Protocol No.: MDCO-PCS-17-08 (ORION-11)

A Placebo-Controlled, Double-Blind, Randomized Trial to Evaluate the Effect of 300 mg of Inclisiran Sodium Given as Subcutaneous Injections in Subjects with Atherosclerotic Cardiovascular Disease (ASCVD) or ASCVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol (LDL-C)

STATISTICAL ANALYSIS PLAN

12 August 2019

NCT03400800

Protocol No.: MDCO-PCS-17-08
(ORION-11)

A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO EVALUATE THE EFFECT OF 300 MG OF INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR ASCVD-RISK EQUIVALENTS AND ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL (LDL-C)

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1. INTRODUCTION

The Medicines Company is developing a novel synthetic ribonucleic acid (RNA) interference (RNAi) therapeutic, Inclisiran for Injection (subcutaneous [SC] use), formerly referred to as ALN-PCSSC, for the treatment of hypercholesterolemia. This document presents a statistical analysis plan (SAP) for The Medicines Company. Protocol MDCO-PCS-17-08, EudraCT No.:2017-001846-90, Global Amendment 2 (31 Jan 2019), A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C).

2. TRIAL DESIGN

2.1. Type/Design of Trial

This study is a Phase III, placebo-controlled, double-blind, randomized study in 1500 subjects with ASCVD (coronary heart disease [CHD], cerebrovascular disease [CVD] or peripheral arterial disease [PAD]) or ASCVD-risk equivalents (e.g., type 2 diabetes and familial hypercholesterolemia, 20% or greater risk of a cardiovascular (CV) event as assessed by Framingham risk score or equivalent) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of subcutaneous inclisiran injection(s).

Subjects will be screened and approximately 1500 eligible subjects will be randomized: 750 subjects will be randomized to inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) and 750 subjects to placebo. Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will receive four subcutaneous injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450.

On Day 1, all eligible subjects will be randomized and will receive the first SC injection of investigational product (inclisiran or placebo). After the first SC injection, the subject will be observed in the clinic for at least 4 hours post injection in order to have additional laboratory assessments and vital signs completed before being discharged. Subjects will return on Day 90, Day 270, and Day 450 to receive additional investigational product. During these subsequent dosing visits, subjects will be observed in the clinic for at least 30 minutes after administration of each injection and have additional laboratory assessments completed if needed. Subjects will also have in clinic visits on Day 30, Day 150, Day 330, and Day 510 for follow-up and limited laboratory assessments. The end of study (EOS) visit will be conducted on Day 540.

Samples for pharmacodynamic assessments will be collected at the time points in the Schedule of Assessments (Table 1) and include LDL-C levels as well as other lipids and lipoproteins (eg, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), non HDL-C, very low-density lipoprotein cholesterol [VLDL-C], apolipoprotein A1 [Apo-A1], apolipoprotein B [ApoB], lipoprotein(a) [Lp(a)], high sensitivity C-reactive protein [hsCRP], and proprotein convertase subtilisin/kexin type 9 [PCSK9]).

Safety assessments including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and safety laboratory parameters will also be collected during the study. In addition, formation of anti-drug antibodies (ADA) and further characterization of ADA will be evaluated.

End of study evaluations will be conducted at the Day 540 visit.

Subjects who have completed the study to Day 540 will be given the opportunity to enroll in a separate open-label long-term extension study to collect long-term safety and efficacy data for inclisiran.

The Independent Data Monitoring Committee (IDMC) will review safety data after the first 40 subjects receive the first SC injection of inclisiran or placebo and have completed 1 month follow-up. Thereafter the IDMC will review safety data every 3 months until the EOS unless requested otherwise by the IDMC. A recommendation may be taken to stop or amend the study at any of these reviews.

2.2. Objectives of Trial

Primary Objectives:

The primary objectives of this study are to evaluate the effect of inclisiran treatment on:

- LDL-C levels at Day 510
- Time adjusted percent change in LDL-C levels from baseline after Day 90 and up to Day 540 levels

Secondary Objectives:

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

- PCSK9, total cholesterol, ApoB and non-HDL-C at Day 510
- LDL-C and PCSK9 levels over time to Day 540
- Mean maximum reduction in LDL-C levels
- LDL-C and PCSK9 levels over time in individual subjects
- Other lipids, lipoproteins, apolipoproteins
- Proportion of subjects achieving prespecified LDL-C targets
- Safety and tolerability profile of inclisiran

Exploratory Objectives:

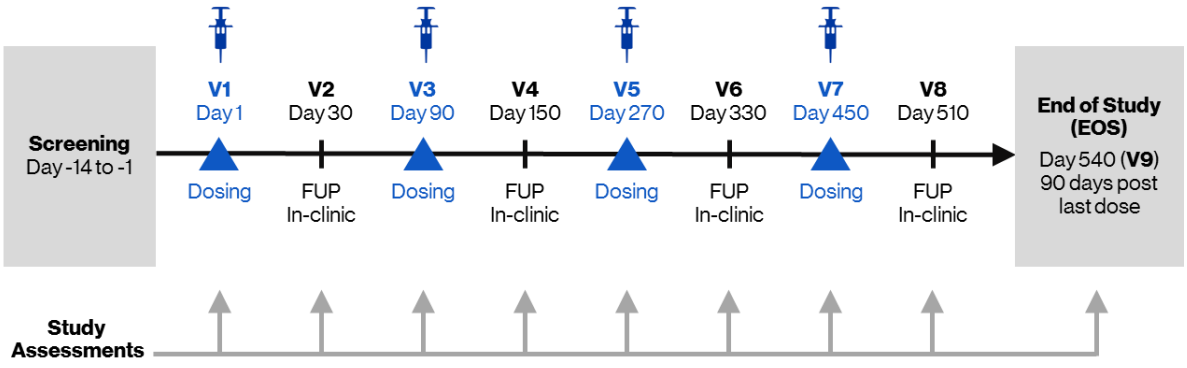
The exploratory objectives of this study are to collect/evaluate the effect of inclisiran on the following:

- Cardiovascular (CV) events such as CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), and non-fatal stroke (ischemic and hemorrhagic)

2.3. Schematic Diagram of Trial Design

The study design is presented in Figure 1:

Figure 1: Study Design



FUP=follow-up; V=visit

2.4. Schedule and Sequence of Procedures

The Schedule of Assessments (Table 1) summarizes the study assessments by time point.

This study consists of four periods: Screening, Randomization, Treatment, and End of Study.

- **Screening period (Days -14 to -1)**: occurs prior to randomization and consists of confirming eligibility and collecting baseline assessments.
- **Randomization (Day 1)**: occurs on the day of initial administration of investigational product.
- **Treatment period (Day 1 through Day 510)**: occurs from the start of investigational product administration through the final clinic visit.
  - Dosing: Day 1, Day 90, Day 270, and Day 450 (final dose)
  - Additional clinic visits: Day 30, Day 150, Day 330, and Day 510
- **End of study (EOS) visit:** Day 540 (90 days past last dose)

  For subjects who decided to prematurely and permanently discontinue from study treatment and who decline further follow-up visits, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

The expected duration of the subjects' involvement in the study will be approximately 554 days which includes screening, investigational product administration, and the EOS period to Day 540.

