NOVARTIS

Clinical Development

KJX839

CKJX839A1US01 / NCT04873934

A randomized, controlled, multicenter, open-label trial comparing a hospital post-discharge care pathway involving aggressive LDL-C management that includes inclisiran with usual care versus usual care alone in patients with a recent acute coronary syndrome (VICTORION-INCEPTION)

Statistical Analysis Plan (SAP)

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16-Jun-2021, Final v1.0	Prior to DB lock	Creation of final version	N/A - First version	NA
29-Aug-2024, Final Amendment 01	Prior to DB lock	Necessary correction or clarification; harmonization across inclisiran studies	Clarification on use of calculated LDL-C for statistical analysis and use of SI and/or US conventional units for selected lab parameters.	Section 2. 1
			Definition of screening value	Section 2.1.1
			Subgroups for subgroup analyses of primary efficacy variables added and updated.	Section 2.2.1
			List of demographic variables updated.	Section 2.3.2
			Definition of changes in lipid-lowering therapies prior to baseline was added.	Section 2.4.2
			Methodology in case of non-convergence of statistical models was added.	Section 2.5.2
			Sensitivity analyses were added to address participants with low baseline LDL-C.	Section 2.5.5
			Common adverse event tables using 3% within either treatment group as the threshold was added.	Section 2.7.1
			Addition of adverse events of special interest terms.	Section 2.7.1.1
			Reference and definition of eGFR derivation were added. Summary tables for new onset or worsening of diabetes were added. Update of baseline diabetes status to baseline glycemic status.	Section 2.7.3
			Summary tables for participants satisfying Hy's Law will be repeated excluding the normal baseline value requirement.	Section 2.7.3
			[redacted]	[redacted]

Date, Version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Added time to event analyses for composite MACE and individual components.	Section 2.12
			[redacted]	[redacted]
			Updated partial AE and medication imputation section in accordance with Novartis standards.	Section 5.1.2
			Other minor changes were made to the text.	Various sections

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List of abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AE	Adverse Event
AHA	American Heart Association
apoB	Apolipoprotein B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CK	Creatine Kinase
CRF	Case Report Form
CSR	Clinical Study Report
CS	Clinically significant
CV	Cardiovascular
dL	Deciliter
EHR	Electronic Health Record
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
H_0	Null hypothesis
H_A	Alternative hypothesis
hsCRP	High sensitivity C-Reactive protein
LDL-C	Low density lipoprotein cholesterol
LLN	Lower Limit Normal
LLT	Lipid lowering therapies
Lp(a)	Lipoprotein(a)
MACE	Major adverse cardiovascular events
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligram(s)
MI	Myocardial Infarction
MMRM	Mixed-effects Model for Repeated Measures
PCS	Potentially clinically significant
PCSK9	Proprotein convertase subtilisin/kexin type 9
PFS	Prefilled syringe
PT	Preferred Term

SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAS	Statistical Analysis System
s.c.	subcutaneous
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
[redacted]	[redacted]
ULN	Upper Limit Normal
VLDL	Very low density lipoprotein cholesterol
WHO	World Health Organization

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses which will be performed in the Phase 3b clinical trial CKJX839A1US01.

The aim of the trial and the described statistical analysis methodologies is to study the effect of implementation of a systematic low density lipoprotein cholesterol (LDL-C) management pathway including treatment with inclisiran in participants who have experienced a recent acute coronary syndrome (ACS) and have an increased LDL-C (≥70 mg/dL) despite being treated with a statin drug.

Analysis plans in this document refer to the related statistical analysis sections in the Clinical Study Report (CSR). Data will be analyzed by Summit Analytical, LLC using Statistical Analysis Software (SAS®, version 9.4), according to Section 12 (Data analysis and statistical methods) of the study protocol which is available in Appendix 16.1.1 of the CSR.

Please refer to the following document: Clinical Protocol CKJX839A1US01 v04 (amended protocol dated 20-Oct-2022) and CRF v16.0 (dated 18-Dec-2023).

1.1 Study design

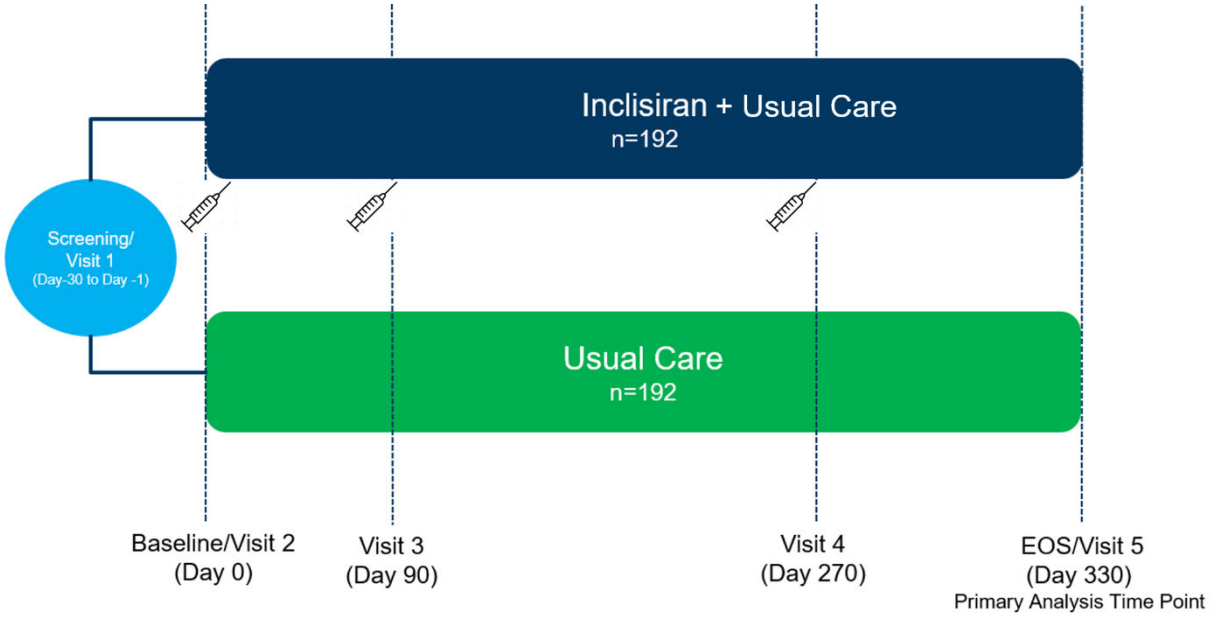
This is a randomized, parallel-group, open-label, multicenter study comparing an LDL-C management strategy including inclisiran plus usual care with usual care. A total of approximately 384 participants will be randomized 1:1 to aggressive LDL-C management with inclisiran plus usual care (intervention arm) and usual care (control arm). Identification of participants will take place during hospitalization or in the weeks following discharge with screening soon thereafter. Screening of participants must take place within 5 weeks after discharge. The randomization schedule will not be stratified by any factors.

Potential participants who are discharged after an ACS on statin therapy (which is considered routine care) or have documented statin intolerance will be screened and receive an LDL-C test within 5 weeks post-discharge (to allow for the realization of the full effect of statin therapy). After the LDL-C test, participants with an LDL-C ≥70 mg/dL are eligible for the trial as long as they meet all other inclusion criteria. Participants will be randomized to inclisiran + usual care or usual care. All participants will be maintained on statin therapy during inclisiran treatment, but concomitant lipid-lowering therapy and LDL-C assessments will be at the discretion of the treating (primary) physician, mimicking real-world clinical decision-making and enabling the evaluation of inclisiran compared to usual care in patients with a recent ACS. Usual care may therefore include addition of ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting monoclonal antibodies and/or commercially available inclisiran (Note: participants treated with inclisiran should not be treated with PCSK9-inhibiting monoclonal antibodies). After randomization, the treating physician will not have access to LDL-C values obtained as part of the study but will be able to perform LDL-C assessments at their discretion, to mimic usual care. The rationale of not providing the treating physician the LDL-C values obtained as part of the study is that those results might influence decisions made by him/her and could therefore undermine “usual care”. Commercially available inclisiran may be used for appropriate patients in the usual care arm at the sole discretion of the treating physician, without any influence from the PI. LDL-C measurement and assessment of lipid

lowering medications at each visit will be performed to assess adherence to background statin therapy.

