NOVARTIS

Clinical Development

KJX839

**CKJX839A1US02 / NCT04929249**

# A randomized, multicenter, open-label trial comparing the effectiveness of an "inclisiran first" implementation strategy to usual care on LDL cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease and elevated LDL-C (≥70 mg/dL) despite receiving maximally tolerated statin therapy (VICTORION-INITIATE)

## Statistical Analysis Plan (SAP)

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| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
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| 19-Jun-2021 | Prior to DB lock | Creation of final version | N/A - First version | NA |
| 21-Dec-2021 | Prior to DB lock | Updated after creation of TLF shells | Secondary efficacy variable absolute change in LDL-C will also be analyzed by subgroup. Subgroups for subgroup analyses of primary efficacy variables and absolute change in LDL-C added. | Section 2.2.1 |
| | | | List of demographic variables updated. | Section 2.3.2 |
| | | | Additional summaries added. | Section 2.4.2 |
| | | | Common adverse event tables using 5% 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 |
| | | | Summary tables for new onset or worsening of diabetes were added. | 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 |
| | | | Other minor changes were made to the text. | Various sections |
| 07-Nov-2023 | Prior to DB lock | Updated after creation of TLF shells and further Novartis review | Updated number of sites to 50 and added note that inclisiran is now commercially available. | Section 1.1 |
| | | | Added note clarifying that 'absolute' change from baseline is calculated as post-baseline value minus baseline value. Corrected inequality sign: Achievement of LDL-C <100 mg/dL | Section 1.2 |

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| to be evaluated in participants with LDL-C ≥100 mg/dL at baseline. | |
| Clarified wording for population of primary estimand #2. | Section 1.2.1 |
| [redacted] | [redacted] |
| Various updates made to clarify definitions. | Section 2.1.1 |
| Clarifications added to analysis sets. | Section 2.2 |
| Updates and clarifications added to subgroups. | Section 2.2.1 |
| Clarifications added to analyses of patient disposition, demographics, and other baseline characteristics. Only summarizing FAS now. | Sections 2.3, 2.3.1, and 2.3.2 |
| Clarifications added to analyses of study treatment/compliance and prior, concomitant and post therapies. | Sections 2.4.1 and 2.4.2 |
| Clarifications added for analyses supporting primary objectives. | Sections 2.5.1, 2.5.2, 2.5.3, 2.5.4, 2.5.5, and 2.5.6 |
| Clarifications added for analyses supporting secondary objectives. Removed handling of incurrent events section. Added supplementary analyses. | Sections 2.6.1, 2.6.3, and 2.6.5 |
| Clarifications added for AE analyses. Updated MedDRA dictionary to v26.1. Updated common TEAE definition to 3%. Missing severity and relationship will not be imputed but will be identified as 'missing' in the tables. Updated sorting methods. Updated methods for identifying AEs of special interest. | Sections 2.7.1 and 2.7.1.1 |
| Clarified and updated laboratory data analyses. | Section 2.7.3 |
| Updated vital signs analyses. | Section 2.7.4.2 |

| | |
|---|---|
| [redacted] | |
| Updated text for potentially clinically significant and clinically significant laboratory tests | Section 5.2.1 |
| Added updates to changes in protocol specified analyses. | Section 4 |
| Moved concomitant medication data imputation to a new section. | Section 5.1.3 |
| Added section on handling data with special symbols. | Section 5.2.1 |
| Updated rule for excluding participants from the safety analysis set. | Section 5.5 |
| Added a reference. | Section 6 |
| Other minor changes were made to the text. | Various sections |

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## List of abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| AE | Adverse Event |
| ALP | Alkaline phosphatase |
| AHA | American Heart Association |
| ApoB | Apolipoprotein B |
| ALT | Alanine Aminotransferase |
| ASCVD | Atherosclerotic cardiovascular disease |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| [redacted] | [redacted] |
| CK | Creatine Kinase |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CS | Clinically significant |
| DILI | Drug induced liver injury |
| dL | Deciliter |
| eGFR | estimated Glomerular Filtration Rate |
| EHR | Electronic Health Record |
| ECG | Electrocardiogram |
| EOS | End of Study |
| FAS | Full Analysis Set |
| [redacted] | [redacted] |
| HDL-C | High density lipoprotein cholesterol |
| HLGT | High-Level Group Terms |
| HLT | Highest Level Terms |
| HRSA | Health Resources and Services Administration |
| ICF | Informed consent form |
| IRT | Interactive Response Technology |
| LDL-C | Low density lipoprotein cholesterol |
| Lp(a) | Lipoprotein(a) |