Schedule of Assessments

Table 1: Study Design and Schedule of Assessments

	Screen-ing	Random-ization	Treatment							EOS[1]
Visits		**V1 (baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 (90 days post last dose)**
Timelines	Day -14 to -1	Day 1	Day 30	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540
Visit windows (± days)			±2	±30	±30	±30	±30	±30	±14	±14
Informed consent	X									
Assessment of eligibility	X	X[2]								
Demographics and medical history	X									
Pregnancy test	X[3]	X[3]		X[3]		X[3]		X[3]	X[3]	X[3]
Randomization		X								
Investigational product administration		X[4,5]		X[4,5]		X[4,5]		X[4,5]		
Physical examination	X									X
Neurological examination		X								X
Weight/height/waist circumference	X[6]									X
Vital signs[7]	X	X		X		X		X		X
12-lead ECG	X	X								X
Fasted lipid profile/biomarkers[8]	X	X		X	X	X	X	X	X	X
ADA		X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Full Serum chemistry[10]		X								X
Limited serum chemistry[10]	X			X	X	X	X	X	X	
Urinalysis (local)[11]	X	X								X
Hematology and coagulation[12]	X	X			X					X
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X
AEs/SAE reporting	X	X	X	X	X	X	X	X	X	X

ADA=anti-drug antibodies; AE=adverse event; ECG=electrocardiogram; EOS=end of study; SAE=serious adverse event; V=visit

1. For subjects who decided to prematurely and permanently discontinue from study treatment and who decline further follow-up visits, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.
2. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
3. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test)
4. Subjects will be observed in the clinic for at least 4 hours following the first injection only (Randomization visit) and 30 minutes for each subsequent visit in order to have additional vital and/or laboratory assessments completed if needed.
5. For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as logically possible).
6. Height will be measured at baseline only and used to calculate body mass index.
7. On Day 1 vital signs will be measured prior to injection and 4 hours post injection; all other visits, vital signs are measured only prior to injection. When available, an automated BP device is recommended for collection of blood pressure (BP) and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (heart rate (HR), BP) is required per applicable visit.
8. See Section 3.9 for details of specific tests to be analyzed.
9. ADA serum samples will be collected on Day 1 prior to injection and 4 hours after injection. At all other visits, ADA serum samples will be collected prior to injection only if an injection is scheduled for that visit. As presented in Section 6, serum samples for analysis are collected at every visit but assessment of ADA will only occur for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. Samples will be stored for assessment (if needed) for samples collected at the following visits: Randomization (after injection), Day 90, Day 270, Day 450, End of Study Visit.
10. See Section 3.8.8.3 for details of specific tests to be analyzed.
11. See Section 3.8.8.5 for details of specific tests to be analyzed.
12. See Section 3.8.8.1 and Section 3.8.8.2 for details of specific tests to be analyzed.

3. GENERAL CONDUCT OF TRIAL

Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all subjects before the performance of any protocol-specific procedure.

Please see the Schedule of Assessments (Table 1) for a detailed schedule.

3.1. Screening Period (Days –14 to –1)

All screening laboratory tests will be collected and shipped to the Central Laboratory, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using the testing materials provided by the Central Laboratory. The results of all screening laboratory tests should be reviewed prior to enrollment. If results do not confirm subject eligibility or suggest any contraindication to treatment with inclisiran, and/or other required ancillary medication(s), the subject must not be enrolled.

The following procedures will be performed within 14 days prior to randomization:

- Informed consent
- Assessment of inclusion and exclusion criteria
- Demographics and medical history
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only)
- Physical examination (including height, weight, and waist circumference)
- Vital signs (blood pressure and heart rate) (Section 3.8.3)
- 12-lead ECG
- Fasting lipid profile/biomarkers (Section 3.9)
- Central clinical laboratory (limited serum chemistry, hematology and coagulation) (Section 3.8.8)
- Urinalysis (performed locally, using central laboratory supplies)
- Previous and concomitant medications
- AE/SAE reporting (beginning from time of consent)

Central laboratory blood draws should be performed after all other screening tests have been confirmed. Results must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria (Protocol Section 4.2 and 4.3). Please refer to Section 3.8.8 and Section 3.9 for details of laboratory tests performed during the screening period.

3.2. Randomization

Randomization should only occur once subject eligibility is confirmed and will be conducted via an automated interactive response technology (IRT) to assign subjects to investigational product.

All treatment groups will be studied concurrently. A total of 1500 randomized subjects are planned for inclusion in the study: 750 subjects per group.

The following procedures will be performed prior to the injection:

- Assessment of inclusion and exclusion criteria
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only)
- Randomization
- Neurological examination (Protocol Appendix C)
- Vital signs: blood pressure and heart rate (Section 3.8.3)
- 12-lead ECG
- Fasting lipid profile/biomarkers (Section 3.9)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 3.8.8)
- Urinalysis (performed locally, using central laboratory supplies)
- Assessment of ADA (Section 3.8.8.7)

The following procedures will be performed after the injection:

- Vital signs: blood pressure and heart rate (4 hours after injection) (Section 3.8.3)
- Collection and storage of serum samples for possible future use to detect the formation of ADA (4 hours after injection)
- Concomitant medications
- AE/SAE reporting

Investigational product administration will occur at this visit for all subjects as per Protocol Section 5.1.1 and the Pharmacy Manual.

Subjects must be observed in the clinic for at least 4 hours after injection.

Should a subject develop signs or symptoms of anaphylaxis when investigational product is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logically possible).

If a local reaction around the injection site occurs that requires the patient be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site should be obtained at first presentation and at each of the follow-up visits until the injection site reaction resolves, if possible. Photographs should be submitted to the study inbox of global safety office at The Medicines Company.

Detailed instructions for investigational product administration are found in the Pharmacy Manual.

3.3. Day 30 Visit

Subjects will return to the clinic for a follow-up visit 30 days following the first dose of investigational product. The following assessment will be completed during this visit:

- Assessment of ADA (Section 3.8.8.7)
- Concomitant medications
- AE/SAE reporting

3.4. Additional Dosing Visits (Days 90, 270, and 450)

Subjects will return on Day 90 for a second investigational product injection. Subsequent investigational product injections will be administered on Day 270 and Day 450.

The following assessments will be completed during these visits prior to investigational product administration:

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Vital signs: blood pressure and heart rate (Section 3.8.3)
- Fasting lipid profile/biomarkers (Section 3.9)
- Collection and storage of serum samples for possible future use to detect the formation of ADA (Section 3.8.8.7)
- Central clinical laboratory (limited serum chemistry) (Section 3.8.8)
- Concomitant medication
- AE/SAE reporting

Administration of the investigational product is identical to Day 1 and is per Section 5.1.1 of the protocol and the Pharmacy Manual.

Subjects must be observed in the clinic for at least 30 minutes after injection.

Should a subject develop signs or symptoms of anaphylaxis on days when investigational product is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logically possible).

3.5. Additional NON DOSING Clinic Visits (Days 150, 330, and 510)

Subjects will return to the clinic for dosing follow-up visits 60 days following each dose of investigational product. The following assessments will be completed during these visits:

3.5.1. Day 150

- Fasting lipid profile/biomarkers (Section 3.9)
- Assessment of ADA (Section 3.8.8.7)
- Central clinical laboratory (limited serum chemistry and hematology and coagulation) (Section 3.8.8)

- Concomitant medications
- AE/SAE reporting

3.5.2. Day 330

- Fasting lipid profile/biomarkers (Section 3.9)
- Assessment of ADA (Section 3.8.8.7)
- Central clinical laboratory (limited serum chemistry) (Section 3.8.8)
- Concomitant medications
- AE/SAE reporting

3.5.3. Day 510

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Fasting lipid profile/biomarkers (Section 3.9)
- Assessment of ADA (Section 3.8.8.7)
- Central clinical laboratory (limited serum chemistry) (Section 3.8.8)
- Concomitant medications
- AE/SAE reporting

3.6. End of Study (EOS) Visit (Day 540 – 90 days post last dose)

A subject's participation in the study is complete when the final visit, 90 days after the last dose of investigational product, has occurred. The following assessments will be completed during this visit:

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Physical examination (including weight and waist circumference)
- Neurological examination (Protocol Appendix C)
- Vital signs: blood pressure and heart rate (Section 3.8.3)
- 12-lead ECG
- Fasting lipid profile/biomarkers (Section 3.9)
- Collection and storage of serum samples for possible future use to detect the formation of ADA (Section 3.8.8.7)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 3.8.8)
- Urinalysis (performed locally, using central laboratory supplies)

- Concomitant medication
- AE/SAE reporting
- All ongoing SAEs have been followed to resolution

3.7. Interim Analysis

No interim analysis will be performed in this study.

3.7.1. Interim Safety Reviews

The IDMC will review safety data after the first 40 subjects receive the first SC injection of inclisiran or placebo and have completed one month follow-up. Thereafter the IDMC will review safety data every 3 months until the EOS unless requested otherwise by the IDMC. A recommendation may be taken to stop or amend the study at any of these reviews.

3.8. Assessment of Safety

3.8.1. Adverse Events

Subjects will be carefully monitored for AEs by the investigator during the designated study period (see Section 4).

3.8.2. Demographics and Medical History

Baseline demographic information will be collected during screening, and will include age, sex and race/ethnicity.

Relevant medical history includes all ongoing medical or surgical issues and any statin intolerance documentation. Remote medical and surgical history >5 years from the time of screening should only be included if considered relevant to the study.

3.8.3. Vital Signs

Vital signs include heart rate and blood pressure. When available, an automated blood pressure device is recommended for collection of blood pressure and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (heart rate and blood pressure) is required per applicable visit.