The collection of data from trial sites through eCRFs may also be complemented with Electronic Health Record (EHR) data and claims data (e.g., lipid measurements and concomitant medications), if available. While study visits will be preferentially performed in-person at the study sites, phone or virtual home-visits are an acceptable alternative if in-person visits are not permitted or impractical (e.g., due to a public health emergency). Site or home health nursing service may be used to assist with blood draws and/or study medication administration if required at these visits.

Figure 1-1 Study Design



Additional important considerations of the study design include:

- **Recruitment:** Potentially eligible participants, recently hospitalized for an ACS (in-patient/out-patient), will be identified by the primary investigator and be invited to contact the research site for screening and inclusion. Eligible participants will need to consent to having health records made available as part of the collection of medical and pharmacy claims in order to [redacted].
- **Open label:** The study will be performed as an open-label study to mimic decision making in usual care, following from the primary objective of the study. For example, if the study would have been performed as a double-blind placebo-controlled study, it would not be possible to study the effect of inclisiran treatment on statin discontinuation as participants and investigators would not be aware of treatment allocation.
- **Duration of study period:** The study is designed as a one-year trial with a total of three inclisiran doses. The Phase III trials of inclisiran had a follow-up duration of 18 months. A follow-up duration of one year enables: 1) observation of the steady-state LDL-C lowering effect of inclisiran, 2) observation of a meaningful difference in statin discontinuations,

should such a difference exist, and 3) observation of potential differences in variables that likely require longer-term treatment of inclisiran to become apparent, such as patient reported outcomes.

1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect on LDL-C of implementation of an LDL-C management care pathway that includes initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS with LDL-C ≥70 mg/dL despite receiving statin therapy compared to usual care without inclisiran at Day 330	• Percent change from baseline in LDL-C • Achieving LDL-C < 70 mg/dL (yes, no)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess (1) the absolute change from baseline in LDL-C level by visit, and (2) average of percent and absolute changes from baseline in LDL-C levels to each post-baseline visit, in the inclisiran + usual care group compared to usual care group at Day 330	• Absolute change from baseline in LDL-C • Average percent change from baseline in LDL-C levels to each post-baseline visit • Average absolute change from baseline in LDL-C levels to each post-baseline visit
• To assess the proportion of participants reaching pre-specified LDL-C targets in the inclisiran + usual care group compared to usual care group at Day 330	• Achieving ≥ 50% reduction from baseline in LDL-C (yes, no) • Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline) • Achieving LDL-C < 55 mg/dL (yes, no)
• To assess plasma lipoproteins and triglycerides in the inclisiran + usual care group compared to usual care group at Day 330	• Percent change and absolute change from baseline in apoB • Percent change and absolute change from baseline in VLDL • Percent change and absolute change from baseline in non-HDL-C • Percent change and absolute change from baseline in total cholesterol • Percent change and absolute change from baseline in Lp(a) • Percent change and absolute change from baseline in HDL-C • Percent change and absolute change from baseline in triglycerides
• To assess changes in and adherence to background lipid-lowering therapy in the inclisiran + usual care group compared to usual care group at Day 330	• Intensity of lipid lowering therapy (decrease in dose, no change in dose, increase in dose) • Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days)

Objective(s)	Endpoint(s)
	• Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)
• To assess overall safety and tolerability of inclisiran	• Adverse events
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	
• To assess major adverse cardiovascular events (MACE) (investigator determination) in the inclisiran + usual care group compared to usual care group at Day 330	• Cardiovascular death (yes, no) • Non-fatal MI (yes, no) • Resuscitated cardiac arrest (yes, no) • Non-fatal ischemic stroke (yes, no) • Composite MACE (cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke) (yes, no)
[redacted]	

Note that endpoints identified as “absolute” change from baseline correspond to values that are calculated as a change from baseline (post-baseline value minus baseline value).

1.2.1 Primary estimand(s)

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

The primary clinical question of interest in this study is to evaluate the effect on LDL-C of implementation of an LDL-C management care pathway with inclisiran versus usual care in participants who are discharged after an ACS on statin therapy or have documented statin intolerance and do not have their LDL-C at the target level. The justification for the primary estimand is that it will evaluate the LDL-C lowering effect of inclisiran on both the percent change in LDL-C and the achievement of the target LDL-C (<70 mg/dL) compared to a usual care of implementation pathway in participants following a recent ACS, including potential changes in concomitant therapy. Further details can be found in Section 12 of the protocol.

Primary estimand 1: The primary analysis of primary efficacy variable 1 (percent change from baseline in LDL-C) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis. 3. Use of prohibited medication (monoclonal antibodies directed against PCSK9) in the inclisirian + usual care group. This intercurrent event will be ignored in the analysis.
- Summary measure: Least-squares mean difference between inclisiran + usual care group and usual care group

Primary estimand 2: The primary analysis of primary efficacy variable 2 (achieving LDL-C < 70 mg/dL) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Achieving LDL-C < 70 mg/dL (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis. 3. Use of prohibited medication (monoclonal antibodies directed against PCSK9) in the inclisirian + usual care group. This intercurrent event will be ignored in the analysis.
- Summary measure: Odds ratio of inclisiran + usual care to usual care for achieving LDL-C < 70 mg/dL

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of participants will be available for analysis.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The analysis will be performed at the end of the trial, after the clinical database is locked.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group. For discrete variables, frequency counts and percentages at each time point will be reported by treatment group.

LDL-C values, lipid parameters, and laboratory units

Any statistical analysis involving LDL-C will be based on calculated LDL-C values as provided by the central laboratory. For the remainder of this SAP and the corresponding output shells, the abbreviated term "LDL-C" refers to calculated LDL-C.

Tabular summaries, listings, and figures of lipid parameters, creatinine, and fasting glucose will be provided in US conventional units. Select analyses of these parameters will be provided in SI units as well. All other laboratory parameters will be reported in SI units. Both US conventional and SI units will be included in SDTM and ADaM datasets as applicable per laboratory parameter. The lipid parameters include the following, with US and SI units as applicable in this study:

1. LDL Cholesterol (mg/dL, mmol/L)
2. Total Cholesterol (mg/dL, mmol/L)
3. HDL Cholesterol (mg/dL, mmol/L)
4. Non-HDL Cholesterol (mg/dL, mmol/L)
5. VLDL Cholesterol (mg/dL, mmol/L)
6. Triglycerides (mg/dL, mmol/L)
7. Apolipoprotein B (mg/dL)

8. Lipoprotein(a) (nmol/L)

Due to differences in measurement techniques as well as molecular differences between individuals, a standardized conversion factor is not available to convert Lipoprotein(a) values from standard to US conventional units. Therefore, Lipoprotein(a) results will only be reported in nmol/L.

2.1.1 General definitions

Study treatment

The following are the investigational treatments:

- Inclisiran (KJX839), 284 mg, 1.5 ml liquid in a single-use prefilled syringe (PFS) for s.c. administration plus usual care
- Usual care alone

The following treatment labels will be used for all tables, listings and figures:

- Inclisiran + Usual Care
- Usual Care

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered for the inclisiran + usual care group. If a participant, who is randomized to the inclisiran + usual care group, does not take any study drug then treatment start date will be the randomization date.

For the usual care alone group the study treatment start date will be the randomization date.

"Day 1" will be used to identify study treatment start date for both treatments.

Study treatment end date is defined as the treatment phase completion date recorded on the "Treatment Disposition" CRF for inclisiran + usual care participants. For the usual care alone group, the study treatment end date is the last recorded contact/participation date in the database.

Study start and end date

Study start date is defined as the first date when a non-zero dose of study drug is administered for the inclisiran + usual care group. If a participant, who is randomized to the inclisiran + usual care group, does not take any study drug then study start date will be the randomization date.

For the usual care alone group the study start date will be the randomization date.

Study end date is defined as the date of last recorded contact/participation date in the database.

Duration of exposure to inclisiran

For the inclisiran + usual care group, duration of exposure to inclisiran (in days) is defined as the number of days from Day 1 to the study *treatment* end date. Duration of exposure will not be defined for the usual care alone group.