| | |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| mg | Milligram(s) |
| MI | Myocardial Infarction |
| mmHg | millimeters of mercury |
| MMRM | Mixed-effects Model for Repeated Measures |
| PCS | Potentially clinically significant |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PD | Pharmacodynamics |
| PFS | Prefilled syringe |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PT | Preferred Term |
| SAP | Statistical Analysis Plan |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System |
| s.c. | subcutaneous |
| SMQ | Standardised MedDRA Queries |
| SOC | System Organ Class |
| TBL | Total bilirubin |
| TEAE | Treatment-Emergent Adverse Event |
| TESAEs | Treatment-Emergent Serious AEs |
| [redacted] | [redacted] |
| ULN | Upper Limits Of Normal |
| VLDL-C | Very low density lipoprotein cholesterol |
| WHO | World Health Organization |
| WHODDG | World Health Organization drug dictionary |

# 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 CKJX839A1US02.

The aim of the trial and the described statistical analysis methodologies is to assess the effectiveness of an "inclisiran first" implementation strategy (addition of inclisiran to maximally tolerated statin therapy immediately upon failure to achieve acceptable LDL-C with maximally tolerated statin therapy alone) compared to usual care in an ASCVD population, enriched for minority and medically underserved patients.

Analysis plans in this document refer to the related statistical analysis sections in Clinical Study Report (CSR). Data will be analyzed by [redacted] using [redacted] according to Section 12 (Data analysis and statistical methods) of the study protocol which is available in Appendix 16.1.1 of the CSR. Additional detailed information regarding the analysis methodology will be contained in the Appendix Section 16.1.9 of CSR.

Please refer to the following documents: Clinical Protocol CKJX839A1US02 v02 (amended protocol dated 20-Oct-2022) and CRF v11.0 (dated 13-Jan-2023).

## 1.1 Study design

The study design will be a randomized, two-arm, parallel-group, open-label, multicenter, clinical trial. Approximately 444 participants will be randomized 1:1 to "inclisiran first" implementation strategy or to usual care. Eligible participants have established ASCVD and elevated LDL-C (or non-HDL-C) despite treatment with maximally tolerated statin therapy (but without ezetimibe). The unit of randomization will be the participant. To address the bias that may arise due to differences in access to therapies, randomization will be stratified by [redacted] status, and various statistical methods will be adjusted for [redacted].

To minimize selection bias and increase generalizability of the results, potential study sites and potentially eligible participants will be identified using electronic data sets (EHR, claims and/or laboratory data). The goal in selecting study sites is to ensure a representative sample of sites in terms of geography, patient population, and lipid management practices. For example, the inclusion of specialized lipid clinics in the trial would lead to more intensive treatment than is typical and would therefore reduce the generalizability of the results. Several tactics will aim to enhance inclusion of minority and medically underserved populations, as these populations are traditionally underrepresented in clinical trials. [redacted] Second, investigators will explicitly be ority populations. Third, specific barriers to participation will be addressed, including rapid reimbursement (e.g., of transportation costs) and availability of trial materials (such as informed consent forms [ICFs]) in multiple languages). Selected sites will receive a list of patients who could qualify for the trial that is generated based on EHR, claims and/or laboratory data. All participants who meet the eligibility criteria are to be invited using a standardized invite.

Participants in both groups will remain on maximally tolerated statin therapy, unless they are statin-intolerant at baseline. In the usual care group, treating physicians are recommended to treat patients in accordance with the 2018 ACC/AHA guidelines (Grundy et al 2019). Treatment decisions will be at the discretion of the treating physician (including commercial prescription of inclisiran). In the "inclisiran first" implementation strategy group, inclisiran will be administered initially at randomization, 90 days later and six months thereafter. PCSK9-inhibiting monoclonal antibodies are not to be used in the “inclisiran first” implementation strategy group post-randomization, but addition of other non-statin LDL-C lowering therapies (e.g., ezetimibe or bempedoic acid) is allowed to reach acceptable LDL-C levels. This could be the case, for example, if a patient has an LDL-C ≥70 mg/dL despite treatment with a maximally tolerated statin and inclisiran. The sponsor will not provide access to therapies other than inclisiran (only for patients randomized to the “inclisiran first” implementation strategy group). In both groups, laboratory assessments (including LDL-C) will be performed at screening, Day 0, Day 90, Day 180, Day 270 and Day 330. The results of the laboratory assessments performed as part of the trial will be available to the participants' physicians in both study groups. Hence, to minimize reporting bias, participants in the "inclisiran first" implementation group and participants in the usual care group will have an equivalent number of study visits, and an equivalent number of blood draws (including LDL-C tests).