3.8.4. Physical Examination

The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, abdominal, and extremities evaluations, and recording of weight, waist circumference, and height (baseline and EOS visit only). Significant changes from baseline will be collected as AE data.

3.8.5. Neurological Evaluation

A full neurological examination will be performed as per the Schedule of Assessment (Protocol Appendix C).

3.8.6. Electrocardiograms

Twelve lead ECGs will be collected at the time points in the Schedule of Assessments (Table 1) only, unless clinically indicated. Significant changes from baseline will be collected as AE data.

3.8.7. Cardiovascular Events

Information on CV events such as CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic) will be collected as AE data.

3.8.8. Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 1).

Subjects will be in a fasted state for all clinical laboratory assessments. Screening laboratory tests will be performed by the Central Laboratory, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using testing materials supplied by the Central Laboratory. Results from these screening tests related to eligibility must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual. Note: Efficacy laboratory assessments (e.g., LDL-C and PCSK9) are described in Section 3.9.

3.8.8.1. Hematology

Blood draws for hematology will include:

- Hemoglobin, hematocrit, erythrocytes, reticulocytes, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count with differential.

3.8.8.2. Coagulation

Blood draws for coagulation will include:

- Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT).

3.8.8.3. Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments (Table 1). Analysis will vary based on visit day as follows:

- **Full serum chemistry - Baseline (Day 1) and EOS (Day 540)**
  Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), glycated hemoglobin A1C (HbA1c), and tryptase (as required).

- **Limited serum chemistry - Screening, Days 90, 150, 270, 330, 450 and 510 ONLY**: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, fasting glucose, HbA1c (not at Day 150, 330, and 510) and tryptase (as required).

3.8.8.4. Inflammatory markers (IL6, IFN-γ, and TNF-α, hsCRP)

The hsCRP is performed routinely for safety throughout the study and is part of the central laboratory draws.

Tryptase and other inflammatory markers such as interleukin 6 (IL6), interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) may be performed from centrally stored sample aliquots at a later date, as required. Should a subject develop anaphylaxis on days when inclisiran is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logically possible).

3.8.8.5. Urinalysis

Urinalysis will be performed at the time points defined in the Schedule of Assessments (Table 1) and evaluated by dipstick analyses at the investigational site (a standardized dipstick test will be supplied by the Central Laboratory). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

The following parameters will be assessed:

- Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities).

3.8.8.6. Urine Pregnancy

Urine pregnancy testing will be performed locally at the visits specified in the Schedule of Assessments (Table 1), using the supplies provided by the Central Laboratory.

3.8.8.7. Anti-drug Antibodies

A serum sample for analysis of the induction of antibodies will be collected at the time points in the Schedule of Assessments (Table 1). Collection will be prior to and 4 hours after first investigational product administration (injection) and then as per the Schedule of Assessments. As presented in Section 3, serum samples for analysis are collected at every visit but assessment of ADA will only occur for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. Samples will be stored for assessment (if needed) for samples collected at the following visits: Randomization (after injection), Day 90, Day 270, Day 450, and the End of Study Visit.

3.8.9. Stored samples

The central laboratory will take aliquots of serum and plasma samples from the received routine blood sampling noted above and will store these as frozen samples to permit future analysis of the effect of inclisiran on the expression of these exploratory biomarkers. Analyses may include markers of CV risk (eg, hsCRP, IL6, P-selectin, Lp-PLA2, adiponectin). Biological samples for

biomarker research will be retained on behalf of the Sponsor for a maximum of 1 year following the last subject's last visit in the study. Details regarding the collection, processing, storage, and shipping will be in the Study Laboratory Manual.

3.9. Assessment of Efficacy

Subjects will be in a fasted state for all efficacy laboratory assessments of lipids/lipoproteins/biomarkers. Specimens will be obtained at the time points in the Schedule of Assessments (Table 1). Pharmacodynamic parameters to be assessed will include:

- Total cholesterol (TC), triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, ApoB, lipoprotein (a) [Lp(a)], hsCRP, and PCSK9.

Directly measured (using ultracentrifugation) LDL-C will be done at baseline and at Day 510.

Calculated LDL-C will use the Friedewald calculation, as the Friedewald equation (LDL-C = TC – HDL-C – TG/5) is typically used in clinical practice.

Blood samples for determination of LDL-C concentrations will be collected at the time points in the Schedule of Assessments (Table 1). Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

Additional aliquots of plasma and serum will be collected at each time point and stored for additional analyses, including future analysis of biomarkers of CV risk. Plasma samples will be analyzed using a validated enzyme linked immunosorbent assay to determine PCSK9 protein concentration. Full details of the analytical methods used will be described in a separate bioanalytical report.

3.10. Assessment of Pharmacodynamics

Assessment of lipids/lipoproteins as discussed in Section 3.9 will cover pharmacodynamics.

4. ADVERSE EVENTS

This section will describe how the adverse events will be collected per protocol; analysis methods will be described in Section 6.4.8.1.

4.1. Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

4.2. AE Severity

The severity of AEs will be assessed by the Investigator using the 3-point scale below:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

4.3. Study Drug Causality

The relationship between the AE and the investigational product will be assessed by using a binary assessment. The investigator should determine whether there is a 'Reasonable possibility' or 'No reasonable possibility' that the investigational product caused the event based on the definitions below.

Reasonable possibility - There is a reasonable possibility that the administration of the investigational product caused the AE. There is evidence to suggest a causal relationship between the investigational product and the AE.

No reasonable possibility - There is no reasonable possibility that the administration of the investigational product caused the AE. There is no temporal relationship between the investigational product and event onset, or an alternative etiology has been established.

4.4. Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,

- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction (MI) that may be considered minor could be an SAE if it prolonged hospitalization.

4.5. Additional collection of safety data: Special Situations

4.5.1. Special Situations

Special Situations designated for this study were collected as adverse events and include:

- Medication errors that fall into the following categories
  - wrong investigational product
  - wrong dose (including overdose, underdose, change in dosing regimen, strength, form concentration, amount)
  - wrong route of administration
  - wrong subject (i.e., not administered to the intended subject)
  - accidental exposure
- Pregnancy/lactation exposures with or without any AEs related to the parent or child
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions

4.5.2. Other safety related information

Injection site reactions (ISR) including individual signs or symptoms at the injection site following investigational product administration should be recorded on specifically designed electronic case report form (eCRF) pages. Photographs of ISR, if they were obtained during the study visits, should be forwarded to the study inbox.

Other safety related information that should be reported as adverse events in accordance with the process described in Protocol Section 8.4 are:

- Abnormal neurological examination, e.g., peripheral sensory and motor evaluation, an assessment of gait, pain, position, strength and reflexes (Protocol Appendix C).
- Potential anaphylactic reactions assessed by Sampson criteria (Protocol Appendix D). If Sampson criteria are positive, confirm by elevation of tryptase in blood plasma measured within 30 minutes of symptoms.
- Hyperglycemia-related AEs:

  Report 'New onset of diabetes' in subjects with no medical history of diabetes when:

  - HbA1c becomes ≥6.5% and/or
  - Two consecutive values of fasting plasma glucose that are ≥126 mg/dL
  - If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected.

  Report 'Worsening of the glycemic control' or 'diabetic complications' in subjects with a medical history of disease (HbA1c ≥6.5% at baseline) when:

  - HbA1c increases from baseline > 0.5% and/or
  - New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

5. MEASURES TO MINIMIZE/AVOID BIAS

5.1.1. Blinded Study

This study will employ a double-blind technique with a placebo control. Randomization via automated interactive response technology (IRT) will be used to assign a subject to blinded investigational product. In addition, investigational product will be dispensed and administered in a blinded syringe. Blinding will minimize bias based on subject selection, baseline characteristics, clinical endpoint and AE reporting.

6. STATISTICAL PLAN

6.1. Sample Size

The sample size calculation is performed with the assumption (which is based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL.

Assuming about a 5% drop out rate, the sample size will be approximately 1425 subjects that are evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 1425 evaluable subjects, will provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025. This sample size will also contribute additional sufficient safety data.

6.2. Randomization

Subjects will be screened and approximately 1500 eligible subjects will be randomized by the IRT system: 750 subjects will be randomized to inclisiran sodium 300 mg and 750 subjects to placebo. Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will receive four SC injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450.