Planned and actual treatment definitions

The following definitions will be used for planned and actual treatment.

Table 2-1 Planned and Actual Treatment Definitions

Randomized Treatment Group	Inclisiran Use Scenario During Study (Inclisiran Use Recorded as Study Treatment or Concomitant Medication)	Planned Treatment	Actual Treatment
Inclisiran + Usual Care	Received at least one dose of inclisiran	Inclisiran + Usual Care	Inclisiran + Usual Care
Inclisiran + Usual Care	Never received inclisiran	Inclisiran + Usual Care	Usual Care
Usual Care	Received at least one dose of inclisiran	Usual Care	Inclisiran + Usual Care
Usual Care	Never received inclisiran	Usual Care	Usual Care

Study day

Study day will be calculated as (event date – study treatment start date + 1 day) for events that occurred on or after study treatment start date (e.g., visit, lab samples, AEs). For events prior to study treatment start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study treatment start date). Note that study treatment start date is study Day 1 and the day before study drug start date is study Day -1 (i.e., no study Day 0).

Screening, baseline and post-baseline definitions

A screening value refers to the last available measurement from the set of nominal Screening/Visit 1 records irrespective of collection date being before or after start of study treatment, and any unscheduled visit data collected before (<) study Day 1.

In general, a baseline value refers to the last measurement available prior to administration of the first dose of study treatment (before or on study Day 1). A post-baseline value refers to a measurement taken after the first dose of study treatment (after study Day 1).

Lost to follow up

Participants whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw.

On-treatment period

The period where the participants are exposed to the study treatment or usual care. For this study the treatment phase consists of 330 days.

Study Completer

Completers are defined as a participant who has a Subject Status of ‘completed’ on the Study Completion/Exit CRF page.

Analysis Visit Windows

The following analysis windows will be used for efficacy and safety analyses.

Table 2-2 Analysis Windows for Each Scheduled Visit

Analysis Visit	Target Study Day*	Analysis Window	
		From	To
Baseline	1		Before randomization/First Study Treatment
Day 90	91	1	180
Day 270	271	181	300
Day 330	331	301	375

* Study Day 1 is being used to identify study treatment start date. When calculating study day, the target study day will correspond to the planned study day of the nominal visit. The analysis visit values (Baseline, Day 90, Day 270, and Day 330) will be used for all presentations.

Data collected at scheduled or unscheduled visits will be used in the analysis if they fall into an analysis window for an analysis visit. If more than one visit (scheduled or unscheduled) is made within the window specified above for any analysis visit, the non-missing assessment closest to the target study day will be used in the analysis for that visit. In the case of tied visits, non-missing data from the later visit will be used. In the case of identical collection dates and times, the average of the two visits will be used. However, all data will be included in the participant data listings.

Last Visit Summaries

The protocol uses the term End of Study (EOS) for Day 330. If a participant discontinues from the study early, they will have an early termination visit that is before Day 330. Using the windowing provided in Table 2-2, the early termination visit will be assigned to the nearest analysis visit. Tables that summarize data by visit will include data by analysis visit (Baseline, Day 90, Day 270, and Day 330) along with a Day 330/Last Visit which will combine data from Day 330 for those participants who have data collected within the Day 330 analysis window with the data from the last post-baseline visit for those participants who do not have data collected in the Day 330 analysis window.

2.2 Analysis sets

The **Full Analysis Set** (FAS) comprises all randomized participants. According to the intent-to-treat principle, participants will be analyzed according to the treatment group they have been assigned to during the randomization procedure.

The **Per-Protocol Set** is a subset of the FAS in which participants are not treated with any inclisiran if they are randomized to the usual care treatment group or do not have any major protocol deviations (including deviations from inclusion/exclusion criteria) in either treatment group.

The **Restricted Set 1** is a subset of the FAS which includes only participants without changes in background lipid-lowering therapy. A change includes starting a new lipid-lowering therapy or stopping an existing lipid-lowering therapy after the study treatment start date.

The **Restricted Set 2** is a subset of the FAS which includes only participants who received three doses of inclisiran in the inclisiran + usual care group (i.e., excludes participants in the inclisiran + usual care group who missed one or more doses) and all participants in the usual care group (including participants who may have used commercially available inclisiran).

The **Safety Set** includes all participants who received study treatment. Participants will be analyzed according to the study treatment received. Refer to Table 2-1 for assignment of actual treatment for the different scenarios. Participants in the usual care treatment group who have data collected at the baseline visit will be included in the Safety Set.

2.2.1 Subgroup of interest

Subgroup analyses of the two primary efficacy variables and the secondary endpoint of absolute change from baseline in LDL-C will be performed for the following subgroups (note that results for a subgroup category will only be presented if the total across both treatment groups within the category is at least 10 participants):

- Background lipid-lowering therapy at baseline: Yes, No
- Medical history of statin intolerance: Yes, No (from medical history statin intolerance CRF page)
- Baseline statin intensity: High, Moderate or Low, None
- Age: <65 years, >= 65 years
- Sex: Male, Female
- Race subgroup 1: White, Non-White/Multiple (unknown will be excluded from subgroup analyses)
- Race subgroup 2: White, Black or African American, Non-White/Non-Black or African American/Multiple (unknown will be excluded from subgroup analyses)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino (unknown or not reported will be excluded from subgroup analyses)
- BMI: >=30 vs < 30, and >=25 vs < 25 kg/m2
- Renal impairment by eGFR categories at baseline: <15, ≥15 to <30, ≥30 to <60, ≥60 to <90, or ≥90 mL/min/1.73m2
- Baseline LDL-C: <=100 and > 100 mg/dL; by median; and then by quartiles
- Index myocardial infarction: ST segment elevation myocardial infarction (STEMI), Non-ST-segment elevation myocardial infarction (NSTEMI), No myocardial infarction (from ACS medical history)
- Atrial fibrillation associated with index myocardial infarction: Yes, No (from ACS medical history)
- Revascularization procedure during index ACS event: Yes, No (from ACS medical history)
- History of diabetes: Yes, No (from ACS medical history)
- Baseline glycemic status: Diabetes, Pre-diabetes, Normoglycemia

For definition of baseline glycemic status, refer to Section 2.7.3, Table 2-4.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics and the number and percentage of participants in each category will be presented for categorical variables for each treatment group. The summaries will be reported for the FAS, if not otherwise stated.

2.3.1 Patient disposition

Participant disposition will be summarized as follows:

- The number of participants who signed the informed consent form, are screen failures, are randomized, are treated (Safety Set), completed the study or who discontinued early along with reasons for early study discontinuation, the number of screened subjects, completed screening phase and were randomized, completed screening phase but were not randomized, did not complete screening phase, and primary reason for not completing screening phase will be summarized for all screened participants.
- The number of participants in each analysis population will be summarized by treatment group for all randomized participants.
- The number of participants who complete the treatment phase or who discontinued treatment early along with reasons for early treatment discontinuation will be summarized for the inclisiran + usual care group for the FAS.
- The duration of exposure to inclisiran (in days) will be summarized for the inclisiran + usual care group for the FAS.
- The number of participants who complete the study or who discontinued the study early along with reasons for early study discontinuation will be summarized by treatment group for the FAS.
- The duration on study (number of days from study start date to study end date [last recorded contact/participation date in the database]) will be summarized by treatment for the FAS.

The number and percentage of participants with important protocol deviations will be summarized by treatment group for the FAS.

2.3.2 Demographics and other baseline characteristics

Participant demographics including age, age category (<65 years vs ≥65 years; 18 to <50, 50 to <65, 65 to <75, ≥75 years), race, ethnicity, sex, and child bearing potential status; and baseline characteristics such as source of participant referral, smoking status by substance, body height, weight, BMI, LDL-C, and non-HDL-C will be summarized by treatment group using the FAS.

