NOVARTIS

Clinical Development

KJX839

MDCO-PCS-17-02 (CKJX839A12302) / NCT03851705

A two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH)
ORION-5

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1 INTRODUCTION

Inclisiran (also referred to as KJX839) is a novel synthetic ribonucleic acid (RNA) interference (RNAi) therapeutic for injection (subcutaneous [SC] use) and used for the treatment of hypercholesterolemia. This document presents a statistical analysis plan (SAP) for study protocol MDCO-PCS-17-02 (CKJX839A12302) Amendment 1 dated 08 Oct 2020, A two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH), referred to ORION-5 below.

2 TRIAL DESIGN

2.1 Type/Design of Trial

The ORION-5 study is a Phase III two-part (double-blind placebo-controlled/open-label) multicenter study in subjects with homozygous familial hypercholesterolemia (HoFH) to evaluate the safety, tolerability, and efficacy of subcutaneous inclisiran injection(s). This study has two sequential parts:

- Part 1: 6-month (completion of Day 180) double-blind period in which subjects will be randomized to receive either inclisiran or placebo
- Part 2: 18-month open-label follow-up period; placebo-treated subjects from Part 1 will be transitioned to inclisiran and all subjects will participate in an open-label follow-up period of inclisiran only

Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Subjects who meet study inclusion/exclusion criteria will be instructed to continue to follow a National Cholesterol Education Program Adult Treatment Panel III (or comparable) diet and be required to maintain their current lipid lowering drug therapy for the duration of the study.

In this study, at least 45 subjects will be enrolled and randomized 2:1 to receive either inclisiran sodium 300 mg SC or placebo on Day 1. Inclisiran and placebo will both be administered by a health care provider. Subjects will be observed in the clinic for at least 30 minutes post injection before being discharged. A second dose of inclisiran or placebo will be given at Day 90.

After completion of Part 1, the inclisiran-treated subjects from Part 1 will receive a third dose of inclisiran administered on Day 270 and subsequent doses on Day 450 and Day 630. The placebo-treated subjects from Part 1 will be transitioned to inclisiran starting on Day 180, the start of the open-label, single arm follow-up period of inclisiran only (Part 2). Placebo-treated subjects will receive their first dose of inclisiran on Day 180 and then subsequently receive a dose of inclisiran on Day 270, Day 450, and Day 630.

Subjects on a documented regimen of LDL or plasma apheresis will be allowed to continue their same regimen during the study using approximately the same frequency/timing as done at baseline. When apheresis is performed on a study visit (Dosing or Non-Dosing), blood samples for measurement of LDL-C, other lipids and laboratory assessments must be collected before the apheresis. When apheresis is performed on a Dosing Visit, dosing must occur just after completion of the apheresis. The next scheduled apheresis must not occur within 72 hours of injection of

inclisiran. The subsequent study visit must occur at least 2 weeks after an apheresis was performed to ensure LDL-C levels measured during a study visit are not confounded by the apheresis.

Safety results including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and clinical laboratory parameters will be assessed at specified visits through to the end of study (EOS) visit. All AEs must be reported. Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/Investigator and/or returns to baseline values. Other safety related information that should be reported as AEs include injection site reactions, abnormal results of neurological, potential anaphylactic/hypersensitivity reactions, new onset of diabetes, and worsening of glycemic control.

Samples to detect formation of anti-drug antibodies (ADA; including binding and neutralizing antibodies) will be collected on Day 1 (prior to the injection) and at Day 90, Day 150, Day 330, and Day 720.

The primary endpoint will be measured at Day 150 after which placebo-treated subjects will be transitioned to inclisiran on Day 180. All subjects will be enrolled in a long-term open-label follow-up period through Day 720 (EOS).

Efficacy (pharmacodynamic) assessments will include measurement of the effects of inclisiran on levels of LDL-C, other lipoproteins including total cholesterol (TC), triglycerides, high density lipoprotein cholesterol (HDL-C), non-HDL-C, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], and PCSK9. LDL-C is analyzed by beta-quantification (BQ) on Day 1, Day 150 and Day 720, and calculated using the Friedewald method on all visit days.

The safety and tolerability data from the double-blind and open label part of the study will be reviewed by an Independent Data Monitoring committee (IDMC) at pre-defined frequency. A recommendation will be made to continue, stop, or amend the study at any of these reviews.

After all subjects complete Part 1 of the study, a full set of statistical analyses specified in this SAP will be performed which include data from Part 1 and available data from Part 2 of this study. The data generated from this formal analysis may be used for potential submission to Health Authorities to support an indication in subjects with HoFH.

