Official Title: Two Part (Double-blind Inclisiran Versus Placebo [Year 1] Followed by Open-label Inclisiran [Year 2]) Randomized Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Inclisiran in Adolescents (12 to Less Than 18 Years) With Heterozygous Familial Hypercholesterolemia and Elevated LDL-cholesterol (ORION-16)

NCT Number: NCT04652726

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Appendix 16.1.9 Documentation of statistical methods

History of changes	
Version	**Summary of changes**
1.0	Original version

1 Statistical methods

The planned statistical analysis is described in Section 12 of the clinical study protocol. The most recent version of Statistical Analysis Plan (SAP) is included below.

Two post-hoc analyses were conducted:

1. After Part 1/Year 1 DBL, percentage change in PCSK9 from baseline to Day 330 using ANCOVA with treatment as fixed effect and baseline PCSK9 and baseline age group as covariates, was added, as only descriptive summary statistics of PCSK9 by treatment and visit had been specified in the SAP before the Part 1/Year 1 DBL.

NOVARTIS

Clinical Development

KJX839/inclisiran

CKJX839C12301

Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-16)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
05-Oct-2020	Prior to DB lock	Creation of final version	N/A - First version	NA

[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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[redacted]				

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
[redacted]				

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List of abbreviations

ADA	Anti-drug antibodies
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
[redacted]	[redacted]
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FH	Familial Hypercholesterolemia
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LFT(s)	Liver function test(s)
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein (a)
MMRM	Mixed-effect model for repeated measures
OAS	Open-label Phase Analysis Set
PCSK9	Proprotein convertase subtilisin/kexin type 9
PT	Preferred term
s.c.	Subcutaneous
SAE	Serious adverse event
SAF	Safety set

SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCR	Screened set
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell(s)

1 Introduction

This document contains details of the statistical methods that will be used in the Phase 3 clinical trial CKJX839C12301 (ORION-16). The purpose of this Phase 3 study is to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (aged 12 to <18 years) with heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-cholesterol (LDL-C). The use of inclisiran (as an adjunct to stable, optimal background lipid-lowering therapy) for the treatment of HeFH in adolescent patients who require additional lipid lowering will be investigated to obtain needed pediatric information on inclisiran. Percentage change in LDL-C from baseline to Day 330 (Year 1) is the primary endpoint of this study.

The analysis plan has been prepared based on the ORION-16 study protocol version V02 (protocol amendment 2), content final dated 17-Feb-2023.

Important information is given in the following sections and details are provided, as applicable, in Section 5.

1.1 Study design

This study is a two-part (double-blind, placebo-controlled / open-label) multicenter study in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C (>130 mg/dL / 3.4 mmol/L) on stable, individualized, optimal SoC background lipid-lowering therapy (including maximally tolerated statin treatment). The overall study duration is 748 days.

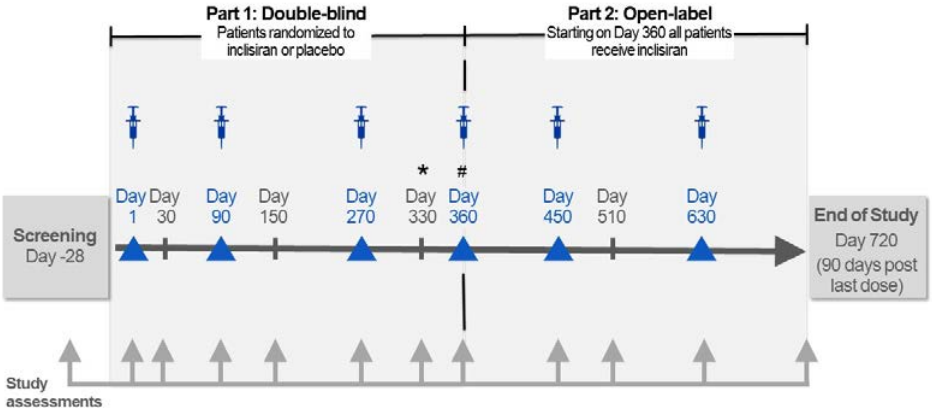
Following an approximately 4 weeks screening/run-in period, the study has two sequential parts (Figure 1-1).

- **Part 1 (Year 1):** 12 months double-blind, parallel group period in which participants will be randomized to receive either inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) s.c. or placebo (given at Days 1, 90 and 270).
- **Part 2 (Year 2):** 12 months single arm, open-label follow-up period with all participants receiving inclisiran sodium 300 mg s.c. Participants randomized to placebo in Part 1 will receive inclisiran starting on Day 360 (“Switch” Day 360). Participants randomized to inclisiran in Part 1 will receive placebo on Day 360. This dose of inclisiran/placebo on Day 360 will remain blinded in order to maintain the blind for Part 1 of the study. All participants will receive subsequent doses of open-label inclisiran on Days 450 and 630.