Medical history (ACS medical history, other medical history, and medical history of statin intolerance) will be summarized by treatment group using the FAS. Other medical history will

be summarized by system organ class and preferred term. Tabulation of ACS medical history will include summaries by treatment group for the following durations:

- Duration from index hospitalization discharge to informed consent: number of days from date of hospitalization discharge for the index ACS event to date of informed consent
- Duration from index hospitalization discharge to study treatment start: number of days from date of hospitalization discharge for the index ACS event to study treatment start date (Day 1)

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

2.4.1 Study treatment / compliance

Study drug administration will be summarized overall and by dosing visits for the Safety Set. Summaries will also include missed doses and number of participants randomized to usual care who received at least one dose of inclisiran on study.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after study treatment start date will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and preferred drug name, by treatment group, for the Safety Set. Additional summaries will be provided for lipid-lowering therapies. ATC Level 3 will be used for summaries of medications. If a medication is not coded at the ATC Level 3, the ATC Level 2 will be utilized. See list of lipid-lowering therapies below. Medications will be coded using the World Health Organization (WHO) drug dictionary, and will be coded/re-coded with up-version during the course of study. The final coding version used in this study will be WHODrug Global B3 March 1, 2024. Medications recorded as part of medical history will be presented separately and will not be considered in any analysis of prior or concomitant therapy.

Partially missing medication dates will be imputed following Appendix 5.1.2. Prior medications include all medications stopped prior to study treatment start date. Concomitant medications include any medications taken on or after study treatment start date. In case the medication date values do not allow unequivocally allocating a medication to prior or concomitant medication, the medication will be considered as concomitant medication in the statistical analysis. This rule does not apply to medications recorded on the “ACS Medical History” or the “Medical History of Statin Intolerance” CRFs as no medication dates were captured on these forms by design.

The statin intensity (none, low, moderate, high) will be defined by clinical review of the data according to American College of Cardiology/American Heart Association (ACC/AHA) classification of high intensity and based on the specific statin drug name, dose (unit), and frequency recorded in the data.

Lipid-lowering therapies (LLT) taken at baseline, changes in lipid-lowering therapies prior to baseline, concomitant lipid-lowering therapies by visit, a shift table from baseline statin

intensity level to post-baseline lipid-lowering therapy addition group, and a shift table for statin intensity from baseline to Day 330/Last Visit will also be provided. To this end, the LLTs and statin intensity for Day 330/Last Visit will be assessed on the Day 330 visit date for participants with recorded Day 330 visit date, or on the study end date (date of last participation) otherwise. For the shift table for statin intensity from baseline to Day 330/Last Visit, the "None" category includes participants who did not take statin post baseline or who stopped the statin during the study.

Changes in LLTs prior to baseline will focus on statin and bempedoic acid taken within 30 days prior to study treatment start date, i.e. any time from day -30 to day -1. Number and percentage of participants will be presented for the following statin categories: initiation of statin therapy (no statin record present at day -30), discontinuation of statin therapy (no statin record present at day -1), increase in statin intensity, decrease in statin intensity, and change of statin within the same intensity group. Treatment gaps and/or overlapping treatment periods in case of two or more statins within the 30-day period will be ignored for analysis. If at least one statin record is present indicating that the statin was taken consistenly on all days within the 30-day period, the participant will not be considered as having had any change in statin therapy.

For the analysis of lipid-lowering therapies at baseline a modified lipid-lowering therapy definition is also employed. For this analysis a modified lipid lowering therapy includes any statin, ezetimibe, PCSK9 inhibiting monoclonal antibodies, or bempedoic acid therapies.

The following medications will be included in the lipid-lowering therapy tables.

Table 2-3 Lipid-lowering Therapies

Medication	Medications included
Lipid Lowering Therapy	ATCCODE2=C10
Statin	ATCCODE2=C10 and CMDECOD contains 'statin', or ATCCODE4=C10AA, C10BA, or C10BX
Ezetimibe	ATCCODE2=C10 and CMDECOD contains 'ezetimibe'
PCSK9 inhibiting monoclonal antibodies	ATCCODE2=C10 and CMDECOD contains 'evolocumab' or 'alirocumab'
Bempedoic acid	ATCCODE2=C10 and CMDECOD contains 'bempedoic acid'
Modified lipid lowering therapy	ATCCODE2=C10 and CMDECOD contains 'statin', 'ezetimibe', 'evolocumab', 'alirocumab', or 'bempedoic acid'

2.5 Analysis supporting primary objective(s)

The primary objective is to assess the effect on LDL-C of implementation of an LDL-C management care pathway that includes initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS with LDL-C ≥70 mg/dL despite receiving statin therapy compared to usual care without inclisiran at Day 330.

2.5.1 Primary endpoint(s)

The primary efficacy variables are the following:

1. Percent change from baseline in LDL-C

2. Achieving LDL-C < 70 mg/dL (yes, no)

The primary analysis time point for both primary efficacy variables is at Day 330.

2.5.2 Statistical hypothesis, model, and method of analysis

Primary efficacy variable 1

The null hypothesis is that the mean percent change from baseline in LDL-C at Day 330 for inclisiran + usual care and usual care treatment groups are equal. The alternative hypothesis is that the mean percent change from baseline in LDL-C at Day 330 for inclisiran + usual care treatment group is not equal to that of the usual care treatment group.

Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit (Day 90, Day 270, Day 330), baseline, treatment-by-visit interaction, and baseline-by-visit interaction as explanatory variables. An unstructured covariance matrix will be assumed for this model. Least-squares mean of each treatment group, least-squares mean treatment difference, two-sided 97.5% confidence intervals for the treatments, two-sided 97.5% confidence interval for the treatment difference, and p-value based on the fitted MMRM will be reported for each applicable visit (day). If the p-value based on a two-sided test for treatment at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ([inclisiran + usual care] - usual care) is less than 0, statistical significance in favor of inclisiran + usual care is shown. All efforts will be made to follow up participants until the end of the study. Participants will be expected to follow the visit schedule and assessments even after discontinuation of study treatment. Data after participants discontinued study treatment will be used in the analysis ("retrieved dropout"). In case of non-convergence of a model while using an unstructured covariance matrix, compound symmetry will be tried instead.

The primary analysis of primary efficacy variable 1 will be based on the FAS. The primary analysis of this variable will be repeated for the Per-Protocol Set, Restricted Set 1, and Restricted Set 2.

Primary efficacy variable 2

Let π_j denote the probability of achieving LDL-C < 70 mg/dL at Day 330 for treatment group j, j = 0, 1, where 0 corresponds to usual care and 1 corresponds to inclisiran + usual care. Accordingly, $\pi_j/(1 - \pi_j)$ is the odds for treatment group j, j = 0, 1.

The following null hypothesis (H_0) will be tested against the alternative hypotheses (H_A), corresponding to the comparison inclisiran + usual care versus usual care:

H_0: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] \leq 1$ versus H_A: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] > 1$

Primary efficacy variable 2 will be analyzed at each post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables (Stokes et al. 2012). The odds ratio, two-sided 97.5% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. If the p-value based on a two-sided test for inclisiran + usual care versus usual care at Day 330 is < 0.025 and the corresponding odds ratio is greater than 1, statistical significance in favor of inclisiran + usual care is shown. In case of non-

convergence of a logistic regression model, the model will be updated to use Firth's penalized likelihood method (Firth 1993). If the model using Firth's method still shows convergence issues then the baseline LDL-C covariate may be removed from the model. Two-sided 97.5% confidence intervals for the proportion of participants who achieve LDL-C < 70 mg/dL in each treatment group will be calculated, using the normal approximation to the binomial distribution.

The primary analysis of primary efficacy variable 2 will be based on the FAS. The primary analysis of this variable will be repeated for the Per-Protocol Set, Restricted Set 1, and Restricted Set 2.

2.5.3 Handling of intercurrent events

The remaining intercurrent event of the primary estimand for the two primary efficacy variables are the following:

1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran.
2. Discontinuation of study treatment (in inclisiran + usual care participants). This intercurrent event will be ignored in the analysis.
3. Use of prohibited medication (monoclonal antibodies directed against PCSK9, as defined in Table 2-3) in the inclisiran + usual care group. This intercurrent event will be ignored in the analysis.

2.5.4 Handling of missing values not related to intercurrent event

For the primary analysis of primary efficacy variable 1, the MMRM implicitly imputes missing data under a missing at random assumption.