2.2 Objectives of the Trial

Primary Objective:

The primary objective of this study is to evaluate the effect of inclisiran treatment on:

- Low-density lipoprotein cholesterol (LDL-C) levels at Day 150

Secondary Objectives:

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

- LDL-C levels over time
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels over time
- Other lipids, lipoproteins, and apolipoproteins

- Individual responsiveness of subjects to inclisiran including proportion of subjects achieving prespecified global lipid guidelines for their indication
- Proportion of subjects with at least 30% LDL-C reduction from Day 1 over time

and to assess the:

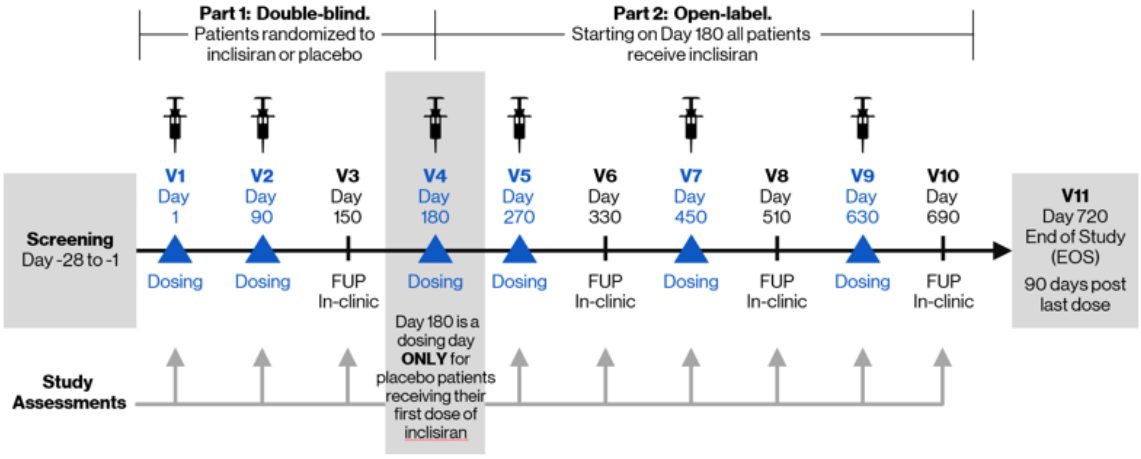
- Safety and tolerability profile of inclisiran

[redacted]

2.3 Schematic Diagram of Trial Design

The study design is presented in Figure 2-1:

Figure 2-1 Study Design



FUP=follow-up; V=visit

2.4 Schedule and Sequence of Procedures

The Schedule of Events/Assessments (Table 2-1) summarizes the study assessments by time point.

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

- **Screening period (Days -28 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 (inclisiran or placebo).
- **Treatment period (Day 1 through Day 690)**: occurs from the start of investigational product administration through the final clinic visit.
  - Dosing: Day 1 (inclisiran or placebo), Day 90 (inclisiran or placebo), Day 180 (inclisiran for placebo subjects switching to inclisiran), Day 270 (inclisiran), Day 450 (inclisiran), and Day 630 (inclisiran; final dose)
  - Additional clinic visits: Day 150, Day 180 (non-dosing visit for subjects randomized to the inclisiran arm), Day 330, Day 510, and Day 690
- **End of study (EOS) visit:** Day 720 (90 days after final dose)

The expected duration of a subject's participation in this study is approximately 734 days, which includes screening, investigational product administration, and the EOS period to Day 720.

Schedule of Assessments

Table 2-1 Study Design and Schedule of Assessments

	Screening	Randomization and Treatment	Treatment									EOS[13]
Visit	Day -28 to -1	**V1 (baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 (90 days post last dose)**
Timelines		Day 1	Day 90	Day 150	Day 180	Day 270	Day 330	Day 450	Day 510	Day 630	Day 690	Day 720
Visit windows (+/-weeks)		1	3	3	3*	3*	3*	3*	3*	3*	3*	3*
Informed Consent	X											
Medical history and prior meds	X											
Assessment of eligibility[1]	X	X										
β-HCG pregnancy test [2]	X	X	X	X	X	X	X	X		X	X	X
Study drug administration (inclisiran)		X	X			X		X		X		
Study drug administration (placebo; switch to inclisiran at Day 180)		X	X		X	X		X		X		
Physical examination [3]	X											X
Neurological examination[4]		X		X			X					X
Weight/Height/Waist circumference [5]	X			X	X		X					X
Vital signs[6]	X	X	X	X	X	X		X		X		X
12-lead ECG	X											X
Fasted lipid profile/biomarkers[7]	X	X	X	X	X	X	X	X	X	X	X	X
Full serum chemistry [8]		X										X
Limited serum chemistry [9]	X		X	X	X	X	X	X	X	X	X	

Hematology and coagulation[10]	X	X		X								X
Urinalysis (local) [11]	X	X										X
[redacted]												
ADA assessment		X	X	X			X					X
Previous/concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

β-HCG=beta-human chorionic gonadotrophic hormone; ADA=anti-drug antibodies; BP=blood pressure; CPK=creatine phosphokinase; CV=cardiovascular; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOS=end of study; HbA1C=glycated hemoglobin A1C; HDL-C=high density lipoprotein cholesterol; HR=heart rate; LDL-C=low density lipoprotein cholesterol; SC=subcutaneous; V=visit

*: The visit window is extended to +/- 2 months during the COVID-19 pandemic, to allow on-site visits (rather than remote visits) to occur as much as possible.

1. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
2. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test).
3. Physical examination is the responsibility of the principal investigator or medically qualified designee.
4. Full neurological examination will be performed as described in Appendix C of the protocol
5. Height will be measured at baseline only and used to calculate body mass index.
6. On dosing days, vital signs will be measured prior to injection. When available, an automated BP device is recommended for collection of 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 (HR, BP) is required per applicable visit
7. See Section 3.9 for details of specific tests to be analyzed
8. See Section 3.8.8.3 for details of specific tests to be analyzed
9. See Section 3.8.8.3 for details of specific tests to be analyzed
10. See Section 3.8.8.1 and Section 3.8.8.2 for details of specific tests to be analyzed
11. Performed locally using the central laboratory kit supplies

[redacted]

13. For subjects prematurely and permanently discontinued from study treatment, 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.