6.3. General Statistical Considerations and Definitions

6.3.1. General Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Categorical variables will be summarized using counts and percentages. Percentages are based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including changes from Day 1, will be summarized using descriptive statistics (n, mean, standard deviation [SD], median and interquartile range [first and third quartiles], minimum and maximum).

All p-values will be two-sided. All p-values will be rounded to three decimal places using the following algorithm. If the fourth digit of the p-value is less than or equal to 4, the p-value will be rounded down. If the fourth digit of the p-value is greater than or equal to 5, the p-value will be rounded up. All p-values rounded to 0.000 will be presented as ‘<0.001’ and p-values that round to 1.000 will be presented as ‘1.000’.

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

- Absolute Change =Value at Day X – Baseline value.
- Percent Change = (Absolute Change/Baseline value)*100%.

6.3.2. Analysis Populations

The following populations will be used for data analyses and/or presentation.

6.3.2.1. Intent-to-Treat (ITT) Population

All subjects randomized into the study will comprise the intent-to-treat (ITT) population. Treatment classification will be based on the randomized treatment. The ITT population will be used for analysis of the primary and secondary endpoints.

6.3.2.2. Full Analysis Set (FAS)

All subjects who are randomized into the study, take any study medication and have at least one post treatment lipid data measured will comprise the full analysis set (FAS) population. Treatment classification will be based on the randomized treatment.

6.3.2.3. Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least one dose of investigational product and have both the baseline and the Day 510 follow-up LDL-C assessment will comprise the modified intent-to-treat (mITT) population. Treatment classification will be based on the randomized treatment.

6.3.2.4. Safety Population

All subjects who received at least one dose of investigational product will comprise the safety population. Treatment classification will be based on the actual treatment received. A subject who receives any amount of inclisiran throughout the study will be analyzed within the inclisiran treatment group for the safety analyses. This will be primary population for the safety analyses.

6.3.3. Analysis Windows and Baseline

The analysis windows around each visit day are provided in Table 2 below.

Table 2: Analysis Windows for Each Scheduled Visit

Scheduled Visit	Analysis Window	
	From	To
Baseline		Before randomization/First Study Treatment
Day 30	Day 1	Day 60
Day 90	Day 61	Day 120
Day 150	Day 121	Day 210
Day 270	Day 211	Day 300
Day 330	Day 301	Day 390
Day 450	Day 391	Day 480
Day 510	Day 481	Day 525
Day 540	Day 526	No upper limit

Data collected at scheduled or unscheduled visits will be used in the analysis if they fall into an analysis window for a scheduled visit. If more than one visit (scheduled or unscheduled) is made

within the window specified above for any scheduled visit, the non-missing assessment closest to the scheduled visit day will be used in the analysis for that visit. However, all data will be included in the subject data listings.

Unless otherwise specified, data collected from assessments that occur more than once prior to initiation of investigational product administration, the latest assessment will be considered the "Baseline" evaluation for analysis.

6.3.4. Missing data handling

6.3.4.1 Efficacy

The sponsor will diligently follow up with each subject during the study through Day 540 ±14 days on all efficacy laboratory assessments of lipids/lipoproteins/biomarkers to keep missing data to a minimum regardless of whether the subject is on study treatment, uses ancillary therapies, experiences an adverse event, or adheres to the protocol (these data points are referred to as retrieved data). However, if missing data, defined as data not available from either scheduled (within the protocol defined visit window) or unscheduled visits, occurs for the primary or any of key secondary efficacy endpoints then that data will be imputed.

The primary method to impute missing data for the first co-primary efficacy endpoint (percentage change in LDL-C from baseline to Day 510) will be a multiple imputation washout model. The washout model will be performed on actual values, change and percentage change values are calculated after the imputation. All retrieved data for subjects who dropped out from study treatment are considered as non-missing data and will be utilized in all analyses. See Appendix 2 for full details of the multiple imputation washout model.

In addition, sensitivity analyses using MMRM without multiple imputation and a control-based pattern mixture model (PMM, see details in Appendix 3) will be performed on the co-primary and key secondary efficacy endpoints to assess the impact of missing values. Note that the control-based PMM will be the primary method for imputing data for the second co-primary efficacy endpoint (time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540).

Unless otherwise specified, missing data for all parameters not listed in the primary and key secondary endpoints will not be imputed and will be excluded from the associated analysis.

6.3.4.2 Safety

Safety analyses are based on observed values. Any missing safety data including laboratory data will not be imputed. For adverse events (AEs), any events with missing start or stop date will be considered as treatment emergent AEs. For concomitant medications, any medication with missing start or stop dates are considered as Day 1 concomitant medication.

Adverse events with incomplete dates will be categorized as treatment emergent unless there was sufficient specificity to the onset date to document that the event began before the first dose of study medication. No missing dates will be imputed.

6.4. Statistical Analyses

6.4.1. Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects who signed the informed consent form, are screen failures, are randomized, are treated (Safety Population), completed the study or who discontinued early along with reasons for early discontinuation will be summarized overall and by site for all screened subjects.
- The number of subjects in each analysis population along with reasons for exclusion from each analysis population will be summarized by treatment group for all randomized subjects.
- The number of subjects who complete the study or who discontinued early along with reasons for early discontinuation will be summarized by treatment group for each analysis population.
- The duration on study (number of days from the first date of treatment to the date of last recorded contact/participation date in the database) will be summarized by treatment for each analysis population.
- The number of subjects who are screened, screen failures, and randomized will be summarized by country and site for all screened subjects.
- The number of subjects in each treatment group will be summarized by country and site for each analysis population.

Completers are defined as a subject who completes the Day 540 visit.

A summary of inclusion/exclusion criteria will be provided by treatment group for all screened subjects and for the ITT population.

A summary of the number of subjects by visit will be provided by treatment group for each analysis population.

6.4.2. Protocol Deviations

The number and percentage of subjects with any protocol deviations will be summarized by treatment group. The protocol deviation categories are provided below.

- Subjects with at least one protocol deviation
- Inclusion and/or exclusion criteria violation
- Laboratory assessments not drawn at Day 1, Day 510 or Day 540 (EOS) visits
- Mis-dosing for any reason other than subject safety or withdrawal
- Prohibited concomitant medication / Change in baseline statin or other lipid-lowering therapy dose
- SAE form not reported to MDCO within 24 hours
- Informed consent not signed prior to study entry

6.4.3. Demographic and Background Characteristics

Subject demographics including age, age category (<65 years vs ≥65 years; 18 to <50, 50 to <65, 65 to <75, ≥75 years), race, gender, ethnicity, and country, baseline characteristics such as body height, weight, BMI, waist circumference, current use of statins or other lipid-modifying therapies (yes, no), status of statin intolerance, baseline eGFR, and baseline diabetes status based on HbA1c and fasting glucose will be summarized by treatment group using the ITT, FAS, mITT, and Safety populations.

Medical history (targeted medical history, other medical history, and medical history of statin intolerance) will be summarized by treatment group using the ITT, FAS, mITT and Safety populations.

6.4.4. Study Drug Exposure

Study drug administration will be summarized overall by treatment group and by dosing visits (including, missed doses, and injection site location) for safety population.

6.4.5. Concomitant Medications

Summaries of each prior (pre- baseline, defined as medication stopped 1 day before first dose date of study medication) medication and concomitant (Day 1 or later, any medications started or continued after study medication on Day 1 are considered as Day 1 concomitant medication) medications will be provided by treatment group for ITT, FAS, mITT, and safety population. Additional summaries will be provided for lipid modifying therapy use. Medications will be coded using the World Health Organization (WHO) drug dictionary (B3 WHO DDE+HD Sep 2017). Subjects will be counted only once within each period by medication.

The statin intensity (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. The high intensity group will include simvastatin 40 mg. A shift table for lipid modifying therapy statin intensity from baseline to Day 540 (EOS) will also be provided. The statin intensity of the last statin taken on or prior to Day 540 (EOS) will be used for the post-baseline statin.

6.4.6. Efficacy Analysis

The ITT population will be the primary population for the efficacy analysis. Efficacy analyses will also be performed for the FAS and mITT populations as supportive analyses.

6.4.6.1. Primary Efficacy Endpoints

The co-primary endpoints for this study are:

- Percentage change in LDL-C from baseline to Day 510
- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

Note: The time adjusted percentage change in LDL-C from Baseline after Day 90 and up to Day 540 analysis reflects LDL-C effect at a steady state. As such, this analysis assesses the effect on LDL-C levels seen with a more chronic dosing regimen. The Day 90 dose is the start of the 6 monthly dosing regimen.