The study will identify approximately 50 sites for participation. Each site will have a principal investigator (PI) who is responsible for study visits, while all aspects of the participants' routine care will remain the responsibility of the participants' own treating physician in both groups. While it is expected that most patients will have a treating physician who is distinct from the PI, a PI who wishes to include his or her own patients in the trial would have to (temporarily) transition routine care to a separate physician. This will reduce the effect that trial participation might have on treatment decisions if the PI and treating physician were the same individual (e.g., more aggressive treatment due to more frequent touchpoints).

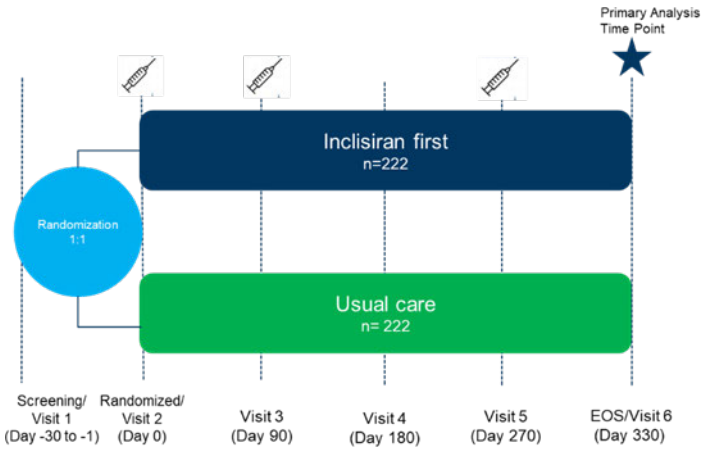
Since inclisiran is commercially available in the US as of late-2021, utilization of it in the usual care group at the sole discretion of the treating physician will not be encouraged, but will also not be prohibited to avoid withholding of appropriate care. If treatment with a PCSK9-inhibiting monoclonal antibody was initiated and a patient would have to be transitioned to inclisiran, the PCSK9-inhibiting monoclonal antibody should be discontinued.

The collection of data from trial sites through eCRFs will be complemented with EHR data and claims data (e.g., lipid measurements and concomitant medications).

Participants randomized to “inclisiran first” implementation strategy group will receive inclisiran at Day 0, Day 90 and Day 270, consistent with the dosing regimen studied in the Phase III trials.

While study visits will be preferentially performed in-person at the study sites, phone or virtual visits are an acceptable alternative if in-person visits are not permitted or impractical 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. Informed consent forms will be available in English and Spanish.

**Figure 1-1 Study Design**




Additional important considerations of the study design include:

**Recruitment:** Potentially eligible participants will be pre-screened using EHR, claims and/or laboratory databases. This will maximize the representativeness of the sample because it will reduce selection bias that occurs when investigators identify all participants by convenience sampling. Moreover, centrally identifying potential study sites and participants using EHR, claims and/or laboratory data will allow us to ensure that the study sites are representative while excluding sites that manage lipids more aggressively than is typical (for example specialized lipid clinics). Eligible participants will need to consent to having health records made available as part of the collection of medical and pharmacy claims. Several tactics will aim to enhance inclusion of minority and medically underserved populations, as these populations are traditionally underrepresented in clinical trials.

**Responsibilities of principal investigator / routine care physician:** Study visits will be done by the PI while routine care is performed by the participant's own treating physician. Communication and coordination between the PI and treating physician is allowed. However, PIs are asked to refrain from influencing treatment decisions that are usually made by the treating physician to maximize external generalizability (i.e., the influence of study participation on routine care should be as limited as possible). The PI and treating physician can be from the same practice.

**Open-label:** The study will be performed as an open-label study to mimic routine care decision-making, 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 (a total of three inclisiran doses). 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) assessment of variables that likely require longer-term treatment to observe meaningful treatment differences, such as patient reported outcomes.