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 2-1) for a detailed schedule.

3.1 Screening Period (Days –28 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 28 days prior to randomization:

- Informed consent
- Assessment of inclusion and exclusion criteria
- Demographics and medical history including disease history (prior history related to the disease and prior use of disease related medication, e.g. monoclonal antibodies to PCSK9)
- 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)
- 12-lead ECG
- Fasting lipid profile/biomarkers
- Central clinical laboratory (limited serum chemistry, hematology and coagulation)
- Urinalysis (performed locally, using central laboratory supplies)
- Previous and concomitant medications
- [redacted]

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.

3.2 Randomization (Day 1)

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. At least 45 subjects are planned to be randomized 2:1 (inclisiran: placebo) for inclusion in the study.

The following procedures will be performed prior to the injection:

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

The following procedures will be performed after the injection:

- Recording of concomitant medications
- AE/SAE reporting

Investigational product (inclisiran or placebo) 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 30 minutes 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 subject to be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site may be obtained if deemed necessary. Photographs should be submitted to the study inbox.

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

3.3 Day 150

The following assessments will be completed during this visit:

- Pregnancy test (performed locally, prior to any dosing, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Weight and waist circumference
- Fasting lipid profile/biomarkers
- Assessment of ADA
- Vital signs: blood pressure and heart rate
- Central clinical laboratory (limited serum chemistry, hematology, and coagulation)
- Neurological examination (Protocol Appendix C)
- Recording of concomitant medications
- AE/SAE reporting

3.4 Additional Dosing Visits (Days 90, 180, 270, 450, and 630)

Subjects will return on Day 90 for a second investigational product injection. Subsequent inclisiran injections will be administered to all subjects on Day 270, Day 450 and Day 630. In addition, on Day 180 subjects originally randomized to the placebo group will be switched to inclisiran and receive their first dose of inclisiran on Day 180.

Note: For subjects randomized to the inclisiran arm, Day 180 will be a non-dosing visit but the same assessments as described below will be performed except for investigational product administration.

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

- Pregnancy test (performed locally, prior to any dosing, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Vital signs: blood pressure and heart rate
- Weight and waist circumference (Day 180 only)
- Fasting lipid profile/biomarkers
- Assessment of ADA (Day 90 only)
- Central clinical laboratory (limited serum chemistry)
- Recording of concomitant medication
- AE/SAE reporting

Administration of the investigational product is identical to Day 1 and is per Protocol Section 5.1.1 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 330, 510 and 690)

Subjects will return to the clinic for dosing follow-up visits on Days 330, 510, and 690.

Note: for subjects randomized to the inclisiran group the Non-dosing visit on Day 180 is described in Section 3.4. The following assessments will be completed during these visits:

3.5.1 Day 330

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Weight and waist circumference
- Fasting lipid profile/biomarkers
- Assessment of ADA
- Central clinical laboratory (limited serum chemistry)
- Neurological examination

- Recording of concomitant medications
- AE/SAE reporting

3.5.2 Day 510

- Fasting lipid profile/biomarkers
- Central clinical laboratory (limited serum chemistry)
- Recording of concomitant medications
- AE/SAE reporting

3.5.3 Day 690

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Fasting lipid profile/biomarkers
- Central clinical laboratory (limited serum chemistry)
- Recording of concomitant medications
- AE/SAE reporting

3.6 End of Study (EOS) Visit (Day 720 – 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
- 12-lead ECG
- Fasting lipid profile/biomarkers
- Assessment of ADA
- Central clinical laboratory (full serum chemistry, hematology and coagulation)
- Urinalysis (performed locally, using central laboratory supplies)
- Recording of concomitant medication
- AE/SAE reporting
- All ongoing AEs or abnormal test findings have been followed until the event (or its sequelae) or the abnormal test finding resolved, stabilized at a level acceptable to the Sponsor/Investigator and/or returned to baseline values

3.7 Interim Analysis

No formal interim analysis will be performed in this study.

3.7.1 Interim Safety Reviews

The independent Data Monitoring Committee (IDMC) will review safety data 90 days after the first 20 subjects receive the first injection of inclisiran or placebo. Thereafter the IDMC will review safety data every 3 months until all patients have reached Day 180 unless requested otherwise by the IDMC. A recommendation will be made to continue, stop or amend the study at any of these reviews. Following Day 180 unblinded data will be reviewed by the IDMC.

3.8 Assessment of Safety

3.8.1 Adverse Events

Subjects will be carefully monitored for adverse events (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, blood pressure) is required per applicable visit.

3.8.4 Electrocardiograms

Twelve lead ECGs will be collected at the time points in the Schedule of Assessments (Table 2-1) unless clinically indicated.

3.8.5 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 only). Clinically relevant changes from baseline will be collected as AE data.

3.8.6 Neurological Evaluation

A full neurological examination (Protocol Appendix C) will be performed as per the Schedule of Assessment (Table 2-1). Clinically relevant changes from baseline will be collected as AE data.