The statistical hypotheses for the co-primary endpoint of the percentage change in LDL-C from baseline to Day 510 are as follows:

H01: The difference (inclisiran minus placebo), between subjects treated with inclisiran 300mg and placebo in the least squares mean percentage change in LDL-C from baseline at Day 510 = 0.

HA1: The difference (inclisiran minus placebo), between subjects treated with inclisiran 300mg and placebo in the least squares mean percentage change in LDL-C from baseline at Day 510 < 0.

The statistical hypotheses for the co-primary endpoint of the time adjusted percentage change from baseline after Day 90 and up to Day 540 are as follows:

H02: The difference (inclisiran minus placebo), between subjects treated with inclisiran 300mg and placebo in the least squares mean time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 = 0.

HA2: The difference (inclisiran minus placebo), between subjects treated with inclisiran 300mg and placebo in the least squares mean time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 < 0.

The family-wise type I error rate is controlled at a two-sided significance level of alpha=0.05 by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 will be tested first. If the null hypothesis is rejected at a two-sided significance level of alpha=0.05 and superiority of inclisiran over placebo is claimed, then the time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 will be tested, also at a two-sided significance level of alpha=0.05.

The primary endpoints will use a reflexive LDL-C approach: either calculated LDL-C (based on the Friedewald formula) will be used, or if the calculated LDL-C is less than 40 mg/dL or triglycerides are greater than 400 mg/dL, or calculated LDL-C is missing, directly measured (using ultracentrifugation) LDL-C will be used if it is available.

Percentage change in LDL-C from baseline to Day 510

Missing values will be imputed for LDL-C after a reflexive approach using the multiple imputation (100 total imputed datasets) washout model specified in Appendix 2. The percentage change in LDL-C at each visit will be calculated after the missing data imputation has been performed.

The primary analysis will be conducted on the ITT population and based on an ANCOVA model on the percentage change in LDL-C from baseline to Day 510 on each multiply imputed dataset (100 total). The model will include fixed effects of treatment group and current use of statins or other lipid-modifying therapies at baseline (yes or no) and baseline LDL-C as a covariate.

Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's Method via the SAS PROC MIANALYZE procedure. The difference in the least squares means

between treatment groups and corresponding two-sided 95% confidence interval will be provided for hypothesis testing.

See Appendix 2 for more details on this analysis.

Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

A control-based pattern-mixture model (PMM), following the methods described in Ratitch and O'Kelly (2011), will be utilized to explore the possibility of data missing not at random (MNAR) for subjects who discontinued the study. For subjects who discontinued the study without any further follow-up data, their missing values after study discontinuation will be imputed under the assumption that their outcome would be similar to those in the placebo group with similar background characteristics. For subjects who did not discontinue the study, their intermittent missing values will be imputed based on the MAR assumption. Multiple imputations will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method [Rubin, 1987]. See Appendix 3 for more details on this analysis.

The primary analysis will be conducted on the ITT population and based on a mixed-effects model for repeated measurements (MMRM) on the percentage change in LDL-C from baseline over all visits on each multiply imputed dataset (100 total). The model will include fixed effects for treatment, visit, baseline value, interaction between treatment and visit, and current use of statins or other lipid-modifying therapies. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured" (refer to Appendix 1 for further details on the MMRM).

The time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 will be calculated from the MMRM. Linear combinations of the estimated means after Day 90 and up to Day 540 will be used to compare treatment effects.

Treatment effects from these 100 MMRM analyses will then be combined using Rubin's Method via the SAS PROC MIANALYZE procedure. The difference in the least squares means between treatment groups and corresponding two-sided 95% confidence interval will be provided for hypothesis testing.

6.4.6.1.1. Sensitivity Analysis for Primary Efficacy Endpoints

In order to support the robustness of the conclusions drawn from the co-primary efficacy analyses, we will perform the following sensitivity analyses for the co-primary efficacy endpoints.

Percentage change in LDL-C from baseline to Day 510

- A control-based pattern-mixture model (PMM), using the same imputed datasets and MMRM model that was used for the second co-primary efficacy endpoint primary analysis will be used to compare treatments at Day 510. Multiple imputations will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method. (Refer to Appendix 3 for details)
- A mixed model for repeated measurements (MMRM) analysis without multiple imputation, that assumes missing data are missing at random (MAR), will be performed. The model will include fixed effects for treatment, visit, baseline value, interaction

between treatment and visit, and current use of statins or other lipid-modifying therapies. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured". A linear contrast at Day 510 will be used to compare treatment groups. This will be the same model that is used as a sensitivity analysis for the second co-primary endpoint.

- The impact of country will be assessed by including country (possibly pooled into a region) and the treatment-by-country interaction fixed effects into the primary efficacy analysis ANCOVA (using multiple imputation washout model data).
- A tipping point analysis will be performed to search for the tipping point that reverses the study conclusion. In the tipping point analysis, we will independently vary the deltas in the treatment groups (inclisiran group progressively worse while the placebo group is not impacted and inclisiran group progressively worse while the placebo group progressively improves) until the hypothesis test on the co-primary efficacy endpoint becomes statistically insignificant. The MNAR(ADJUST) statement in SAS PROC MI will be used to adjust the delta of the imputed missing values analyzed using the ANCOVA model with washout model multiply imputed data.

Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

- A mixed model for repeated measurements (MMRM) analysis without multiple imputation, that assumes missing data are MAR, will be performed. The model will include fixed effects for treatment, visit, baseline value, interaction between treatment and visit, and current use of statins or other lipid-modifying therapies. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured". A linear combination of the estimated means after Day 90 and up to Day 540 will be used to compare treatment groups. This will be the same model that is used as a sensitivity analysis for the first co-primary endpoint.
- The impact of country will be assessed by including country (possibly pooled into a region) and the treatment-by-country interaction fixed effects into the primary efficacy analysis MMRM (using multiple imputation control-based PMM data).
- The time adjusted percentage change will also be calculated by taking the arithmetic mean of calculated percent change in LDL-C from baseline at each visit after Day 90 through Day 540. This analysis will be based on the control-based PMM imputed datasets (100 multiple imputation datasets). The two sample t-test will be performed to test the treatment difference between inclisiran and placebo. Results will be combined and summarized using Rubin's method.
- A tipping point analysis will be performed to search for the tipping point that reverses the study conclusion. In the tipping point analysis, we will independently vary the deltas in the treatment groups (inclisiran group progressively worse while the placebo group is not impacted and inclisiran group progressively worse while the placebo group progressively improves) until the hypothesis test on the co-primary efficacy endpoint becomes statistically insignificant. The MNAR(ADJUST) statement in SAS PROC MI will be used to adjust the delta of the imputed missing values analyzed using the MMRM model with control-based PMM multiply imputed data.

Other sensitivity analysis may be performed.

6.4.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will not be tested if either one of the co-primary efficacy endpoints' null hypothesis fails to be rejected.

The key secondary endpoints of this study are:

- Absolute change in LDL-C from baseline to Day 510.
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540.
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C.

The Hochberg procedure [Hochberg, 1988] will be applied to control the family-wise type I error rate at a two-sided significance level of alpha=0.05 for the key secondary endpoints.

Missing values will be imputed using the control-based PMM (see Appendix 2 for more details) on LDL-C, PCSK9, total cholesterol, ApoB, and non-HDL-C, absolute change or percent change from baseline will be calculated based on imputed data before any analysis is performed.

The absolute change in LDL-C from baseline to Day 510 and percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C will be analyzed using a MMRM with covariates as specified in Appendix 1 and Appendix 3. Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 will be analyzed similarly to that of time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

MMRM without multiple imputation (see Appendix 1) will be used as sensitivity analyses for the key secondary endpoints.

The other secondary endpoints of this study are:

- Maximum percentage change in LDL-C. This is calculated by finding the smallest LDL-C value across all post baseline visits for each individual subject. This value will be used to compare with each subject's baseline value and calculate the percent change from baseline to the lowest LDL-C value.
- Absolute change from baseline to Day 510 in PCSK9, total cholesterol, ApoB and non-HDL-C.
- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540.
- Individual responsiveness defined as the number of subjects reaching on treatment LDL C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510.
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline.
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540.

- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk.