**Choice of non-inferiority margin for discontinuation of statin therapy:** The sample size of the trial is partially based on the co-primary efficacy variable of discontinuation of statin therapy. The non-inferiority margin of 0.15 in the proportion of participants who discontinue statin therapy by Day 330 was chosen to reflect a clinically meaningful difference in statin discontinuation rates between the groups, while considering statin discontinuation rates described in other studies (Khunti et al 2018).

## 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 an "inclisiran-first" implementation strategy compared to usual care at Day 330 in participants with ASCVD and an LDL-C ≥70 mg/dL despite maximally tolerated statin therapy | • Percent change from baseline in LDL-C |
| • To assess the non-inferiority of an "inclisiran first" implementation strategy compared to usual care on discontinuation of background statin therapy at Day 330 | • Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no) |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To assess the absolute change in LDL-C of an "inclisiran first" implementation strategy compared to usual care at Day 330, as well as average of percent and absolute changes in LDL-C levels to each post-baseline visit | • Absolute change from baseline in LDL-C<br>• Average percent change from baseline in LDL-C levels to each post-baseline visit<br>• Average absolute change from baseline in LDL-C to each post-baseline visit |
| • To assess the proportion of participants reaching pre-specified LDL-C targets among those receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 | • Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)<br>• Achieving LDL-C < 100 mg/dL (among the subset of participants with LDL-C ≥100 mg/dL at baseline) (yes, no)<br>• Achieving LDL-C < 70 mg/dL (yes, no)<br>• Achieving LDL-C < 55 mg/dL (yes, no) |
| • To assess plasma lipids, lipoproteins and triglycerides in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 | • Percent change and absolute change from baseline in apoB<br>• Percent change and absolute change from baseline in non-HDL-C<br>• Percent change and absolute change from baseline in VLDL-C<br>• Percent change and absolute change from baseline in total cholesterol<br>• Percent change and absolute change from baseline in Lp(a)<br>• Percent change and absolute change from baseline in HDL-C<br>• Percent change and absolute change from baseline in triglycerides |

| Objective(s) | Endpoint(s) |
|---|---|
| • To assess changes in and adherence to background lipid-lowering therapy in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 | • Intensity of lipid lowering therapy (decrease in dose, no change in dose, increase in dose)<br>• Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days) |
| • To assess visit-to-visit LDL-C variability from Day 90 until Day 330 | • LDL-C measures of variability (standard deviation, coefficient of variation) |
| • To assess overall safety and tolerability of inclisiran | • Adverse events |

[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 is:

What is the effectiveness of an "inclisiran first" implementation strategy compared to usual care in patients who have not reached their LDL-target despite treatment with a maximally tolerated statin? Inclisiran will be added to maximally tolerated statin therapy and will be compared to usual care. Eligible participants will have established ASCVD and elevated LDL-C despite being treated with maximally tolerated statin therapy and should not be on ezetimibe or PCSK9 inhibiting monoclonal antibodies. Although at baseline there should be no plans to modify background lipid-lowering therapy, the participants' treating physicians are recommended to treat patients in accordance with the 2018 ACC/AHA cholesterol guideline (Grundy et al 2019).

The justification for the primary estimands is that these will capture both the effects of the inclisiran and the effect of changes in, adherence to, and discontinuation of additional medications, mirroring the conditions in clinical practice.

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 first" implementation strategy 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 (in inclisiran participants). This intercurrent event will be ignored in the analysis.
- Summary measure: Least-squares mean difference between "inclisiran first" implementation strategy and usual care

Primary estimand 2: The primary analysis of primary efficacy variable 2 (discontinuation of statin therapy) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population and if a participant did not have a medical history of statin intolerance
- Variable: Discontinuation of statin therapy (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: "Inclisiran first" implementation strategy 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 (in inclisiran participants). This intercurrent event will be ignored in the analysis.
- Summary measure: Treatment difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy

### 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 data for all participants are available.

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.

**Lipid Parameters Units**

All tabular summaries, listings, and figures of lipid parameters will be provided in traditional units). All other laboratory parameters will be analyzed in SI units. Both traditional and SI units will be included in SDTM and ADaM datasets. The lipid parameters include the following:

1. LDL Cholesterol (mg/dL)
2. Total Cholesterol (mg/dL)
3. HDL Cholesterol (mg/dL)
4. Non-HDL Cholesterol (mg/dL)
5. VLDL Cholesterol (mg/dL)

6. Triglycerides (mg/dL)
7. Apolipoprotein B (mg/dL)
8. Lipoprotein(a) (mg/dL)

[redacted]

### 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 First
- 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 group. If a participant, who is randomized to the Inclisiran First 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 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 group. If a participant, who is randomized to the Inclisiran First 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.