[redacted]

3.8.8 Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 2-1). If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and prior to the administration of study drug (on dosing visits).

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 2-1). Analysis will vary based on visit day as follows:

- **Full serum chemistry - Baseline (Day 1) and EOS (Day 720)**
  AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, urea (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, 180, 270, 330, 450, 510, 630, and 690**
  ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, fasting glucose, HbA1C (not at Day 150, 330, or 510), and tryptase (as required).

3.8.8.4 Inflammatory markers

High sensitivity C-reactive protein (hsCRP) testing 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 2-1) 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 2-1), using the supplies provided by the Central Laboratory.

3.8.8.7 Lipids / Lipoproteins

Lipids and lipoproteins assessments are described in Section 3.9. If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and prior to the administration of the study drug (on dosing visits).

3.8.8.8 Anti-drug Antibodies

A serum sample for analysis of the presence of antibodies will be collected at the time points in the Schedule of Assessments (Table 2-1). Collection will be prior to investigational product administration (injection) and per the Schedule of Assessments.

3.8.9 Stored samples

[redacted] Biological samples for biomarker research will be retained on behalf of the Sponsor for a maximum of 15 years 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 2-1). Parameters to be assessed will include:

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

LDL-C using ultracentrifugation will be done additionally at baseline, Day 150, and Day 720.

If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and, prior to the administration of the study drug (on dosing visits).

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. Reflexive testing of LDL-C using ultracentrifugation will be performed if triglycerides are > 400 mg/dL or LDL-C is < 40 mg/dL.

Blood samples for determination of LDL-C concentrations will be collected at the time points in the Schedule of Assessments (Table 2-1). For all study visits, LDL-C will be calculated (using the Friedewald method), in addition at baseline (Day 1), Day 150 and Day 720 LDL-C will be analyzed by BQ. Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

[redacted] 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.

Pharmacodynamic biomarker samples will be collected and stored for up to 15 years following the completion of the last subject for research purposes to identify and/or verify biomarkers that are predictive of response to inclisiran treatment (in terms of efficacy, safety and tolerability).

[redacted]

4 ADVERSE EVENTS

This section describes how 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 (e.g., 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 MI that may be considered minor could be an SAE if it prolonged hospitalization.

4.5 Additional Collection of Safety Data

4.5.1 Special Situations

Special Situations designated for this study 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 eCRF pages. Photographs of ISR, if they were obtained during the study visits, should be forwarded to the study inbox if available.

Other safety related information that should be reported as adverse events in accordance with the process described in study protocol Section 8.4 (Hochberg 1988) include:

- 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 Blinded Study

Part 1 of this study will employ double-blinded technique with a placebo control. Randomization via automated interactive response technology (IRT) will be used to assign 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. Specifics on how the blind for the investigational product is maintained are provided in Protocol Section 5.5.

6 STATISTICAL PLAN

6.1 Sample Size

The sample size calculation was performed with the hypothesis that the difference of mean percent change from baseline to Day 150 between inclisiran and placebo will be > 20% (20% standard deviation) in subjects with HoFH when treated with inclisiran. The sample size of at least 45 subjects (randomized 2:1 to inclisiran : placebo), with at least 30 subjects in the inclisiran arm, will provide >80% power to detect a 20% reduction of placebo-adjusted LDL-C levels from baseline in the inclisiran group compared to that in the placebo at one-sided significance level of 0.025 based on two-sample t-test.

6.2 Randomization

Randomization should only occur once subject's eligibility is confirmed and will be conducted via an automated interactive response technology (IRT) to assign subjects to blinded investigational product at 2:1 ratio to inclisiran versus placebo. Each subject will receive SC injections of blinded inclisiran or placebo on Day 1 and Day 90. The inclisiran-treated subjects will receive a third dose of inclisiran administered on Day 270 and subsequent doses on Day 450 and Day 630. The placebo-treated subjects from Part 1 will transition to an open-label, single arm follow-up period of inclisiran only; placebo-treated subjects will receive their first dose of inclisiran on Day 180 and then subsequently receive a dose of inclisiran on Day 270, Day 450, and Day 630.

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).

In general, any data captured during Part 1 (up to and including the Day 180 visit date) will be presented by treatment group (inclisiran or placebo). Part 1 will begin on Day 1 (the date of first dose) and end on the Day 180 visit (Visit 4). The Visit 4 date is the date that placebo treated subjects begin inclisiran dosing. Any assessments performed prior to inclisiran dosing for the placebo subjects will be included in the Part 1 analyses.

Any data captured during Part 2 (after the Day 180 visit date) will be presented in two separate groups, (1) inclisiran since Day 1 and (2) placebo-to-inclisiran. The column labels for these two groups will be inclisiran-inclisiran and placebo-inclisiran. Note that data captured prior to the Day 180 visit date will not be included in the Part 2 presentations. Any data captured on the Day 180 visit date after the first inclisiran dose for placebo subjects will be included in the Part 2 summaries. Any change from baseline summaries during Part 2 will utilize Day 1 (date of first dose) as the baseline.

Note that select analyses will summarize data over both parts of the study. These analyses are described later in the SAP.

All p-values will be based on two-sided tests. 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 '<0.0001' 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 Population

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 as the primary population for efficacy.