For the primary analysis of primary efficacy variable 2, participants with missing LDL-C data will be assumed to have LDL-C ≥ 70 mg/dL (i.e., “non-responder”).

2.5.5 Sensitivity analyses

The sensitivity analysis of primary efficacy variable 1 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis. 3. Use of prohibited medication (monoclonal antibodies directed against

PCSK9, as defined in Table 2-3) in the inclisirian + usual care group. This intercurrent event will be ignored in the analysis.

- Summary measure: Probability of observing the same or a more favorable response with inclisiran + usual care relative to usual care

For the above estimand, primary efficacy variable 1 will be analyzed at each time point for the FAS using the Wilcoxon rank-sum test.

The probability of observing the same or a more favorable response (θ_0) with inclisiran + usual care relative to usual care will be estimated using nonparametric methods, and the associated two-sided 97.5% confidence interval will also be reported (Chen and Kianifard 2000).

The sensitivity analysis of primary efficacy variable 2 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Achieving LDL-C < 70 mg/dL (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis. 3. Use of prohibited medication (monoclonal antibodies directed against PCSK9, as defined in Table 2-3) in the inclisiran + usual care group. This intercurrent event will be ignored in the analysis.
- Summary measure: Treatment difference ([inclisiran + usual care] – usual care) in the proportion of participants who achieve LDL-C < 70 mg/dL

For the above estimand, primary efficacy variable 2 will be analyzed at each post-baseline visit for the FAS using the two-sample z-test (normal approximation to the binomial distribution) to compare inclisiran + usual care versus usual care. Two-sided 97.5% confidence intervals will be calculated, using the normal approximation to the binomial distribution.

For both primary efficacy variables 1 and 2, additional sensitivity analyses will be conducted by repeating the corresponding primary analyses on participants in the Full Analysis Set but excluding participants with baseline LDL-C < 70 mg/dL.

2.5.6 Supplementary analyses

A supplementary analysis of primary efficacy variable 1 will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]

- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. 2. Discontinuation of study treatment. 3. Use of prohibited medication (monoclonal antibodies directed against PCSK9, as defined in Table 2-3) in the inclisirian + usual care group. Data after the occurrence of either one of the above three intercurrent events will be excluded from the analysis (using MMRM).
- Summary measure: Least-squares mean difference between inclisiran + usual care group and usual care group

A supplementary analysis of primary efficacy variable 2 will be conducted by repeating the primary analysis based on observed LDL-C values per visit. Missing data will not be imputed. Therefore, the denominator for deriving the proportion of participants achieving LDL-C <70 mg/dL will be the number of participants with non-missing LDL-C per visit and treatment group.

2.5.7 Subgroup analyses

The primary analysis for primary efficacy variables 1 and 2 will be repeated for subgroups of participants according to the subgroup categories defined in Section 2.2.1. To this end, the same approach as defined in Section 2.5.2 for the primary analysis will be applied separately to the sets of participants within each subgroup category. Note that results for a subgroup category will only be presented if the total across both treatment groups within the category is at least 10 participants.

2.6 Analysis supporting secondary objectives

The secondary efficacy objectives include the following:

- To assess (1) the absolute change from baseline in LDL-C level by visit, and (2) average of percent and absolute changes from baseline in LDL-C levels to each post-baseline visit, in the inclisiran + usual care group compared to usual care group at Day 330
- To assess the proportion of participants reaching pre-specified LDL-C targets in the inclisiran + usual care group compared to usual care group at Day 330
- To assess plasma lipoproteins and triglycerides in the inclisiran + usual care group compared to usual care group at Day 330
- To assess changes in and adherence to background lipid-lowering therapy in the inclisiran + usual care group compared to usual care group at Day 330

2.6.1 Secondary endpoint(s)

The secondary efficacy variables are the following:

1. Absolute change from baseline in LDL-C
2. Average percent change from baseline in LDL-C levels to each post-baseline visit
3. Average absolute change from baseline in LDL-C levels to each post-baseline visit

4. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)
5. Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)
6. Achieving LDL-C < 55 mg/dL (yes, no)
7. Percent change from baseline in apoB
8. Absolute change from baseline in apoB
9. Percent change from baseline in VLDL
10. Absolute change from baseline in VLDL
11. Percent change from baseline in non-HDL-C
12. Absolute change from baseline in non-HDL-C
13. Percent change from baseline in total cholesterol
14. Absolute change from baseline in total cholesterol
15. Percent change from baseline in Lp(a)
16. Absolute change from baseline in Lp(a)
17. Percent change from baseline in HDL-C
18. Absolute change from baseline in HDL-C
19. Percent change from baseline in triglycerides
20. Absolute change from baseline in triglycerides
21. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)

    Intensity of therapy is only available for statins, not for other lipid-lowering therapies used in this study. Therefore, for each participant and analysis visit, the highest statin intensity on each nominal visit date will be compared to baseline statin intensity. The decrease, no change, and increase in statin intensity at each visit will be assigned as follows:

Statin Intensity		Post-baseline Visit			
Baseline		High	Moderate	Low	None
	High	No change	Decrease	Decrease	Decrease
	Moderate	Increase	No change	Decrease	Decrease
	Low	Increase	Increase	No change	Decrease
	None	Increase	Increase	Increase	No change

22. Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days)

    If a participant did not take any of the three medications, then the total number of days will be assumed to be zero. Total number of study days is the total study duration (not treatment duration).

23. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)

    If a participant is considered a study completer and has a non-missing visit date for the nominal Day 330 visit recorded, a statin assessment date (to assess if the participant was taking statins at this point in time) will be calculated by subtracting 30 days from the Day 330 visit date (e.g., study Day 300 if the participant completes on study Day 330). The statin assessment date will be compared to the maximum statin end date of all statin medications taken by the participant. If the last statin is recorded as ongoing at study end date, the maximum statin end date will be set to the study end date.

    If the participant was on a statin on or after this statin assessment day (maximum statin end date ≥ statin assessment date), the participant will be considered as discontinued statin = 'no'.

    If the participant was not on a statin on and after this statin assessment day (maximum statin end date < statin assessment date), or they were a completer who did not have a Day 330 visit, the participant will be considered as discontinued statin = 'yes'.

    All early termination participants will be considered to not be on a statin for this endpoint (the participant will be considered as discontinued statin = 'yes').

    Participants who were not taking any statin while on study will be considered to not be on a statin for this endpoint (the participant will be considered as discontinued statin = 'yes').

    The analysis will be based on the FAS excluding participants who had medical history of statin intolerance.

2.6.2 Statistical hypothesis, model, and method of analysis

Analyses of secondary efficacy variables 1 and 7 - 20 will be similar to the primary analysis of primary efficacy variable 1 (using MMRM, but with a two-sided 95% confidence interval for the treatment difference).

Secondary efficacy variables 2, 3, and 22 will be analyzed using an analysis of covariance (ANCOVA) linear model with treatment and baseline LDL-C as explanatory variables. Least-squares mean of each treatment group, 95% confidence interval for the treatment group least-squares means, least-squares mean treatment difference, 95% confidence interval for the treatment difference, and p-value based on the fitted model will be reported. Variables 2 and 3 are calculated by averaging the observed post-baseline values (change or percent change) for each participant across analysis visits Day 90, Day 270, and Day 330. The outcome value for variable 22 is a proportion that is calculated for each participant with total number of study days equal to duration on study as defined in Section 2.3.1.

Secondary efficacy variables 4 - 6 and 23 will be analyzed at each applicable post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables (Stokes et al. 2012). The odds ratio, 95% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. Confidence intervals for the percentages per treatment group will be presented and will be derived from the normal approximation to the

binomial distribution. Missing data will be imputed using "non-responder" (i.e., "negative" outcome) imputation.

Secondary efficacy variable 21 will be analyzed at each post-baseline visit using a proportional odds model with treatment and baseline LDL-C as explanatory variables (Stokes et al. 2012). The odds ratios, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported. Confidence intervals for the percentages per treatment group will be presented and will be derived from the normal approximation to the binomial distribution. Missing data will not be imputed.

Analyses of secondary efficacy variables will be based on the FAS.

2.6.3 Handling of missing values

For the analysis of secondary efficacy variables 1 and 7-20, the MMRM implicitly imputes missing data under a missing at random assumption.