The two-sided 95% confidence interval for least squares means will be provided for continuous variables at a single point using an analysis of covariance model or using MMRM methods for variables measured over time (see Appendix 1 for more details). The odds ratio and 95% confidence interval for the odds ratio will be provided for binary variables using logistic regression models. Nominal p-values will be provided when applicable.

Descriptive and graphical summaries by treatment group will also be presented.

6.4.6.3. Exploratory Endpoints

The exploratory endpoints of this study are:

- Incidence of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic and hemorrhagic)

  A major cardiovascular event (MACE) is defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or hemorrhagic). Refer to Appendix 5 for details on the search terms used. The number and percentage of subjects with MACE or any of the individual events will be presented by treatment group.

- Proportion of subjects in each group with any LDL-C reduction from baseline at any visit (responders).

  The number and percentage of subjects with any LDL-C reduction at any visit will be presented by treatment group. The odds ratio and 95% confidence interval for the odds ratio will be provided using a logistic regression model. The number and percentage of subjects with any LDL-C reduction will also be summarized at each visit.

6.4.7. Subgroup Analysis

Analysis of efficacy and safety will also be performed for subgroups of interest including:

Table 3: Subgroups for Analysis

Number	Subgroup	Categories and comments			
1	Gender	Male	Female		
2	Age #1	< 65 vs ≥ 65 years			
3	Age #2	< 75 vs ≥ 75 years			
4	Body mass index #1	≤ vs > median			
5	Body mass index #2	Quartiles			
6	Race	White	Black	Other	
7	Baseline statin use	Yes	No		
8	Baseline statin intensity	High intensity	Not high intensity		
9	Other lipid management therapy	Any statin with other lipid management therapy	No statin but other lipid management therapy	No lipid management therapy	
10	Baseline triglyceride level #1	<200 mg/dL vs ≥200 mg/dL			
11	Baseline triglyceride level #2	≤ vs > median			
12	Metabolic disease [1]	Diabetes	Metabolic syndrome without diabetes	Neither	
13	ASCVD status	ASCVD	ASCVD risk equivalents		
14	Renal impairment by eGFR categories - mL/min/1.73m^2 [2]	≥15 to <30	≥30 to <60	≥60 to <90	≥90
15	History of allergy [3]	Yes	No		
16	Baseline LDL-C #1	≤ vs > median			
17	Baseline LDL-C #2	Quartiles			
18	Study center region	North America	Europe	South Africa	
19	Post baseline LDL-C [4]	≤25 at any time point vs >25 mg/dL at all time points			

[1] Metabolic syndrome is not based on medical history but will be defined according to the American Heart Association (AHA) definition (see Reference 1).
[2] Creatinine clearance (CrCl) values using the Cockroft and Gault estimation:
CrCl = {((l40–age) x weight)/(72xSerum Creatinine)}x 0.85 (if female)
[3] A history of allergy was identified using the following high-level group term (HLGT): allergic conditions.
[4] For descriptive summary of PCSK9 data only.

Baseline variables to be analyzed by subgroup:

Disposition
Protocol Deviations
Demographics and Baseline Characteristics
Targeted Medical History
Other Medical History
Medical History of Partial or Complete Statin Intolerance
Study Drug Administration
Day 1 Concomitant Medications
New or Changed Concomitant Medications

Prior Medications
Prior Lipid Modifying Therapies
Day 1 Lipid Modifying Therapy Usage
New or Changed Lipid Modifying Therapy Usage
Shift from Baseline in Statin Intensity

Safety variables to be analyzed by subgroup:

Treatment Emergent Adverse Events
Treatment Emergent Serious Adverse Events
Treatment Emergent Adverse Events at the Injection Site
Withdrawals due to TEAEs

Efficacy variables to be analyzed by subgroup:

Co-Primary #1: Percentage change in LDL-C from baseline to Day 510 – ANCOVA – Washout Imputation
Co-Primary #2: Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540 – MMRM – control-based PMM
Key Secondary #1: Absolute change in LDL-C from baseline to Day 510 – MMRM – control-based PMM
Key Secondary #2: Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 – MMRM – control-based PMM
Key Secondary #3: Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C – MMRM – control-based PMM
Other Secondary #3: Actual value, absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540 – Descriptive Stats
Other Secondary #6: Actual value, absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540 – MMRM
Other Secondary #6: Actual value, absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540 – Descriptive Stats*

* Post baseline LDL-C subgroup included for PCSK9 summary table only.

6.4.8. Safety Analysis

The safety objectives of this study are to evaluate the safety and tolerability profile of inclisiran.

6.4.8.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (v20.1) will be used for coding AEs. 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 SOC and PT
- TEAEs by PT
- Common (2% within either treatment group) by PT
- TEAEs by SOC, PT, and Severity

- TEAEs by SOC, PT, and Relationship to Study Drug
- 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 Drug
- 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 preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

For common (2% within either treatment group) TEAEs, serious TEAEs and TEAEs leading to withdrawal of study medication, risk ratios along with 95% confidence intervals will be presented to compare treatment groups with respect to risk.

The following additional adverse events (Refer to Appendix 5, Additional Adverse Events Investigations) will also be assessed:

1. Adverse Events at the Injection Site
2. Hepatic events
3. Renal events
4. Hypersensitivity
5. Neurological events and Neurocognitive disorders
6. Ophthalmological events

Clinically relevant TEAEs at the injection site will also be tabulated. See Appendix 6 for a list of clinically relevant injection site preferred terms.

The time to the first TEAE at the injection site will also be summarized. Only subjects with a TEAE at the injection site will be included in the analysis. The time (hours) will be calculated from the date of the most recent administration of study drug. The duration of the TEAE will also be summarized. The same analyses will be performed for each individual TEAE PT at the injection site. The time to the first clinically relevant adverse event at the injection site will be analyzed similarly.

Any immune-related events will be identified in the SOC of immune system disorders.

Listings will be presented for subjects with SAEs/AEs leading to a discontinuation or death. Listings of SAEs and Death will also be provided.

6.4.8.2. Laboratory Tests

Laboratory values will be summarized by treatment group, including the observed value, changes and percent changes from baseline at each time point.

A shift analysis using the normal range (except for eGFR and HbA1c) will be done which counts the number of subjects 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 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 subject was not fasting will not be analyzed.

The number and percentage of subjects with potentially clinically significant (PCS) laboratory values and clinically significant (CS) laboratory values (refer to Appendix 4 for the criteria) will be summarized by treatment group. Hemoglobin A1c criteria is explicitly stated in Appendix 4. All other PCS and CS criteria are met when both of the following occur:

- Post-baseline values meet the thresholds listed in Appendix 4
- Baseline values or any prior post-baseline values do not meet the thresholds listed in Appendix 4

PCS chemistry laboratory values will also be classified as follows:

- Abnormal baseline:
  - Non HbA1c: >1 and ≤3x ULN at baseline and >1 and ≤3x ULN at final visit
  - HbA1c: ≥6.5% at baseline and ≥6.5% and ≥0.5% change from baseline at final visit

- Elevated further:
  - Non HbA1c: >1 and ≤3x ULN at baseline or post baseline and becoming > 3x ULN post baseline

- Final visit:
  - Non HbA1c: >1 and ≤3x ULN at final visit only but not at baseline or previous visits
  - HbA1c: ≥6.5% and ≥0.5% change from baseline at final visit only but not at baseline or previous visits

- Persistently elevated:
  - Non HbA1c: >1 and ≤3x ULN at a post baseline visit and remains >1 and ≤3x ULN until final visit
  - HbA1c: ≥6.5% and ≥0.5% change from baseline at a post baseline visit and remains ≥6.5% and ≥0.5% change from baseline until final visit

- Resolved:

- Non HbA1c: >1 and ≤3x ULN at baseline or post baseline, resolved to < ULN at any post baseline visit, and remaining < ULN at final visit
- HbA1c: ≥6.5% at baseline or ≥6.5% and ≥ 0.5% change from baseline for post-baseline, resolved to <6.5% and <0.5% change from baseline at any post baseline visit, and remaining <6.5% and <0.5% change from baseline at final visit

Separate listings of all subjects with PCS and CS laboratory values will be presented. Subjects will appear once per lab parameter but may appear under multiple lab parameters. The worst post-baseline value will be utilized in the analyses.

The number and percentage of subjects 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

Subjects must meet all of the criteria listed above at the same time point and have normal lab parameters (ALT, AST, TBL) at baseline to be considered a Hy's Law case.