**Planned and actual treatment definitions**

**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 First | Received at least one dose of inclisiran | Inclisiran First | Inclisiran First |
| Inclisiran First | Never received inclisiran | Inclisiran First | Usual Care |
| Usual Care | Received at least one dose of inclisiran | Usual Care | Inclisiran First |
| 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 treatment start date is study Day -1 (i.e., no study Day 0).

**Baseline and post-baseline definitions**

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 planned 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 Visit for Each Scheduled Visit**

| Analysis Visit | Target Study Day* | Analysis Window | |
|---|---|---|---|
| | | From | To |
| Baseline | 1 | | Before randomization/First Study Treatment |
| Day 90 | 91 | 1 | 135 |
| Day 180 | 181 | 136 | 225 |
| Day 270 | 271 | 226 | 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 180, 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 180, 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, and 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 first" implementation strategy group (i.e., excludes patients in the "inclisiran first" implementation strategy group who missed one or more doses) and all participants in the usual care group.

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; do not use this subgroup for the co-primary efficacy endpoint discontinuation of statin therapy)
- Baseline statin intensity: High, Moderate or Low, None
- Age: <65 years, >= 65 years
- Baseline LDL-C: <=100 and > 100 mg/dL; median; and then by quartiles
- Most recent ASCVD event: <1 year, >= 1 year (from targeted medical history CRF page, see below for more details)
- Diabetes at baseline: Yes, No (from targeted medical history CRF page)
- Renal impairment by eGFR categories at baseline: <15, ≥15 to <30, ≥30 to <60, ≥60 to <90, or ≥90 mL/min/1.73m$^2$
- Sex: Male, Female
- Race: White, Non-White/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)
- [redacted]
- Coronary heart disease (CHD): Yes, No (from targeted medical history CRF page)
- Peripheral artery disease (PAD): Yes, No (from targeted medical history CRF page)
- Cerebrovascular disease (CVD): Yes, No (from targeted medical history CRF page)
- Polyvascular disease (>1 of CHD, PAD, or CVD): Yes, No (from targeted medical history CRF page)
- [redacted]

Most recent ASCVD event (<1 year, >= 1 year) is derived from data recorded on the "Medical History Targeted" form. The derivation is based on the timing of the most recent percutaneous coronary intervention, myocardial infarction, cardiovascular arterial bypass graft, or ischemic stroke. If a participant has multiple events with different timings, the earlier (<1 year) timing will be utilized. Participants without events are excluded from the subgroup.

## 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 along with reasons for exclusion from each analysis population will be summarized by treatment group for all randomized participants.
- The number of participants who completed the study or who discontinued 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.

A summary of failed inclusion/exclusion criteria will be provided for all screened participants and by treatment group for the FAS.

A summary of the number of participants by visit will be provided by treatment group 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 insurance type, income level, highest completed education, smoking

status by substance, body height, weight, [redacted] will be summarized by treatment for the FAS.

Medical history (targeted 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.

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

### 2.4.1 Study treatment / compliance

Study drug administration will be summarized overall for the Safety Set.

### 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. See list of lipid-lowering therapies below. Medications will be coded using the World Health Organization (WHO) drug dictionary (WHODDG March 2021, B3 format) initially, and will be coded/re-coded with up-version during the course of study.

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.

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 post baseline, 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 (study Day 1) to Day 330/End of Study (EOS) will also be provided. The statin intensity of the last statin taken on or prior to Day 330 (EOS) will be used for the post-baseline statin intensity.

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.

| **Medication** | **Medications included** |
|---|---|
| Lipid Lowering Therapy | ATCCODE2=C10 |
| Statin | ATCCODE2=C10 and CMDECOD contains ‘statin’ |

| | |
|---|---|
| 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 an "inclisiran-first" implementation strategy compared to usual care at Day 330 in participants with ASCVD and an LDL-C ≥70 mg/dL despite maximally tolerated statin therapy and to assess the non-inferiority of an "inclisiran first" implementation strategy compared to usual care on discontinuation of background statin therapy 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. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)

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

The following provides additional details on the derivation of primary efficacy variable 2.

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’).

### 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 first" implementation strategy and usual care groups are equal. The alternative hypothesis is that the mean percent change from baseline in LDL-C at Day 330 for "inclisiran first" implementation strategy group is not equal to that of the usual care group.

Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit (Day 90, Day 180, Day 270, Day 330), baseline, [redacted], 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 effect at Day 330 is $< 0.025$ and the corresponding least squares mean treatment difference ("inclisiran first" implementation strategy – usual care) is less than 0, statistical significance in favor of "inclisiran first" implementation strategy 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").

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

The null hypothesis is that the difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy at Day 330 is at least 0.15 (non-inferiority margin). The alternative hypothesis is that the difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy at Day 330 is less than 0.15.

For primary efficacy variable 2, a one-sided 98.75% confidence interval for treatment difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinued statin therapy at Day 330 will be computed using the normal approximation to the binomial distribution. Non-inferiority of the "inclisiran first" implementation strategy to usual care will be declared if the upper limit of the confidence interval does not exceed the non-inferiority margin of 0.15. The difference in proportions and associated two-sided 97.5% confidence interval will also be provided.

The primary analysis of primary efficacy variable 2 will be based on the FAS excluding participants who had medical history of statin intolerance. The primary analysis of this variable will be repeated for the Per-Protocol Set and Restricted Set 2.

### 2.5.3 Handling of intercurrent events

The remaining intercurrent events 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 participants). 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 for whom it cannot be ascertained that they are on statin therapy at the end of study will be assumed to have discontinued statin therapy (discontinued statin = 'yes').

### 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 first" implementation strategy 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 (in inclisiran participants). This intercurrent event will be ignored in the analysis.
- Summary measure: Probability of observing the same or a more favorable response with "inclisiran first" implementation strategy relative to usual care

For the above estimand, primary efficacy variable 1 will be analyzed at each time point for the Full Analysis Set using the van Elteren test, adjusting for [redacted] (Stokes et al 2012).

The probability of observing the same or a more favorable response ($\theta_0$) with "inclisiran first" implementation strategy relative to usual care will be estimated using nonparametric methods, and the associated 97.5% confidence interval will also be reported (Chen and Kianifard 2000).

For both primary efficacy variable 1 and primary efficacy variable 2, an additional sensitivity analysis will be performed where participants for whom [redacted] entered at

randomization (via Interactive Response Technology (IRT)) did not match [redacted] entered at baseline (via CRF) were excluded from the analysis.

### 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 first" implementation strategy or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. 2. Discontinuation of study treatment (in inclisiran participants). Data after the occurrence of either one of the above two intercurrent events will be excluded from the analysis (using MMRM).
- Summary measure: Least-squares mean difference between "inclisiran first" implementation strategy and usual care

## 2.6 Analysis supporting secondary objectives

The secondary objectives include the following:

- To assess the absolute change in LDL-C of an "inclisiran first" implementation strategy compared to usual care at Day 330, as well as average of percent and absolute changes in LDL-C levels to each post-baseline visit
- To assess the proportion of participants reaching pre-specified LDL-C targets among those receiving an "inclisiran first" implementation strategy compared to usual care at Day 330
- To assess plasma lipids, lipoproteins and triglycerides in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330
- To assess changes in and adherence to background lipid-lowering therapy in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330
- To assess visit-to-visit LDL-C variability from Day 90 until Day 330
- To assess overall safety and tolerability of inclisiran

### 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 ≥ 50% reduction from baseline in LDL-C (yes, no)
5. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)
6. Achieving LDL-C < 70 mg/dL (yes, no)
7. Achieving LDL-C < 55 mg/dL (yes, no)
8. Percent change from baseline in apoB
9. Absolute change from baseline in apoB
10. Percent change from baseline in non-HDL-C
11. Absolute change from baseline in non-HDL-C
12. Percent change from baseline in VLDL-C
13. Absolute change from baseline in VLDL-C
14. Percent change from baseline in total cholesterol
15. Absolute change from baseline in total cholesterol
16. Percent change from baseline in Lp(a)
17. Absolute change from baseline in Lp(a)
18. Percent change from baseline in HDL-C
19. Absolute change from baseline in HDL-C
20. Percent change from baseline in triglycerides
21. Absolute change from baseline in triglycerides
22. 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 |

23. Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies prescribed taken during the study divided by total number of study days)

    If a participant did not take any of the four 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).

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

Analyses of secondary efficacy variables 1 and 8 - 21 will be similar to the primary analysis of primary efficacy variable 1 (using MMRM, but with a two-sided 95% confidence interval for all applicable estimates).