For the analysis of secondary efficacy variables 4 – 6 and 23, participants with missing data will be imputed using "non-responder" (i.e., "negative" outcome) imputation.

For the analysis of secondary efficacy variables 2, 3, 21 and 22, missing data will not be imputed.

2.6.4 Sensitivity analyses

Not applicable.

2.6.5 Supplementary analyses

Secondary efficacy variables 2 and 3 will be analyzed using MMRM similar to the analysis of primary efficacy variable 1 and secondary efficacy variable 1, respectively. A linear combination of the estimated means will be used to estimate the time-adjusted percent change and absolute change from baseline in LDL-C, where "time-adjusted" refers to the estimated average from Day 90 through Day 330. Least-squares mean of each treatment group, least-squares mean treatment difference, 95% confidence interval for the treatment difference, and p-value based on the fitted model will be reported.

Secondary efficacy variables 4 – 6 will be analyzed similar to the supplementary analysis of primary efficacy variable 2 based on observed data only.

2.6.6 Subgroup analyses

The analysis for secondary efficacy variable 1 (absolute change from baseline in LDL-C) will be repeated for subgroups of participants according to the subgroup categories defined in Section 2.2.1. To this end, the same approach as defined in Section 2.6.2 for the analysis of secondary efficacy variable 1 will be applied separately to the sets of participants within each subgroup category. Note that results for a subgroup category will only be presented if the total across both treatment groups within the category is at least 10 participants.

2.7 Safety analyses

All safety analyses will be performed on the Safety Set.

2.7.1 Adverse events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs, and up-versioning will be applied during the course of study. The final MedDRA version used in this study will be v27.0. Partially missing AE dates will be imputed following Appendix 5.1.2. An AE (classified as preferred term) occurring during the treatment period will be counted as a treatment-emergent AE (TEAE) either if it is not present at Day 1 before treatment or if it is present before treatment but increased in severity during the treatment period. Therefore, all recorded AEs with onset on or after the study treatment start date will be counted as TEAE. In case the AE date values do not allow unequivocally allocating an AE record to TEAE or non-TEAE, the AE will be considered as TEAE in the statistical analysis.The following summary tables will be presented:

- Overall Summary of TEAEs
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by PT
- Common (≥3% within either treatment group) by PT
- TEAEs by SOC, PT, and Severity
- TEAEs by SOC, PT, and Relationship to Study Treatment
- Related TEAEs by SOC, PT, and Severity
- Treatment Emergent Serious AEs (TESAEs) by SOC and PT
- TESAEs by PT
- TESAEs by SOC, PT, and Severity
- TESAEs by SOC, PT, and Relationship to Study Treatment
- Related TESAEs by SOC, PT, and Severity
- TEAEs Leading to Withdrawal of Study Treatment by SOC and PT
- TEAEs with a Fatal Outcome by SOC and PT

If more than one event occurred with the same PT for the same participant, the participant will be counted only once for that PT using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

Missing severity and relationship will not be imputed and will be identified as ‘missing’ in the tables.

For common (*3*% within either treatment group) TEAEs, serious TEAEs and TEAEs leading to withdrawal of study treatment, risk ratios along with 95% confidence intervals will be presented to compare treatment groups with respect to risk.

For tables presented by SOC and PT, system organ classes are sorted alphabetically and within each system organ class, the preferred terms are sorted in descending order of total frequency.

For tables presented by PT, preferred terms are sorted in descending order of total frequency.

Listings will be presented for participants with SAEs and AEs leading to discontinuation of study treatment.

2.7.1.1 Adverse events of special interest / grouping of AEs

TESAEs and TEAEs of special interest will be tabulated.

SAEs of special interest include:

1. Hepatotoxicity
2. Renal events

AEs of special interest include:

1. TEAE at the injection site
   - TEAE identified as being an AE at the injection site on the AE CRF page
   - Injection site reaction (HLT)
2. Hepatotoxicity
   - Drug related hepatic disorders - comprehensive search (SMQ, broad and narrow)
3. Renal events
   - Acute renal failure (SMQ, broad and narrow)
4. New-onset/worsening of diabetes
   - Hyperglycemia/new-onset diabetes mellitus (SMQ, narrow)
   - Diabetic Complications (HLGT)
   - Diabetes Mellitus (HLT)
   - Carbohydrate tolerance analyses (HLT), excluding PT “Blood glucose decreased”
5. Hypersensitivity
   - Hypersensitivity (SMQ, broad and narrow) excluding
     - PTs ‘infusion site %’ (e.g., ‘'infusion site dermatitis', 'infusion site eczema’, 'infusion site hypersensitivity', 'infusion site rash', 'infusion site urticaria', 'infusion site vasculitis) and
     - PTs ‘injection site %’ (e.g., 'injection site dermatitis', 'injection site eczema’, 'injection site hypersensitivity', 'injection site rash', 'injection site urticaria' and 'injection site vasculitis')

TEAEs at the injection sites will be presented for all participants and then by baseline glycemic status, specifically for participants with diabetes at baseline and for participants without diabetes at baseline (i.e., participants with pre-diabetes or normoglycemia). The definition of baseline glycemic status is provided in Table 2-4.

2.7.2 Deaths

Listings will be presented for participants with SAEs/AEs leading to a death.

2.7.3 Laboratory data

Laboratory values will be summarized by treatment group, including the observed value, changes and percent changes from baseline at each analysis visit (including Day 330/Last Visit).

Estimated glomerular filtration rate (eGFR) in mL/min/1.73m^2 will be derived using the Modification of Diet in Renal Disease approach according to the following formula based on serum creatinine values in mg/dL (Levey et al. 2006):

$$eGFR = 175 \times Serum\ Cr^{-1.154} \times Age^{-0.203} \times 1.212 \text{ (if participant is black)} \times 0.742 \text{ (if female)}.$$

Fasting glucose parameter, when used in any analysis, will require the lab sample to be taken while fasting. Glucose values recorded under non-fasting conditions will not be used. For all safety analyses, baseline fasting glucose uses the **average of the last two assessments** measured under fasting conditions at or prior to baseline. If only one fasting glucose value is available at or prior to baseline, the analysis will be based on the available data.

A shift analysis using the normal range (except for eGFR and HbA1c) will be done which counts the number of participants with a low, normal or high value at baseline and a low, normal or high value post baseline.

The following ranges will be used for eGFR and hemoglobin A1c (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; and Normal = ≥90 mL/min/1.73m^2.
- For HbA1c, the categories will be ≤5.6%, ≥5.7% to ≤6.4%, and ≥6.5%.

The baseline and worst post-baseline value will be utilized for the shift tables. Note that 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 CSR purposes, HbA1c will be reported under clinical chemistry, not hematology.

New onset or worsening of diabetes during the study will be identified by evaluating different components: 1) adverse events, 2) laboratory measures of either fasting glucose of glycated hemoglobin (HbA1c) and 3) initiation of antidiabetic medication. New onset or worsening of diabetes is defined if ANY of the following conditions are met post-baseline:

- Laboratory results indicating diabetes, which can be any of the following:
  - The participant has HbA1c ≥6.5% on two consecutive tests.
  - The participant has fasting glucose ≥126 mg/dL on two consecutive fasted tests.
  - The participant has HbA1c ≥6.5% and fasting glucose ≥126 mg/dL on the same occasion.
  - The participant has HbA1c ≥6.5% on one occasion and has fasting glucose ≥126 mg/dL on the succeeding occasion.
  - The participant has fasting glucose ≥126 mg/dL on one occasion and has HbA1c ≥6.5% on the succeeding occasion.
- Diabetic TEAEs identified by the search terms:
  - Hyperglycaemia/new onset diabetes mellitus (SMQ, narrow)
  - Diabetic complications (HLGT)
  - Diabetes mellitus (incl subtypes) (HLT)

- Carbohydrate tolerance analyses (incl diabetes) (HLT), excluding PT "Blood glucose decreased"
- Initiation of anti-diabetic medication (ATC level 2 code: A10) at any time post-baseline.