6.3.2.2 Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least one dose of investigational product and have both the baseline and Day 150 follow-up LDL-C assessment will comprise the modified intent-to-treat (mITT) Population. Treatment classification will be based on the randomized treatment.

6.3.2.3 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 and all Part 2 analyses.

6.3.3 Analysis Windows and Baseline

The analysis windows around each visit day are provided in Table 6-1 below. These analysis windows will be used for all analyses by visit and supersede the visit windows provided in the protocol. Data will be partitioned into Part 1/Part 2 first using the rules defined in Section 6.3.1 then the analysis windows will be implemented.

Table 6-1 Analysis Windows for Each Scheduled Visit

Scheduled Visit	Analysis Window	
	From	To
Baseline		**Before randomization/First Study Treatment**
Day 90	Day 61	Day 120
Day 150	Day 121	Day 171
Day 180	Day 172	Day 225
Day 270	Day 226	Day 300
Day 330	Day 301	Day 390
Day 450	Day 391	Day 480
Day 510	Day 481	Day 570
Day 630	Day 571	Day 660
Day 690	Day 661	Day 705
Day 720	Day 706	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 each subject from randomization until the end of study (Day 720±3 weeks), and make every effort to keep each subject visit within the protocol specified window on all efficacy laboratory assessments of lipids/lipoproteins/biomarkers to keep missing data to the minimum regardless of whether a subject is on study treatment, uses ancillary therapies, experiences an adverse event, or adheres to the protocol.

However, if missing LDL-C data, defined as data not available from either scheduled (within the protocol defined visit window) or unscheduled visits, occurs during Part 1 of the study up to Day 180 then that data will be imputed.

The primary method to impute missing data for the primary efficacy endpoint (percentage change in LDL-C from baseline to Day 150) during Part 1 of the study 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 primary and key secondary efficacy endpoints of Part 1 of the study to assess the impact of missing values.

Unless otherwise specified, missing data for all parameters not listed in the primary and key secondary efficacy 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 medication, 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 (completion and discontinuation status will be broken out by study part) 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 study part and study part 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 study part and study part treatment group for the ITT 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 study part and study part treatment for the ITT population.
- The number of subjects who are screened, screen failures, and randomized will be summarized by site for all screened subjects in Part 1 of the study.
- The number of subjects in each study part and study part treatment group will be summarized by site for the ITT population.

Overall study completers are defined as a subject who completes the Day 720 visit.

A summary of inclusion/exclusion criteria will be provided by Part 1 treatment group (inclisiran or placebo) for all screened subjects and for the ITT population.

A summary of the number of subjects by visit will be provided by study part and study part 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 study part and study part 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 150, Day 510 or Day 720 (EOS) visits
- Mis-dosing for any reason other than subject safety or withdrawal (defined as missing dose or a dose delayed by more than 30 days)
- Prohibited concomitant medication / Change in baseline statin or other lipid-lowering therapy dose
- SAE form not reported to the sponsor 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), race, gender, ethnicity, 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, genetic testing results, and

baseline diabetes status based on HbA1c and fasting glucose will be summarized by Part 1 treatment group (inclisiran or placebo) using the ITT Population.

Medical history (targeted medical history, other medical history, and medical history of statin intolerance) will be summarized by Part 1 treatment group (inclisiran or placebo) using the ITT and Safety Populations.

6.4.4 Study Drug Exposure

Study drug administration will be summarized by study part by treatment group and by dosing visits (including missed doses and injection site location). Study drug administration will also be summarized over the entire study for subjects who received inclisiran in both parts of the study.

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 the ITT and Safety Populations. 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 2018). 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. For these analyses the moderate intensity group will include simvastatin 40 mg. A shift table for lipid modifying therapy statin intensity from baseline to Day 720 (EOS) will also be provided. The statin intensity of the last statin taken on or prior to Day 720 (EOS) will be used for the post-baseline statin.

Note that prior and Day 1 summaries will be performed for Part 1 only. Summaries of new or changed or shift analyses will be done for both parts.

6.4.6 Efficacy Analysis

This study is sufficiently powered to show the effect in the primary and key secondary endpoints, all other secondary [redacted] endpoints are supportive hence statistical testing on all other secondary [redacted] endpoints will be performed only if the null hypothesis on primary and the key secondary endpoints are rejected. No adjustment for multiplicity is planned among the other secondary [redacted] endpoints. Note that all testing will be performed for Part 1 of the study only.

Testing of the primary and key secondary efficacy endpoints from Part 1 of the study will be carried out using a fixed sequential testing strategy for multiplicity where the tests will be carried out in the order they are listed below. Each endpoint will be tested using a two-sided alpha of 0.05.

Efficacy data from both parts of the study will be summarized descriptively using actual values and change from baseline (where applicable) using observed cases without imputation.

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

6.4.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from baseline to Day 150 in LDL-C. This endpoint is from Part 1 of the study.

The statistical hypotheses for the primary efficacy endpoint of the percentage change in LDL-C from baseline to Day 150 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 150 = 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 150 < 0.

The primary endpoint 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.

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 150 on each multiply imputed dataset (100 total). The model will include the fixed effect of Part 1 treatment group (inclisiran or placebo) 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. The p-value for testing equal mean percent change from baseline to Day 150 in LDL-C will also be provided.

See Appendix 2 for more details on this analysis.