6.4.8.3. Diabetes Assessment

Diabetes will be assessed by the analysis of:

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

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

6.4.8.3.1. Diabetes TEAE

New onset/worsening of diabetes will be identified using SMQ and AE terms (refer to Appendix 5 on Standardized MedDRA Queries (SMQ) and AE terms). The analysis will be performed for all subjects and then by baseline diabetes status. A subject will be identified as being diabetic at baseline if the targeted medical history notes that the subject is diabetic or the baseline HbA1c value is ≥ 6.5%.

6.4.8.3.2. Change in Glucose-related Laboratory Values Over Time

This analysis only utilizes laboratory data (fasting glucose and HbA1c). The change from baseline to the last on-treatment observation and the worst on-treatment observation will be summarized separately for fasting glucose and HbA1c overall and then by baseline glucose

control status. Baseline glucose control status will be identified separately for fasting glucose and HbA1c using the values provided in the table below (note that medical history will not be taken into account for this analysis). Figures will also be created showing mean fasting glucose and HbA1c values over time by baseline glucose control status.

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

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

6.4.8.3.3. Shifts from Baseline in Glucose Control Category

Shifts from baseline in glucose control category will be summarized two different ways. The change from baseline to the worst-on-treatment and then again for the last-on-treatment laboratory values will be used to classify the on-treatment glucose control category. Note that medical history will not be taken into account for this analysis. If consecutive fasting glucose measurements fall in two separate categories, or if only one pre- or post-baseline fasting glucose measurement is available, then the classification will be based on the HbA1c measurements only. If HbA1c is missing then both consecutive fasting glucose measurements must fall in a category otherwise the lower category will be used.

Shift Category*	Baseline Values**	Post-baseline Values
Normal to Normal (no change)	Fasting glucose <100 mg/dL on Screening or Day 1 AND HbA1c <5.7%	Fasting glucose <100 mg/dL on two consecutive occasions AND HbA1c <5.7%
Normal to Impaired	Fasting glucose <100 mg/dL on Screening or Day 1 AND HbA1c <5.7%	Fasting glucose ≥100 and <126 mg/dL on two consecutive occasions OR HbA1c ≥5.7 and <6.5%
Normal to Diabetes	Fasting glucose <100 mg/dL on Screening or Day 1 AND HbA1c <5.7%	Fasting glucose ≥126 mg/dL on two consecutive occasions OR HbA1c ≥6.5%

Impaired to Normal	Fasting glucose ≥100 and <126 mg/dL on Screening and Day 1 OR HbA1c ≥5.7 and <6.5%	Fasting glucose <100 mg/dL on two consecutive occasions AND HbA1c <5.7%
Impaired to Impaired (no change)	Fasting glucose ≥100 and <126 mg/dL on Screening and Day 1 OR HbA1c ≥5.7 and <6.5%	Fasting glucose ≥100 and <126 mg/dL on two consecutive occasions OR HbA1c ≥5.7 and <6.5%
Impaired to Diabetes	Fasting glucose ≥100 and <126 mg/dL on Screening and Day 1 OR HbA1c ≥5.7 and <6.5%	Fasting glucose ≥126 mg/dL on two consecutive occasions OR HbA1c ≥6.5%
Diabetes to Normal	Fasting glucose ≥126 mg/dL on Screening and Day 1 OR HbA1c ≥6.5%	Fasting glucose <100 mg/dL on two consecutive occasions AND HbA1c <5.7%
Diabetes to Impaired	Fasting glucose ≥126 mg/dL on Screening and Day 1 OR HbA1c ≥6.5%	Fasting glucose ≥100 and <126 mg/dL on two consecutive occasions OR HbA1c ≥5.7 and <6.5%
Diabetes to Diabetes (no change)	Fasting glucose ≥126 mg/dL on Screening and Day 1 OR HbA1c ≥6.5%	Fasting glucose ≥126 mg/dL on two consecutive occasions OR HbA1c ≥6.5%

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

**If one fasting glucose value is missing (Screening or Day 1), the assessment will be based on the available data.

6.4.8.3.4. Incidence of Post-baseline New-Onset of Diabetes

The number of subjects who shift from no diabetes at baseline (defined as no medical history of diabetes in the targeted medical history CRF, HbA1c <6.5% at baseline, and fasting glucose <126 mg/dL at baseline (note that baseline is defined as the average of Screening and Day 1 fasting glucose values, if one fasting glucose value is missing (Screening or Day 1), the assessment will be based on the available data) to diabetes will be summarized. A 4-component definition of diabetes will be utilized. The 4 components are provided below.

1. Diabetic TEAEs identified by the SMQ search (see Appendix 5), or
2. Post-baseline fasting glucose ≥126 mg/dL on two consecutive occasions, or
3. Initiation of anti-diabetic medication at any time post-baseline, or
4. At least one post-baseline Hba1c ≥6.5%.

The number of subjects who have any of the 4 components will be summarized (post-baseline new-onset of diabetes) along with each component. This analysis will be performed for those subjects who have fasting glucose at baseline < 100 mg/dL and then for those with fasting glucose at baseline ≥100 and <126 mg/dl (normoglycemic).

The time to new-onset diabetes will also be summarized. Only subjects without diabetes at baseline will be included in the analysis. The time (weeks) to new-onset diabetes will be calculated from the date of the first administration of study drug.

6.4.8.4. Anti-Drug Antibody

ADA is being assessed and will be listed in a separate ADA report. If there are ADA findings, further characterization and additional evaluations may be performed on safety and efficacy parameters.

6.4.8.5. Vital Signs

Observed value, change, and percent change from Day 1 in vital signs will be summarized descriptively at each scheduled time point by treatment group.

The change from baseline to EOS will also be summarized by the following categories:

- Systolic blood pressure (mmHg):
  - ≤ -20
  - > -20 to ≤ -10
  - > -10 to ≤ -5
  - > -5 to < 5
  - ≥ 5 to < 10
  - ≥ 10 to < 20
  - ≥ 20
- Diastolic blood pressure (mmHg):
  - ≤ -10
  - > -10 to ≤ -5
  - > -5 to ≤ -3
  - > -3 to < 3
  - ≥ 3 to < 5
  - ≥ 5 to < 10
  - ≥ 10

6.4.8.6. Electrocardiograms

The percentage of subjects with abnormal ECG findings reported as AEs will be summarized by treatment group within the overall assessment of cardiac safety.

6.4.8.7. Neurological Examinations

The percentage of subjects with a treatment-emergent abnormal neurological event and the specific abnormality reported as adverse events, will be summarized by treatment group.

7. COMPUTER METHODS

Statistical analyses will be performed using SAS (version 9.4 or later version).

8. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

The following items were changed between the final version of the protocol and the final SAP.

- Primary efficacy endpoint analyses were modified per FDA feedback.
- Imputation methods were modified per FDA feedback.
- Subgroup analyses were added for select variables.
- A secondary efficacy endpoint was renamed from mean maximum percent change to maximum percent change.
- The exploratory endpoint, proportion of subjects in each group with any LDL-C reduction from baseline at any visit (responders), was added
- Identification of PCS/CS laboratory values were modified.

9. REFERENCES

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3. Ratitch B, O'Kelly M: Imputation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, PharmaSUG2011 - Paper SP04.
4. Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.

APPENDIX 1. DETAILS OF MMRM USED FOR EFFICACY ANALYSES

A number of efficacy analyses will utilize a mixed-effects model for repeated measures (MMRM). This includes the co-primary efficacy endpoints (in the case of the first co-primary efficacy endpoint, it will be used as a sensitivity analysis), the key secondary efficacy endpoints, and other secondary efficacy endpoints.

The models will generally include fixed effects for treatment, visit, baseline value, interaction between treatment and visit, and current use of statins or other lipid-modifying therapies. The visits will include Days 90, 150, 270, 330, 450, and 510, with Day 510 as the primary time-point. Linear combinations of the estimated means will be created for the various hypothesis tests.

The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured." The least squares means will be calculated for each treatment at each visit.

The analysis will be carried out using the SAS PROC MIXED procedure.

