysis. The time (weeks) to new-onset diabetes will be calculated from the date of the first administration of study drug.

2.8.5 ECG and cardiac imaging data

All ECG data will be summarized by visit and treatment group. A listing will be provided.

2.8.6 Vital signs

Change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group. For SBP and DBP, average of 3 readings will be used for analysis while all 3 readings in addition to the average will be provided in listing. Abnormalities will be flagged. The number and percentage of participants meeting clinical notable vital signs as defined below at any time (considering all data collected after first dose of double-blind treatment from scheduled, unscheduled, and premature discontinuation visit) will also be summarized.

Table 2.8 Clinically notable vital signs

Vital sign		Notable abnormalities (at any visit)
Pulse (beats/min)		either ≥120 & increase ≥25* or > 130 either ≤50 + decrease ≥30* or < 40
BP (mmHg)	systolic	either ≥180 & increase≥30* or > 200 either ≤90 & decrease≥30* or < 75
	diastolic	either ≥105 & increase≥20* or > 115 either ≤50 & decrease≥20* or < 40

*Refers to post-BL value as compared to BL value

[redacted]

[redacted]

2.10 Immunogenicity

ADA evaluations, including treatment-emergent ADA findings and titers, will be summarized by visit and treatment group and listed. Additional analyses may be performed to describe the relationship between ADA and other study.

[redacted]

2.12 Interim analysis

There is no interim analysis planned.

3 Sample size calculation

Approximately 308 participants will be randomized by the IRT system: 100 participants for inclisiran sodium dose groups 200 mg and 300 mg; plus 54 participants in the placebo group and inclisiran sodium dose group 100 mg. Randomization will be stratified by current use of statins or other lipid-modifying therapies, LDL-C category at screening, [redacted].

The sample size assumption was based on the observed results from a previously completed Phase II Dose Finding Study (ORION-1). The difference in mean percentage change from baseline between the active dose groups and the placebo group for LDL-C at Day 180 is expected to be >30% with a standard deviation of approximately 20%.

The sample size of 308 will provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one inclisiran sodium dose group compared to the placebo. Dunnett's test is used in order to control the family-wise type I error rate at a significance level of alpha=0.025 (one-sided test). [redacted].

[redacted]

4 Change to protocol specified analyses

The following change to protocol specified analyses was made:

- Proportion of participants in each group who attain lipid control target pre-specified by JAS 2022 was added because JAS 2017 was updated in July, 2022.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention

YYYY < TRTY	**(2.a)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start	**(2.b)** Before Treatment Start
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Treatment Start	**(4.c)** Uncertain	**(4.c)** After Treatment Start
YYYY > TRTY	**(3.a)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start	**(3.b)** After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

- If the AE end date month is missing, the imputed end date should be set to the earliest of the (follow up period date, 31DECYYYY, date of death).
- If the AE end date day is missing, the imputed end date should be set to the earliest of the (follow up period date, last day of the month, date of death).
- If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.2 Concomitant medication date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a)) Before Treatment Start	(2.b)) Before Treatment Start	(2.b)) Before Treatment Start	(2.b)) Before Treatment Start
YYYY = TRTY	(4.a)) Uncertain	(4.b)) Before Treatment Start	(4.a)) Uncertain	(4.c)) After Treatment Start
YYYY > TRTY	(3.a)) After Treatment Start	(3.b)) After Treatment Start	(3.b)) After Treatment Start	(3.b)) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a) If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b) Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a) If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

b) Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:
   a) And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   b) Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c) Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

- If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of disposition date and the last day of the month.
- If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of disposition date and the end of the year (31DECYYYY).
- Only include if ongoing records will not be imputed.
- If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Above rules apply to concomitant surgical and medical procedures as well.

5.1.2.1 Prior therapies date imputation

Same imputation rules as for concomitant medication date imputation.

5.1.2.2 Other imputations

Not applicable.

5.2 AEs coding/grading

Coding of AE will be done per MedDRA dictionary.

5.2.1 Search criteria for other safety topics:MACE

The search criteria of MACE will be based on the eCRS and the following outcome data (fatal/non-fatal).

Major cardiovascular events (MACE)

Cardiac death

- Fatal SAEs in Cardiac disorders SOC

- Fatal SAEs in General disorder SOC: PTs 'Death', 'Sudden cardiac death', 'Cardiac death', 'Apparent death'

Cardiac arrest

- PT 'Cardiac arrest'

Non-fatal MI

- Myocardial infarction (SMQ, broad and narrow), nonfatal events only

Stroke

- Central Nervous System hemorrhages and cerebrovascular accidents (HLT), non-fatal events

5.3 Laboratory parameters derivations

Notable laboratory values are defined as follows.