Secondary efficacy variable 2, 3, and 23 will be analyzed using a linear model with treatment, baseline LDL-C, and [redacted] as explanatory variables. 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. 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 180, Day 270, and Day 330. The outcome value for variable 23 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 - 7 will be analyzed at each applicable post-baseline visit using a logistic regression model with treatment, baseline LDL-C, and [redacted] as explanatory variables (Stokes et al 2012). The odds ratio, 95% confidence intervals for the odds ratio, and p-value based on the fitted model will be reported. Missing data will be imputed using "non-responder" (i.e., "negative" outcome) imputation.

Secondary efficacy variable 22 will be analyzed at each post-baseline visit using a proportional odds model with treatment, baseline LDL-C, and [redacted] 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. Missing data will not be imputed.

Visit-to-visit LDL-C variability from Day 90 until Day 330 will be reported, using various measures of variability (standard deviation and coefficient of variation) (Bangalore et al 2015).

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 8-21, the MMRM implicitly imputes missing data under a missing at random assumption.

For the analysis of secondary efficacy variables 4 – 7, participants with missing data will be imputed using "non-responder" (i.e., "negative" outcome) imputation.

For the analysis of secondary efficacy variables 2, 3, 22 and 23, 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.

## 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 study. The final MedDRA version used in this study was v26.1. 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.

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 TEAEs (≥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')

### 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). 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.

A shift analysis using the normal range (except for eGFR [redacted]) 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 estimated Glomerular Filtration Rate (eGFR) [redacted]

- 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$^2$.
- [redacted]

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.

New onset of diabetes during the study will be identified by evaluating different components: 1) adverse events, [redacted] 3) initiation of antidiabetic medication. This analysis will only be conducted in participants who do not have diabetes at baseline (determined by either targeted medical history, prior concomitant therapies, [redacted] and fasting plasma glucose). Additionally, new onset or worsening of diabetes will be identified using SMQ and AE terms for diabetic treatment emergent adverse events (TEAEs). 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 ANY of the following conditions are met:

- Targeted medical history of diabetes (using targeted medical history CRF).
- Anti-diabetic medication (ATC level 2 code: A10) at baseline.
- [redacted] AND fasting glucose ≥126 mg/dL at baseline.

For this analysis, 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.

New onset or worsening of diabetes is defined if ANY of the following conditions [redacted]

- Laboratory results indicating diabetes, which can be any of the following:
  - The participant has [redacted] on two consecutive tests.
  - The participant has fasting glucose ≥126 mg/dL on two consecutive fasted tests.
  - The participant has [redacted] and fasting glucose ≥126 mg/dL on the same occasion.
  - The participant has [redacted] 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 [redacted] 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 subjects with potentially clinically significant (PCS) laboratory values or clinically significant (CS) laboratory values (refer to Appendix 5.2.2 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 following two categories will also be presented in addition to the CS criterion:

1) Subjects with the baseline value ≤ 2 mg/dL and any post-baseline value > 2 mg/dL.
2) Subjects who are not in the first category but has ≥ 50% increase 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, blood pressure, weight, [redacted] will be summarized descriptively at each analysis visit (including Day 330/Last Visit) by treatment group.

Blood pressure categories will be summarized at each analysis visit (including Day 330/Last Visit) by treatment group. The categories are summarized below. The worst category at an analysis visit will be used in the analysis. A shift table from baseline to each visit will also be created.

| Blood Pressure Category | Systolic Blood Pressure (mmHg) | | Diastolic Blood Pressure (mmHg) |
|---|---|---|---|
| Normal | <120 | and | <80 |
| Elevated | 120-129 | and | <80 |
| High Blood Pressure Stage 1 | 130-139 | or | 80-89 |
| High Blood Pressure Stage 2 | 140-180 | or | 90-120 |
| Hypertensive Crisis | >180 | or | >120 |

Reference: Whelton et al 2017.

## 2.8 Pharmacokinetic endpoints

Not applicable.

## 2.9 PD and PK/PD analyses

Not applicable.

[redacted]

## 2.11 Biomarkers

See Section 2.6.

[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 first" implementation group compared to the usual care group, and 2) the ability to add non-statin lipid lowering therapy in the usual care group. [redacted]

Table 3-1 considers total sample sizes for expected mean treatment differences of 15, 20, and 25 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 at Day 330 and a power of 0.90 were chosen to provide a total sample size of 354 participants.