6.4.6.1.1 Sensitivity Analysis for Primary Efficacy Endpoint

In order to support the robustness of the conclusions drawn from the primary efficacy analysis, we will perform the following sensitivity analyses for data collected during Part 1 of the study.

- 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. Note that this analysis will only use visits up to Day 180 (Part 1 of the study).

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 for each multiply imputed dataset (100 total). The model will include fixed effects for Part 1 treatment (inclisiran or placebo), visit (Days 90, 150, and 180), baseline value, and the interaction between treatment and visit. 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). A linear contrast at Day 150 will be used to compare treatment groups.

Treatment effects at Day 150 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.

- 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 Part 1 treatment (inclisiran or placebo), visit (Days 90, 150, and 180), baseline value, and the interaction between treatment and visit. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured". A linear contrast at Day 150 will be used to compare treatment groups. Refer to Appendix 1 for further details on the MMRM.
- An ANCOVA model without multiple imputation at Day 150 will be performed using the mITT population. The model will include the fixed effect of Part 1 treatment group (inclisiran or placebo) and baseline LDL-C as a covariate.
- A two-sample t-test utilizing observed cases (without imputation) will be performed to compare Part 1 treatment groups (inclisiran or placebo) on the percent change from baseline to Day 150 in LDL-C.
- A Wilcoxon rank-sum test, a nonparametric method, utilizing observed cases (without imputation) will be performed to compare Part 1 treatment groups (inclisiran or placebo) on the percent change from baseline to Day 150 in LDL-C.
- 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 Part 1 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 primary efficacy endpoint becomes statistically insignificant.

6.4.6.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints will not be tested if the primary efficacy endpoint's null hypothesis failed to be rejected. The key secondary efficacy endpoints will be tested in a sequential manner. These endpoints are all from Part 1 of the study.

The key secondary efficacy endpoints of this study include:

- Absolute change in LDL-C from baseline to Day 150.
- Percentage change in Apo-B from baseline to Day 150.
- Percentage change in non-HDL-C from baseline to Day 150.
- Percentage change in total cholesterol from baseline to Day 150.
- Proportion of subjects in each group with ≥ 30% LDL-C reduction from baseline at Day 150.

The following analyses will be performed for the absolute change in LDL-C, percentage change in Apo-B, percentage change in non-HDL-C, and percentage change in total cholesterol from baseline to Day 150.

- An ANCOVA model with the fixed effect of Part 1 treatment group (inclisiran or placebo) and baseline value as a covariate, using the same multiply imputed washout model that was used for the primary efficacy endpoint analysis will be used to compare Part 1 treatments (inclisiran or placebo) at Day 150. (Refer to Appendix 3 for details). This will be the primary analysis for the key secondary efficacy endpoints.
- A control-based pattern-mixture model (PMM), using the same imputed datasets and MMRM model that was used for the primary efficacy endpoint sensitivity analysis will be used to compare Part 1 treatments (inclisiran or placebo) at Day 150. 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 Part 1 treatment (inclisiran or placebo), visit (Days 90, 150, and Day 180), baseline value, and the interaction between treatment and visit. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured". A linear contrast at Day 150 will be used to compare Part 1 treatment groups. This will be a sensitivity analysis for the key secondary efficacy endpoints. Refer to Appendix 1 for further details on the MMRM.

The number and percentage of subjects with greater or equal to 30% LDL-C reduction will be presented at Day 150 by Part 1 treatment group (inclisiran or placebo). Part 1 treatments will be compared using a logistic regression model with treatment as the effect. The odds ratio and 95% confidence intervals for the odds ratio will be provided. The multiply imputed datasets created from both the washout model and the control-based PMM will be utilized in this analysis.

The other secondary efficacy endpoints of this study are:

- Percentage change and absolute change in LDL-C from baseline to each assessment time up to Day 720 (i.e., Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720)
  - A MMRM analysis will be utilized to compare Part 1 treatment groups on percentage change and absolute change in LDL-C until Day 180 utilizing the same model that was used for the primary and key secondary efficacy endpoints. Note that the Day 150 comparisons are already included in the primary and key secondary efficacy analyses. Percentage change and absolute change from baseline in LDL-C will be summarized descriptively over time by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720.
  - Directly measured (using ultracentrifugation) LDL-C results will also be summarized descriptively over time by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by the Part 2 treatment group (inclisiran or placebo/inclisiran) at Day 720.
- Percentage change and absolute change from baseline to Days 90, 150, 180, 330, 510, 690, and 720 in PCSK9
  - A MMRM analysis will be utilized to compare Part 1 treatment groups on percentage change and absolute change in PCSK9 until Day 180 utilizing the same model that was used for the key secondary efficacy endpoint. Percentage change and absolute change from baseline in PCSK9 will also be summarized descriptively over time by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720.
- Percentage change and absolute change from baseline to Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720 in total cholesterol, Apo-B, and non-HDL-C for subjects receiving inclisiran
  - A MMRM analysis will be utilized to compare Part 1 treatment groups on percentage change and absolute change for each endpoint (total cholesterol, Apo-B, and non-HDL-C) until Day 180 utilizing the same model that was used for the key secondary efficacy endpoints. Note that the Day 150 comparisons are already included in the key secondary efficacy analyses. Percentage change and absolute change from baseline in each endpoint will also be summarized descriptively over time by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720.
- Individual responsiveness of subjects 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 Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720 including proportion of subjects in each group who attain global lipid targets for their indication
  - The number and percentage of subjects who reach the various LDL-C levels and who attain global lipid targets (< 70 mg/dL for ASCVD subjects and < 100 mg/dL for ASCVD risk equivalent subjects) will be presented over time and at any time point (separately for each Part) by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720. Part 1 treatments will be compared using the number of subjects who attain global lipid targets at any visit up until Day 180 using a logistic regression model

with Part 1 treatment as the effect. The odds ratio and 95% confidence intervals for the odds ratio will be provided.