Sample SAS statements follow:

```
ods output LSmeans=estimates;
ods output Diffs=lsdiffs;
Proc Mixed Data=ldl_data;
  Class treatment visit_day subject_id statinyn;
  Model percent_change = treatment|visit_day statinyn
base_value/DDFM=KR;
repeated visit_day/type=UN subject=subject_id;
LSMeans treatment*visit_day/cl pdiff=control('0' '510');
run;

(where ('0' '510') is the value of the placebo ['0'] at day 510 ['510']
in interaction term treatment*visit_day)
```

APPENDIX 2. MULTIPLE IMPUTATION WASHOUT MODEL

A multiple imputation washout model will be utilized for the primary efficacy analysis of the percentage change in LDL-C from baseline to Day 510 endpoint. The washout model can be thought of as a modified control-based Pattern-Mixture Model (PMM) that will be used to explore the possibility of data missing not at random (MNAR) for subjects who discontinued the study early. For subjects who discontinued the study early, their missing values will be imputed under the assumption that their outcome would be similar to those in the placebo group with similar background characteristics. For subjects in the inclisiran group only missing Day 510 values will be imputed. For subjects in the placebo group their missing values over all visits after early termination will be imputed based on the missing at random (MAR) assumption. Multiple imputation will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method. Further details are provided below.

Windowing will be performed first (see Section 6.3.3) and any missing data will be imputed using the following steps.

The covariates and baseline characteristics which can be predictive of the response for the inclisiran group will be included in a multiple imputation procedure (SAS PROC MI) and will include the following:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 510 from the placebo group (continuous)
- Current use of statins or other lipid-modifying therapies (categorical)

The covariates and baseline characteristics which can be predictive of the response for the placebo group will be included in a multiple imputation procedure (SAS PROC MI) and will include the following:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 90 (continuous)
- Observed value of efficacy measurement at Day 150 (continuous)
- Observed value of efficacy measurement at Day 270 (continuous)
- Observed value of efficacy measurement at Day 330 (continuous)
- Observed value of efficacy measurement at Day 450 (continuous)
- Observed value of efficacy measurement at Day 510 (continuous)
- Observed value of efficacy measurement at Day 540 (continuous)
- Current use of statins or other lipid-modifying therapies (categorical)

1. Intermittent missing data in the placebo treatment group will be imputed using MCMC methods, assuming MAR. SAS PROC MI will be utilized for this step using the MCMC impute=monotone option. A total of 100 datasets will be created. These datasets will be utilized in Step #2.

2. The remaining missing values in the placebo group with a monotone missing data pattern will be imputed in this step. Missing data will be imputed assuming data are MAR. Only subjects in the placebo group will be utilized in this step. SAS PROC MI will be used to impute missing values utilizing the monotone reg option. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed for the placebo treatment group. These datasets will be utilized in Step #3.
3. The missing values at Day 510 in the inclisiran group will be imputed in this step. Control-based PMM imputation will be performed. With this imputation model, the missing efficacy measurements in the inclisiran group will not be constructed from the observed data in the inclisiran group but rather from the observed and imputed data in the placebo group at Day 510. Baseline data will also be utilized in the imputation. The MNAR statement in SAS PROC MI will be used to impute missing values. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed.
4. A total of 100 fully imputed datasets will be created (M=100). Since multiple imputation is a stochastic method, slight differences in output can be expected for different initial states of the random number generator. The seed numbers will be identified in the SAS programs to allow for reproducibility.
5. After the missing data imputation is completed using the above steps, absolute change/percentage change values will be calculated in each of the imputed datasets at each visit.
6. These 100 datasets will be analyzed using ANCOVA models with fixed effects of treatment group and current use of statins or other lipid-modifying therapies at baseline (yes or no) and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to Day 510 primary efficacy endpoint.
7. Treatment effects (difference in LS means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

APPENDIX 3. CONTROL-BASED PATTERN MIXTURE MODEL

A control-based Pattern-Mixture Model (PMM) will be used to explore the possibility of data missing not at random (MNAR) for subjects who discontinued the study. For subjects who discontinued the study without any further follow-up data, their missing values after study discontinuation will be imputed under the assumption that their outcome would be the similar to those in the placebo group with similar background characteristics. For subjects who did not discontinue the study, their intermittent missing values will be imputed based on the MAR assumption. Multiple imputation will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method. Further details are provided below.

Windowing will be performed first (see Section 6.3.3) and any missing data will be imputed using the following steps.

The covariates and baseline characteristics which can be predictive of the response will be included in a multiple imputation procedure (SAS PROC MI) and will include the following:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 90 (continuous)
- Observed value of efficacy measurement at Day 150 (continuous)
- Observed value of efficacy measurement at Day 270 (continuous)
- Observed value of efficacy measurement at Day 330 (continuous)
- Observed value of efficacy measurement at Day 450 (continuous)
- Observed value of efficacy measurement at Day 510 (continuous)
- Observed value of efficacy measurement at Day 540 (continuous)
- Current use of statins or other lipid-modifying therapies (categorical)

1. Intermittent missing data will be imputed using MCMC methods, assuming MAR, within each treatment group. SAS PROC MI will be utilized for this step using the MCMC impute=monotone option. A total of 100 datasets will be created. These datasets will be utilized in Step #2.
2. The remaining missing values with a monotone missing data pattern will be imputed in this step. Control-based PMM imputation will be performed. With this imputation model, the missing efficacy measurements in the inclisiran group will not be constructed from the observed data in the inclisiran group but rather from the observed data in the placebo group. We will also use this model to impute missing efficacy measurements in the placebo group. The MNAR statement in SAS PROC MI will be used to impute missing values under the aforementioned assumptions. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed.
3. A total of 100 fully imputed datasets will be created (M=100). Since multiple imputation is a stochastic method, slight differences in output can be expected for different initial states of the random number generator. The seed numbers will be identified in the SAS programs to allow for reproducibility.

4. After the missing data imputation is completed using the above steps, absolute change/percentage change values will be calculated in each of the imputed datasets at each visit.
5. These 100 datasets will be analyzed using the MMRM described in Appendix 1 for the co-primary efficacy endpoints and key secondary efficacy endpoints.
6. Treatment effects (difference in LS means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

APPENDIX 4. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT AND CLINICALLY SIGNIFICANT ABNORMAL LABORATORY TESTS

Hemoglobin A1C criteria is explicitly stated in the table below.

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

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

Parameter	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
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 x 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.
*Clinically significant laboratory boundaries.

APPENDIX 5. ADDITIONAL ADVERSE EVENT INVESTIGATIONS

1) Adverse Events at the Injection Site

    - Injection site reaction (HLT)

2) Hepatic events

    - Drug related hepatic disorders - comprehensive search (SMQ, broad and narrow)

3) Renal events

    - Acute kidney injury (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 %’ (‘'infusion site dermatitis', 'infusion site eczema’, 'infusion site hypersensitivity', 'infusion site rash', 'infusion site urticaria', 'infusion site vasculitis) and
        - PTs ‘injection site %’ ('injection site dermatitis', 'injection site eczema’, 'injection site hypersensitivity', 'injection site rash', 'injection site urticaria' and 'injection site vasculitis')

6) Neurological events and neurocognitive disorders

    Neurological events

    - Demyelination, (SMQ, broad and narrow)
    - Peripheral neuropathy, (SMQ, broad and narrow)

    Neurocognitive disorders

    - Deliria (including confusion), (HLGT)
    - Cognitive and attention disorders and disturbances, (HLGT)
    - Dementia and amnestic conditions, (HLGT)

- Disturbances in thinking and perception (HLGT)
- Mental impairment disorders (HLGT)

7) Ophthalmologic events

- Optic nerve disorders, (SMQ, broad and narrow)
- Retinal disorders, (SMQ, narrow)
- Corneal disorders, (SMQ, narrow)

8) Major cardiovascular events (MACE)

Cardiac death

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

Cardiac arrest

- PT 'Cardiac arrest'

Non-fatal MI

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

Stroke

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

APPENDIX 6. CLINICALLY RELEVANT ADVERSE EVENTS AT THE INJECTION SITE PREFERRED TERMS

Injection site atrophy
Injection site cellulitis
Injection site dermatitis
Injection site eczema
Injection site erythema
Injection site fibrosis
Injection site granuloma
Injection site hypersensitivity
Injection site infection
Injection site inflammation
Injection site ischaemia
Injection site lymphadenopathy
Injection site necrosis
Injection site nerve damage
Injection site photosensitivity reaction
Injection site pruritus
Injection site pustule
Injection site rash
Injection site reaction
Injection site recall reaction
Injection site scar
Injection site thrombosis
Injection site ulcer
Injection site urticaria
Injection site vasculitis
Injection site vesicles