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

| Mean treatment difference | Power = 0.85 | Power = 0.90 |
|---|---|---|
| **15** | **306** | **354** |
| 20 | 172 | 200 |
| 25 | 112 | 128 |

For primary efficacy variable 2, i.e., discontinuation of statin therapy (yes, no), a z-test for a non-inferiority test of two proportions, an allocation ratio of 1:1, and a one-sided significance level of 0.0125 were used in the calculation of sample size. Table 3-2 considers total sample sizes for 0.20 and 0.25 as the true proportions of participants who discontinue statin therapy in each treatment group, and non-inferiority margins of 0.10 and 0.15 for the "inclisiran first" implementation group to be no worse than the usual care group (nQuery Version 8.4.1.0). From Table 3-2, a true proportion of 0.20 for participants who discontinue statin therapy in each treatment group by Day 330, a non-inferiority margin of 0.15, and a power of 0.90 were chosen to provide a total sample size of 354 participants.

**Table 3-2 Sample Size Calculations for Statin Statin Therapy Discontinuation**

| Proportion in usual care group | Non-inferiority margin | Power = 0.85 | Power = 0.90 |
|---|---|---|---|
| 0.20 | 0.10 | 688 | 796 |
| **0.20** | **0.15** | **306** | **354** |
| 0.25 | 0.10 | 806 | 932 |
| 0.25 | 0.15 | 360 | 414 |

Based on the sample size calculations in Table 3-1 and Table 3-2, a total sample size of 354 together with a loss to follow-up rate of 10% at Day 330 and a statin intolerance rate at baseline of 10% (i.e., a total of 20% due to loss to follow-up and statin intolerance at baseline) require

approximately 444 participants (222 participants per treatment group) to be randomized. This will also allow examination of subgroups with reasonable sample sizes.

# 4 Change to protocol specified analyses

Changes from Protocol version 01 (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.
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.

Changes from Protocol version 02 (amended protocol) include the following:

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 #22 (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.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Not applicable.

### 5.1.2 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 (TRTSTD)** | Not used | TRTM | TRTY |

[redacted].

[redacted]

[redacted]

- [redacted]
- [redacted]

### Adverse Event End Date Imputation

- Imputed date = date part of original date, if complete date
- Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing
- Imputed date = min (completion/discontinuation visit 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

### 5.1.3 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication. 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 CM Start Date** | Not used | MON | YYYY |
| **Treatment Start Date (TRTSDT)** | Not used | TRTM | TRTY |

[redacted].

[redacted]

[redacted]

### Concomitant Medication End Date Imputation

If not ongoing then -

- Imputed date = date part of CMENDTC, if complete date
- Imputed date = min(completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)
- Imputed date = min(completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

### Concomitant Medication Date Flag

If not a complete date then

- Y - If year of the imputed date is not equal to YYYY
- Else M – If month of the imputed date is not equal to MON
- Else D.

#### 5.1.3.1 Prior therapies date imputation

Same as above.

#### 5.1.3.2 Post therapies date imputation

Same as above.

#### 5.1.3.3 Other imputations

Same as above.

## 5.2 Laboratory parameters derivations

### 5.2.1 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).

### 5.2.2 Criteria for Potentially Clinically Significant and Clinically Significant abnormal laboratory tests

[redacted] 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.

| Variable | Unit | Lower Boundary | Upper Boundary |
|---|---|---|---|
| **Hematology** | | | |
| Hematocrit | % | ≤0.8 × LLN | N/A |

| Variable | Unit | Lower Boundary | Upper Boundary |
|---|---|---|---|
| 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 |
| **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* |
| [redacted] | | | |
| 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.

## 5.3 AEs coding/grading

Not applicable.

## 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 5-1 Criteria Leading to Exclusion**

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

# 6 References

[redacted]

Bangalore S, Breazna A, DeMicco DA, et al (2015) Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. J Am Coll Cardiol 65(15):1539-48.

[redacted]

Chen M, Kianifard F (2000) A nonparametric procedure associated with a clinically meaningful efficacy measure. Biostatistics 1(3):293-8.

Grundy SM, Stone NJ, Bailey AL, et al (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139(25):e1082-e1143.

Khunti K, Danese MD, Kutikova L, et al (2018) Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe. JAMA Netw Open 1(8):e185554.

Stokes ME, Davis CS, Koch GG (2012) Categorical data analysis using the SAS system. 3rd ed; Cary, NC: SAS Institute, Inc.

Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al (2017) ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 71(6):e13-e115.