A minimum of 102 participants (actual enrolled number of participants: 141), who meet the inclusion/exclusion criteria were to be randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg s.c. or placebo on Day 1 (baseline). Detailed information regarding sample size calculation is provided in Section 3.

Randomization was stratified by age group (≥12 to <15 years and ≥15 to <18 years) to include a minimum of 40 participants in each of the two age strata.

Figure 1-1 Study design



* Primary endpoint assessed at Day 330. # "Switch Day": Participants randomized to placebo in Part 1 will start to receive inclisiran on Day 360. Participants randomized to inclisiran in Part 1 will receive placebo on Day 360 only to maintain the blind for Part 1.

The primary endpoint will be measured at Day 330.

1.2 Study objectives and endpoints

Section 2 of the study protocol lists the following primary, secondary, [redacted]

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective is to demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C	• Percentage change in LDL-C from baseline to Day 330 (Year 1)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [time-adjusted percent change] over Year 1	• Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1)

Objective(s)	Endpoint(s)
• Demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [absolute change] at Day 330 (Year 1)	• Absolute change in LDL-C from baseline to Day 330 (Year 1)
• Demonstrate superiority of inclisiran compared to placebo in reducing Apo B, lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C), and total cholesterol [percent change] at Day 330 (Year 1)	• Percent change in Apo B, Lp(a), non-HDL-C, and total cholesterol from baseline to Day 330 (Year 1)
• Evaluate the effect of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and PCSK9 over time	• Percent change and absolute change in LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo A1) and PCSK9 from baseline to each assessment time up to Day 720 (Year 2)
• Evaluate the safety and tolerability profile of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HeFH	• Incidence, severity and relationship to study drug of treatment-emergent AEs and SAEs; vital signs; laboratory parameters; anti-drug antibodies (ADA) measurement; growth (height, weight, BMI); pubertal development (steroid hormones and Tanner staging)

[redacted]

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis. The most recent version of SAS available in the statistical programming environment of Novartis will be used for the analysis.

Part 1 data are defined as all data collected starting from the screening visit up to the day 360 visit date prior to dosing on this day/date. Part 1 data will be presented by two separate groups (inclisiran and placebo). The total column will be presented in all outputs of Part 1 as needed and will be specified in TFL shell document.

Part 2 data analysis will include all data collected starting from after dosing on day 360. Part 2 data will be presented in two separate groups, (1) inclisiran since Day 1 and (2) placebo-to-inclisiran, unless otherwise specified. The column labels for these two groups will be inclisiran-inclisiran and placebo-inclisiran. The total column will be presented in all outputs of Part 2 as needed and will be specified in TFL shell document.

For instances, where it will not be possible to distinguish whether data belong to Part 1 or Part 2, based on the dosing time on the day 360 visit, all data collected from screening up to the day 360 visit will be considered as Part 1 data and all data captured after the day 360 visit (starting from day 360 visit + 1 day) will be considered as Part 2.

Part 1 data analysis will be performed after all participants completed the day 360 visit (Part 1) or discontinued the study prior to the Day 360 visit. For each participant, data collected in the database till the end of study Part 1 (up-to Day 360 visit as mentioned above) will be included in this analysis. Hence the Day 360 visit of a participant will serve as data cut-off date for that participant. All events with start date before or on the cut-off date and for which the end date has not been reached yet or they are ongoing at final visit will be reported as ‘ongoing’. The same rule will be applied to events starting before or on the cut-off date and not having a documented end date. The assessment of study primary objective and key secondary objectives will be based on this analysis.

Part 2 data analysis will be conducted after all participants either completed the study or discontinued early.

Both Part 1 and Part 2 analyses will be reported in the CSR. For summary of the analyses that will be performed for Part 1 analysis and Part 2 analysis see Appendix 5.3.

Detailed information regarding DMC analysis will be provided in the DMC charter and a separate DMC SAP/TFL shells.

2.1.1 General definitions

Study day

Study day will be defined as the number of days since the date of first dose of double-blind treatment. The date of first dose of double-blind treatment will be defined as Day 1 and the day before the first dose of study drug will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

For dates on or after the first date of double-blind treatment,

Study day = Assessment date – Date of first dose of double-blind treatment + 1;

For dates prior to the first date of double-blind treatment,

Study day = Assessment date – Date of first dose of double-blind treatment.

In case, participant has been randomized but has not received double-blind treatment then randomization visit day will be considered as Day 1.

Baseline definition

In general, for both Part 1 and Part 2, baseline value is defined as the last measurement collected on or prior to the first dose of double-blind treatment.