- Proportion of subjects in each group with greater or equal to 20% and 30% LDL-C reduction from baseline at Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720
  - The number and percentage of subjects with greater or equal to 20% and 30% LDL-C reductions will be presented over time and at any time point (separately for each Part) by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720. Part 1 treatments will be compared using the number of subjects with greater or equal to 20% or 30% LDL-C reductions at any visit up until Day 180 using a logistic regression model with Part 1 treatment as the effect. The odds ratio and 95% confidence intervals for the odds ratio will be provided. Note that the Day 150 comparison for the ≥ 30% analysis noted here will use observed data (without imputation), the key secondary efficacy analysis.
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 720
  - A MMRM analysis will be utilized to compare Part 1 treatment groups on percentage change and absolute change for each endpoint until Day 180 utilizing the same model that was used for the key secondary efficacy endpoint. Percentage change and absolute change in each endpoint will also be summarized descriptively over time by Part 1 treatment group (inclisiran or placebo) up until Day 180 and then by Part 2 treatment group (inclisiran or placebo/inclisiran) from Day 270 through Day 720.

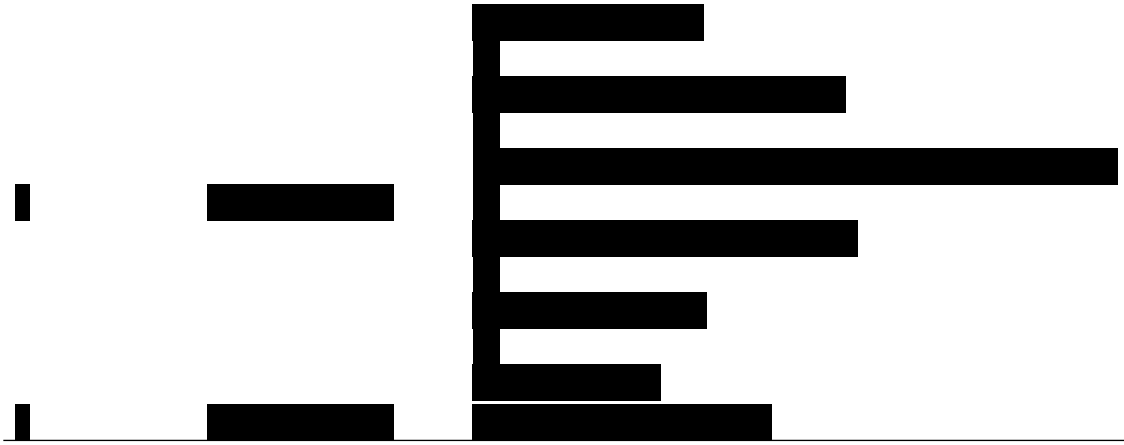
[redacted]

6.4.7 Subgroup Analysis

Analysis of efficacy and safety will also be performed for subgroups of interest include the following. Note that not all variables will be summarized for all subgroups.

Table 6-2 Subgroups for Analysis

Table # [1]		Categories and comments
1	Baseline LDL-C	≤ vs > median
2	Baseline PCSK9	≤ vs > median
3	Sex	Male vs Female
4	Age group	≤ vs > median
5	Race	White vs Asian
6	Region	Europe (Israel/Russia/Serbia/Ukraine) vs Non-Europe (Hong Kong/South Africa/Taiwan/Turkey)
7	Apheresis	Yes vs no



[1] Numbers provide the order that the subgroups will be presented.

* Subgroups with small number of patients will be combined for analysis purpose.

Baseline variables to be analyzed by subgroup (1 - Baseline LDL-C and 2 - Baseline PCSK9):

Disposition
Demographics and Baseline Characteristics
Day 1 Lipid Modifying Therapy Usage
New or Changed Lipid Modifying Therapy Usage

Efficacy variables to be analyzed by subgroup (1 – 9):

Primary: Percentage change in LDL-C from baseline to Day 150 – ANCOVA – Washout Imputation
Key Secondary: Absolute change in LDL-C from baseline to Day 150 – ANCOVA – Washout Imputation
Key Secondary: Percentage change in Apo-B from baseline to Day 150 – ANCOVA – Washout Imputation
Key Secondary: Percentage change in non-HDL-C from baseline to Day 150 – ANCOVA – Washout Imputation
Key Secondary: Percentage change in total cholesterol from baseline to Day 150 – ANCOVA – Washout Imputation
Other Secondary: Percentage change and absolute change in PCSK9 from baseline to Day 150 - MMRM

6.4.8 Safety Analysis

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

Safety variables will be summarized by study part (note that a select set of AE tables will be created that summarize AE data over both parts of the study for subjects who received inclisiran the entire study (in both Parts 1 and 2). Data captured during Part 1 (up to and including the Day 180 visit) will be presented by Part 1 treatment group (inclisiran or placebo). Data captured during Part 2 (after the Day 180 visit date) will be presented by Part 2 treatment group (inclisiran or placebo/inclisiran).