Table 5.3-1 Clinically notable laboratory abnormalities for selected tests

Parameters	Criteria
Hematology	
Hemoglobin	≤ 10 g/dL
Hematocrit	≤ 0.8 × LLN
WBC (total)	≤ 2.8 $\times 10^3$ / µL, ≥ 16 $\times 10^3$ / µL
Platelet count	≤ 75 $\times 10^3$ / µL, ≥ 700 $\times 10^3$ / µL
HbA1c	≥ 6.5% and ≥0.5% change from baseline
Clinically chemistry	
Creatinine	> 2 mg/dL
CK	> 1 and ≤ 3 × ULN
CK	> 3 and ≤ 5 × ULN
CK	> 5 and ≤ 10 × ULN
CK	> 10 × ULN
ALT	> 1 and ≤ 3 × ULN
ALT	> 3 and ≤ 5 × ULN
ALT	> 5 and ≤ 10 × ULN
ALT	> 10 × ULN
AST	> 1 and ≤ 3 × ULN
AST	> 3 and ≤ 5 × ULN
AST	> 5 and ≤ 10 × ULN
AST	> 10 × ULN

Parameters	Criteria
Total bilirubin	> 2 × ULN
ALP	> 2 × ULN

Table 5.3-2 Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
AST > 3 x ULN AST > 5 x ULN AST > 8 x ULN AST > 10 x ULN AST > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin > 1 x ULN Total bilirubin > 1.5 x ULN Total bilirubin > 2 x ULN Total bilirubin > 3 x ULN
TBL >2xULN & DBL >ULN TBL >2xULN & DBL >1.5xULN TBL >2xULN & DBL >2xULN
ALP > 1.5 x ULN ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, DBL = Direct bilirubin

5.4 Statistical models

[redacted]

5.4.3 Key secondary analysis

Same analysis will be applied on the key secondary endpoints.

5.5 Responder definition

The following table explains Japanese lipid modification targets according to participant's background risk categories as per the JAS 2017 guideline.

Participant's background risk categories as per the JAS 2017 guideline	LDL-C targets
Participant with history of CAD with additional risk factors such as HeFH, ACS or diabetes complicated by other risk factors	Serum LDL-C <70 mg/dL
Participant with history of CAD without additional risk factors or HeFH participant without CAD history	Serum LDL-C <100 mg/dL
Participant categorized in 'high risk'	Serum LDL-C <120 mg/dL

The following table explains Japanese lipid modification targets according to participant's background risk categories as per the JAS 2022 guideline.

Participant's background risk categories as per the JAS 2022 guideline	Additional background categories as per the JAS 2022 guideline	LDL-C targets
Participants with a medical history (MH) of cerebral Infarction (Occurrence=Yes) excluding lacunar infarction	MH of CAD, FH, DM [Programming note] CAD: Coronary artery disease (Occurrence=Yes) FH: Heterozygous familial hypercholesterolemia (Ongoing=Yes) DM Diabetes mellitus (Occurrence=Yes)	Serum LDL-C <70 mg/dL
	Except for the above,	Serum LDL-C <100 mg/dL
Participants other than the above and were classified as target value Serum LDL-C ≥100 mg/dL at baseline and Participants with MH of CAD	MH of DM	Serum LDL-C <70 mg/dL
	Except for the above,	Serum LDL-C <100 mg/dL
Participants other than the above and were classified as target value Serum LDL-C ≥70 mg/dL at baseline		Serum LDL-C <70 mg/dL
HeFH (MH of HeFH) participants other than the above	No MH of cerebral Infarction excluding lacunar infarction or No MH of CAD	Serum LDL-C <100 mg/dL

DM (MH of DM) participants other than the above	Smoking (Current) [Programming note] current smoking status category=Current or Retinopathy (ongoing) [Programming note] PT= Diabetic retinopathy & Ongoing=Yes or Nephropathy (ongoing): [Programming note] PT=Diabetic nephropathy & Ongoing=Yes PT=Nephrotic syndrome & Ongoing=Yes or Neuropathy (ongoing): [Programming note] PT=Diabetic neuropathy &Ongoing=Yes PT=peripheral neuropathy & Ongoing=Yes or PAD (ongoing): [Programming note] PT=Peripheral arterial occulusive disease & Ongoing=Yes PT=peripheral artery occlusion & Ongoing=Yes	Serum LDL-C <100 mg/dL
Participants other than the above		Serum LDL-C <120 mg/dL

The following calculations are defined to determine whether a subject has >80% of baseline at Day 180.

1. Threshold=80% * (LDL-C at Baseline - LDL-C at Day180) + LDL-C at Day180.
2. If the subject's LDL-C value is greater than the threshold specified above, or the subject's LDL-C value is greater than or equal to the LDL-C at Baseline, the subject is considered to have >80% of baseline.

5.6 Rule of exclusion criteria of analysis sets

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

6 Reference