The number and percentage of participants presenting with new onset of diabetes post-baseline according to the criteria above will be summarized among participants without diabetes at baseline (i.e., participants with pre-diabetes or normoglycemia). To this end, baseline glycemic status will be determined as per the criteria in Table 2-4. Baseline glycemic status will also be used in the subgroup analysis of the primary and key secondary efficacy endpoints, as well as in the analysis of TEAEs at the injection site (Section 2.7.1.1). Participants for whom the baseline glycemic status cannot be determined according to the rules below will be excluded from the analysis.

Table 2-4 Definition of Baseline Glycemic Status

Category	Definition
Diabetes	Participants with diabetes at baseline are those with ANY of the following: • Medical history of diabetes recorded on ACS medical history CRF (diabetes recorded as "Yes"). • Anti-diabetic medication (ATC level 2 code: A10) at baseline • HbA1c ≥6.5% AND fasting glucose ≥126 mg/dL at baseline.
Pre-diabetes	Participants with pre-diabetes at baseline are those with ALL of the following: • No medical history of diabetes recorded on ACS medical history CRF (diabetes not recorded as "Yes"). • No anti-diabetic medication (ATC level 2 code: A10) at baseline. • HbA1c ≥5.7% OR fasting glucose ≥100 mg/dL at baseline, but not both HbA1c ≥6.5% AND fasting glucose ≥126 mg/dL at baseline. *Note: Either baseline HbA1c or baseline fasting glucose have to be non-missing to evaluate this category.*
Normoglycemia	Participants with normal glucose control status at baseline are those with ALL of the following: • No medical history of diabetes recorded on ACS medical history CRF (diabetes not recorded as "Yes"). • No anti-diabetic medication (ATC level 2 code: A10) at baseline. • HbA1c < 5.7% AND fasting glucose < 100 mg/dL at baseline. *Note: Both baseline HbA1c and baseline fasting glucose have to be non-missing to evaluate this category.*

The number and percentage of participants with potentially clinically significant (PCS) laboratory values or clinically significant (CS) laboratory values (refer to Appendix 5.3.2 for the criteria) will be summarized. It is possible that some laboratory values for a parameter may be classified as PCS while others are CS. In this case, the CS laboratory value for that parameter will be used in the summaries. For AST, ALT and CK, the most severe result for each subject will be used. For creatinine, the CS criterion will additionally be broken down into the following three mutually exclusive categories:

1. Subjects with baseline value ≤ 2 mg/dL and any post-baseline value > 2 mg/dL.
2. Subjects with baseline value ≤ 2 mg/dL and any post-baseline ≥ 50% change from baseline but no post-baseline value > 2 mg/dL.
3. Subjects with baseline value > 2 mg/dL and any post-baseline ≥ 50% change from baseline.

For liver chemistry parameters (ALT, AST, ALP, TBIL), the number and percentage of subjects whose PCS/CS value returned to baseline level at the last measurement will also be summarized. Here the baseline level is defined as a value of the same category as the baseline category or a value of a better category than the baseline. For example, if a subject's baseline ALT is >3 and <=5 x ULN and the subject's ALT elevated to >5 and <=10 x ULN at the worst measurement post baseline, the subject is considered to have returned to baseline level at the last measurement if the last ALT value of that subject is <=5 x ULN.

Listings of all subjects with PCS or CS laboratory values will be presented. Subjects will appear once per lab parameter but may appear under multiple lab parameters.

The number and percentage of participants satisfying Hy's Law will also be tabulated by treatment group based on the following lab findings:

- Any elevated post-baseline aminotransferases defined as:
  - ALT > 3 x ULN or
  - AST > 3 x ULN
- Elevated post-baseline serum total bilirubin (TBL) > 2 x ULN and serum alkaline phosphatase (ALP) levels < 2 x ULN

Participants must meet all of the criteria listed above at the same time point and have normal lab variables (ALT, AST, TBL) at baseline to be considered a Hy's Law case. The same analysis will be performed excluding the normal baseline value requirement.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECG results will be listed.

2.7.4.2 Vital signs

Observed value, change, and percent change from baseline in vital signs (pulse rate, [redacted]) will be summarized descriptively at each analysis visit (including Day 330/Last Visit) by treatment group.

[redacted]

[redacted]

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

See Section 2.12.

2.11 Biomarkers

See Section 2.6.

2.12 Other Exploratory analyses

The exploratory efficacy variables are the following:

[redacted]

8. Cardiovascular death (yes, no)
9. Non-fatal MI (yes, no)
10. Resuscitated cardiac arrest (yes, no)
11. Non-fatal ischemic stroke (yes, no)
12. Composite MACE (cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke) (yes, no)

[redacted]

Exploratory efficacy variables 8-12 will be summarized descriptively by total number of events and number and percentage of subjects with any event for each treatment group. In addition, a time-to-event analysis will be carried out. Time to first occurrence of any event in the composite MACE as well as time to first occurrence of each of its components will be derived as study day of onset of the corresponding TEAE, imputing for partially missing dates as needed. Adverse events with missing onset date will not be considered in the time-to-event analysis. Cox proportional hazards models will be used to estimate the corresponding hazard ratios of inclisiran + usual care over usual care with associated 95% confidence intervals. Treatment and baseline LDL-C will be used as explanatory variables in the Cox proportional hazards models. Observation time for participants without the respective event will be censored at their end of study date (date of last participation) or date of death, as applicable.

[redacted]

Table 2-6 MACE Definitions (using TEAEs only)

Category	Details
Cardiovascular death	(1) Fatal SAEs in "Cardiac disorders" SOC (2) Fatal SAEs in "General disorders and administration site conditions" SOC: PTs "Death", "Sudden cardiac death", "Cardiac death", "Apparent death" (3) Central nervous system haemorrhages and cerebrovascular accidents (HLT), fatal events only
Non-fatal MI	Myocardial infarction (SMQ, broad and narrow search), non-fatal events only, excluding PT "Blood creatine phosphokinase increased"
Resuscitated cardiac arrest	PT "Cardiac arrest", non-fatal events only

Non-fatal ischemic stroke	PT “Ischaemic stroke”, non-fatal events only

[redacted]

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

After all participants complete their baseline visit, the demographic and baseline characteristics may be summarized to help design new studies. No analysis will be performed using post-baseline data. Thus, there is no need to adjust the level of significance for such interim analysis of baseline data.

3 Sample size calculation

The sample size was calculated for the two primary efficacy variables with adjustment for multiple testing by using the Bonferroni procedure.

For primary efficacy variable 1, i.e., percent change from baseline in LDL-C, the standard deviation is assumed to be 40, partly based on the results from ORION-10 and ORION-11 clinical trials and considering that the standard deviation will likely be larger in this trial since changes in lipid-lowering therapy are allowed in both treatment groups. An expected mean treatment difference of 15 is assumed, which is smaller than the mean difference observed in the Phase III trials, to account for 1) potential lower utilization of background lipid-lowering therapy in the inclisiran + usual care treatment group compared to the usual care treatment group, and 2) the ability to add non-statin lipid lowering therapy in the usual care treatment group. A z-test, an allocation ratio of 1:1, and a two-sided significance level of 0.025 were also used in the calculation of sample size.

Table 3-1 considers total sample sizes for expected mean treatment differences of 10, 15, and 20, and powers of 0.85 and 0.90 (nQuery Version 8.4.1.0). From Table 3-1, an expected mean treatment difference of 15 (based on means of 40 and 55 at Day 330 in the usual care and inclisiran + usual care treatment groups, respectively) and a power of 0.85 were chosen to provide a total sample size of 306 participants.

Table 3-1 Sample Size Calculations for Percent Change from Baseline in LDL-C

Mean treatment difference	Power = 0.85	Power = 0.90
10	688	796
15	**306**	**354**
20	172	200

For primary efficacy variable 2, i.e., achieving LDL-C < 70 mg/dL (yes, no), a z-test, an allocation ratio of 1:1, and a two-sided significance level of 0.025 were used in the calculation of sample size.

Table 3-2 considers total sample sizes for several expected proportions of participants who achieve LDL-C < 70 mg/dL at Day 330 in the usual care and inclisiran + usual care treatment groups, and powers of 0.85 and 0.90 (nQuery Version 8.4.1.0). From Table 3-2, the expected proportions of 0.55 and 0.75 in the usual care and inclisiran + usual care treatment groups, respectively, and a power of 0.85 were chosen to provide a total sample size of 242 participants.