6.4.8.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (v21.1) 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 by study part:

- Overall Summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by PT
- Common (2 or more subjects with an AE 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

The following summary tables will also be presented for subjects who received inclisiran the entire study (in both Parts 1 and 2):

- TEAEs by SOC and PT
- Related TEAEs by SOC, PT, and Severity
- Treatment Emergent Serious AEs (TESAEs) by SOC and PT
- TEAEs Leading to Withdrawal of Study Treatment 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 or more subjects with an AE 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) 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 during Part 1 of the study. 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.

Additional Analysis of Adverse Events for ClinicalTrials.gov and EudraCT:

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than 2% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

6.4.8.2 Laboratory Tests

Laboratory values will be summarized by treatment group in each study part, 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 $\leq 5.6\%$, $\geq 5.7\%$ to $\leq 6.4\%$, and $\geq 6.5\%$.

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 in each study part. 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 ≤ 3 x ULN at baseline and > 1 and ≤ 3 x 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 ≤ 3 x ULN at baseline or post baseline and becoming > 3 x ULN post baseline
- Final visit:
  - Non HbA1c: > 1 and ≤ 3 x 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 ≤ 3 x ULN at a post baseline visit and remains > 1 and ≤ 3 x 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 ≤ 3 x 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 in each study part 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. A second summary will be presented that includes all subjects who meet all of the criteria listed above at the same time point without regard to the baseline lab parameter results.

6.4.8.3 Diabetes Assessment

Diabetes will be assessed in each study part 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%
	Impaireda	≥ 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.

Diabetic TEAEs identified by the SMQ search (see Appendix 5), or

Post-baseline fasting glucose ≥ 126 mg/dL on two consecutive occasions, or

Initiation of anti-diabetic medication at any time post-baseline, or

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 during Part 1 of the study. 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 in each study part.

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 in each study part 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 in each study part.

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 item was changed between the Protocol Amendment 1 and current SAP:

- the time biological samples are stored after the end of the study was extended from 1 year to 15 years.

9 REFERENCES

Hochberg Y (1988) A sharper Bonferroni procedure for multiple tests of significance. Biometrika.;75:800-2.Protocol MDCO-PCS-17-08 Amendment 2

Ratitch B, O'Kelly M (2011) Imputation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, PharmaSUG2011 - Paper SP04.

Rubin, D.B. (1987) Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.

10 APPENDICES

10.1 Appendix 1: Details of MMRM Used for Efficacy Analyses

A number of Part 1 efficacy analyses will utilize a mixed-effects model for repeated measures (MMRM). The models will generally include fixed effects for treatment, visit, baseline value, and the interaction between treatment and visit. The visits will include Days 90, 150, and 180, with Day 150 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;
  Model percent_change = treatment|visit_day base_value/DDFM=KR;
repeated visit_day/type=UN subject=subject_id;
LSMeans treatment*visit_day/cl pdiff=control('0' '150');
run;

(where ('0' '150') is the value of the placebo ['0'] at day 150
['150'] in interaction term treatment*visit_day)
```

10.2 Appendix 2: Multiple Imputation Washout Model

A multiple imputation washout model will be utilized for the Part 1 primary efficacy analysis of the percentage change in LDL-C from baseline to Day 150 endpoint. Note that this model will also be used for the key secondary efficacy endpoints also. 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 150 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.

For the subjects in the inclisiran group who received 2 doses (Day 1 and Day 90) and have data present at Day 180 (considered to have completed Part 1 of the study) the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MAR:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 150 from the inclisiran group (continuous)

For the remaining subjects in the inclisiran group the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MNAR:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 150 from the placebo group (continuous)

For the placebo group the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MAR:

- 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 180 (continuous)

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 through Day 180 for the placebo treatment group. These datasets will be utilized in Step #4.

3. Subjects in the inclisiran group who received 2 doses of study medication, have the Day 150 value missing, and have evaluable data at Day 180 will be included in this step. Missing values at Day 150 will be imputed assuming data are MAR. Only subjects in the inclisiran group will be included in this step. Observed Baseline and Day 150 data will be utilized to impute missing Day 150 data utilizing SAS PROC MI. This will be performed 100 times to create 100 datasets that are fully imputed at Day 150.
4. The remaining missing values at Day 150 in the inclisiran group will be imputed in this step. Note that the subjects with imputed inclisiran Day 150 data from Step #3 will not be utilized 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 150. 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.
5. The imputed data from Step #3 will be combined with the imputed data from Step #4 to create 100 fully imputed datasets.
6. 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.
7. 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.
8. These 100 datasets will be analyzed using ANCOVA models with fixed effect of treatment group and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to Day 150 primary efficacy endpoint.
9. 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. The p-value will also be provided.

10.3 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 during Part 1 of 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 (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 180 (continuous)

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 primary efficacy endpoint and key secondary efficacy endpoint.

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. The p-value will also be provided.

10.4 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.

10.5 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)

[redacted]

10.6 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