Table 3-2 Sample Size Calculations for Achieving LDL-C < 70 mg/dL

Proportion in usual care group	Proportion in inclisiran + usual care group	Power = 0.85	Power = 0.90
0.50	0.65	464	536
0.50	0.70	256	294
0.55	0.70	446	514
0.55	**0.75**	**242**	**278**

Based on the sample size calculations in the tables above, a total sample size of 306 together with a loss to follow-up rate of 20% at Day 330 require approximately 384 participants (192 participants per treatment group) to be randomized. This will also allow examination of subgroups with reasonable sample sizes.

4 Change to protocol specified analyses

Change from Protocol version 04 (amended protocol) include the following:

1. Protocol Section 12.4.2 states that an unstructured working correlation matrix will be assumed for the MMRM. An unstructured covariance matrix will be used instead. In case of convergence issues, compound symmetry will be tried instead.
2. The protocol uses Day 0 as the first inclisiran dose day. In order to aid in counting of dosing days the first dose day will be referred to as Day 1.
3. Protocol Section 12 notes that the interquartile range will be provided. In order to streamline the tables this statistic was removed.
4. Protocol Section 12.2 notes that relevant medical histories and current medical conditions at baseline would be summarized using the Safety Set, the FAS was used instead.
5. Protocol Section 12.5.1 lists out secondary efficacy variables. The analysis of variable #21 (Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose) was modified slightly. Intensity of therapy is only available for statins, not for other lipid-lowering therapies used in this study. Therefore, for each participant and analysis visit, the highest statin intensity on each nominal visit date will be compared to baseline statin intensity.
6. Protocol Section 12.5.2 notes that all vital signs and all laboratory data will be listed. In order to streamline the listings, only abnormal vital signs and laboratory data will be provided.
7. Use of prohibited medication as defined in Protocol Section 6.2.2 (monoclonal antibodies directed against PCSK9) will be considered as an intercurrent event for participants in the inclisirian + usual care group and was therefore incorporated to all estimands as applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 Adverse event and concomitant medication date imputation

The following table explains the notation used in the logic matrix of partially missing adverse event or prior/concomitant medication start dates. Please note that **completely missing start dates** will not be imputed.

	Day	Month	Year
Partial Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start
YYYY = TRTY	**(B)** Uncertain	**(C)** Before Treatment Start	**(B)** Uncertain	**(A)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start

The following table is the legend to the logic matrix.

- If end date is complete and end date < Treatment start date, or end date is partial and imputed end date < Treatment start date, then start reference = min (informed consent date, earliest visit date from SV).
- Else if end date is partial and end date > = Treatment start date, or is ongoing, then start reference = treatment start date.

Relationship	
Before start reference	Partial date indicates start date prior to start reference
After start reference	Partial date indicates start date after start reference
Uncertain	Partial date insufficient to determine relationship of start date to start reference

Imputation Calculation	
NC/Blank	No date imputation
(A)	01MONYYYY
(B)	Start reference
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
Complete date	No date imputation

End Date Imputation:

- Imputed date = date part of original date, if complete date
- Imputed date = min (study end date, DEC 31, date of death), if month is missing
- Imputed date = min (study end date, last day of the month, date of death), if day is missing

Imputed Date Flag:

- If year of the imputed date is not equal to YYYY then date flag = Y
- Else if month of the imputed date is not equal to MON then date flag = M
- Else if day of the imputed date is not equal to day of original date then date flag = D
- Else date flag = null

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

5.3.1 Handling data with special symbols

Any laboratory parameters with values identified as <x, ≤x, >x, or ≥x will be analyzed using the 'x' value (the analysis will ignore the <, ≤, >, or ≥ symbol).

5.3.2 Criteria for potentially clinically significant and clinically significant abnormal laboratory tests

Hemoglobin A1C criteria are explicitly stated in the table below. For all other parameters, a PCS/CS criterion is met when both of the following occur:

- There is a post-baseline value that meets the threshold
- The baseline value does not meet the threshold

Some examples are:

- For leukocytes, a subject satisfies "<= 2.8 x 10^9/L" criterion as long as the baseline value is > 2.8 x 10^9/L and any post-baseline value is <= 2.8 x 10^9/L; a subject satisfies ">=16 x 10^9/L" criterion as long as the baseline value is <16 x 10^9/L and any post-baseline value is >=16 x 10^9/L.
- For CK, a subject satisfies "> 3 and ≤ 5 × ULN" criterion as long as the baseline value is ≤ 3 x ULN and any post-baseline value is > 3 and ≤ 5 × ULN. A subject satisfies "> 5 and ≤ 10 × ULN" criterion as long as the baseline value is ≤ 5 x ULN and any post-baseline value is > 5 and ≤ 10 × ULN. If a subject satisfies both "> 3 and ≤ 5 × ULN" and "> 5 and ≤ 10 × ULN" criteria and does not satisfy the criteria of any more severe category, the subject will be presented under "> 5 and ≤ 10 × ULN" but not under "> 3 and ≤ 5 × ULN" because the most severe category will be used for CK.
- For serum creatinine, the CS criterion is satisfied if at least one of the following is true:
  - The baseline value is ≤ 2 mg/dL and any post-baseline value is > 2 mg/dL.
  - Any post-baseline value is ≥ 50% increase from baseline, regardless of whether the baseline value is ≤ 2 mg/dL.
- For creatinine, the CS criterion will additionally be broken down into the following three mutually exclusive categories:
  1. Subjects with baseline value ≤ 2 mg/dL and any post-baseline value > 2 mg/dL.
  2. Subjects with baseline value ≤ 2 mg/dL and any post-baseline ≥ 50% change from baseline but no post-baseline value > 2 mg/dL.
  3. Subjects with baseline value > 2 mg/dL and any post-baseline ≥ 50% change from baseline.

Table 5-1 Laboratory Test Criteria

Variable	Unit	Lower Boundary	Upper Boundary
Hematology			
Hematocrit	%	≤0.8 × LLN	N/A
Hemoglobin	g/dL	≤10 g/dL	N/A
Platelet Count	10^9/ L	≤75*	≥700*
White Blood Cell Count	10^9/L	≤2.8	≥16

Variable	Unit	Lower Boundary	Upper Boundary
Serum Chemistry			
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>1 and ≤3 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>3 and ≤5 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>5 and ≤10 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>10 and ≤20 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>20 × ULN*
Alkaline Phosphatase	U/L	N/A	>2 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>1 and ≤3 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>3 and ≤5 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>5 and ≤10 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>10 and ≤20 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>20 × ULN*
Creatine Kinase (CK)	U/L	N/A	>1 and ≤3 × ULN
Creatine Kinase (CK)	U/L	N/A	>3 and ≤5 × ULN
Creatine Kinase (CK)	U/L	N/A	>5 × and ≤10 × ULN*
Creatine Kinase (CK)	U/L	N/A	>10 and ≤20 × ULN*
Creatine Kinase (CK)	U/L	N/A	>20 × ULN*
Hemoglobin A1C	%	N/A	≥6.5% and ≥0.5% change from baseline
Serum Creatinine	mg/dL	N/A	≥50% increase from baseline or >2 mg/dL*
Total Bilirubin	mg/dL	N/A	>2 × ULN*

LLN: Lower limit of the standard reference (normal) range; ULN: Upper limit of the standard reference (normal) range; N/A is Not Applicable.

For AST, ALT, and CK, the most severe result for each subject will be used.

*Clinically significant laboratory boundaries. All others are potentially clinically significant.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Not applicable.

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5-2 Criteria Leading to Exclusion

Analysis Set	Criteria that cause participants to be excluded
FAS	Not randomized
Restricted Set 1	Not randomized Changes in background lipid-lowering therapy
Restricted Set 2	Not randomized Less than three doses of inclisiran in the inclisiran + usual care group (miss one or more doses)
Per Protocol Set	Not randomized Treated with any inclisiran if randomized to usual care treatment group Major protocol deviations
Safety	Participants who have no data collected at baseline or any post-baseline visits.

6 Reference

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