Post-baseline measurement

Post-baseline values are defined as those measurements that were collected after the first dose of double-blind treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Absolute change from baseline = post-baseline value – baseline value.

Percent change from baseline = (post-baseline value – baseline value) / baseline value*100.

Reflexive LDL-C

The endpoints involving LDL-C will use a reflexive LDL-C approach. The calculated LDL-C will be utilized unless triglycerides are greater than 400 mg/dL and/or calculated LDL-C is less than 40 mg/dL, in which case beta quantification LDL-C (i.e., LDL_C directly measured by ultracentrifugation) will be additionally performed and used for the analysis.

VLDL-C

The endpoints involving VLDL-C will follow the same approach as reflexive LDL-C.

Re-derivation of age-strata for mis-stratified participants

If any subject will be mis-stratified for age-group during randomization, collected age of that participant will be used to re-derive the correct age-strata at analysis level and will be used for all analyses, as needed.

Discontinuation visit mapping

For patients who discontinued from the study and come to site for an early exit (EE) visit, the EE visit will be mapped to the next scheduled visit. The mapping details can be found as below:

Table 2-1 Visit mapping

Status	Last attended scheduled visit prior to EE		Mapped visit for EE	
Visit day	**Visit name**	**Visit day**	**Visit name**	**Visit day**
Discontinued (Early exit)	1	Day 1	90	Day 90
Discontinued (Early exit)	90	Day 90	150	Day 150
Discontinued (Early exit)	150	Day 150	270	Day 270
Discontinued (Early exit)	270	Day 270	330	Day 330
Discontinued (Early exit)	330	Day 330	360	Day 360
Discontinued (Early exit)	360	Day 360	450	Day 450
Discontinued (Early exit)	450	Day 450	510	Day 510
Discontinued (Early exit)	510	Day 510	630	Day 630
Discontinued (Early exit)	630	Day 630	720	Day 720
Completed			720	Fay 720

2.2 Analysis sets

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

The Randomized Set (RAN) consists of all participants who received a randomization number, regardless of whether double blind treatment received or not.

The Full Analysis Set (FAS) consists of all randomized participants with the exception of those mis-randomized participants who did not receive study drug. Mis-randomized participants are defined as not qualified for randomization and were inadvertently randomized into the study. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. The FAS will be used in analyses for the primary, secondary, [redacted] objectives in Part 1.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received. This will be the primary population for the safety analyses in Part 1.

Note that the Safety Set allows the inclusion of non-randomized participants who receive double-blind treatment in error.

The Open-label Phase Analysis Set (OAS) includes all participants who entered study Part 2 and received at least one dose of study drug in Part 2. The OAS will be used to analyze the data from participants who entered Part 2.

Note that in Part 1 the number of participants in FAS equals the number of participants in SAF, so only one open-label phase analysis set is defined for Part 2.

[redacted]

2.2.1 Subgroup of interest

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

Table 2-2 Sub-group for efficacy analysis

Number	Subgroup	Categories			
1	Gender	Male	Female		
2	Age-group	≥ 12 - < 15	≥ 15 - < 18		
3	Race	White	Black	Asian	Other
4	Ethnicity	Hispanic or latino	Not Hispanic or latino	Other**	
5	Body mass index	<= median	> median		
6	Study center region*	North America	Europe	Other	
7	Baseline statin use	Yes	No		
8	Baseline LDL-C	<= median	> median		
9	Baseline PCSK9	<= median	> median		

*Region:

North America: Canada, United States;
Europe: Czech Republic, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Russian Federation, Slovakia, Slovenia, Spain, Switzerland, Israel, Turkey, United Kingdom;
Other: Taiwan, South Africa, Malaysia, Lebanon, Jordan, Brazil, Argentina.
**Other: Not reported and Unknown

Subgroup analyses of all treatment emergent adverse events (TEAE) including TEAE at injection site will be displayed by treatment, SOC, and PT. The number (and percentage) of

participants with TEAEs will be provided for each category of sub-group. The following sub-group analyses will be performed on Safety Set.

Table 2-3 Sub-group for safety analysis

Number	Subgroup	Categories			
1	Gender	Male	Female		
2	Age-group	≥ 12 - < 15	≥ 15 - < 18		
3	Race	White	Black	Asian	Other
4	Body mass index	<= median	> median		

2.3 Disposition, demographics and other baseline characteristics

2.3.1 Disposition

The overall number of participants who entered, completed, and discontinued the study will be summarized and listed, including the reasons for discontinuation for each period: screening, Study Part 1, Study Part 2. The screening disposition will be based on SCR. The RAN will be used for the summary and listing of patient disposition for Study Part 1 and 2.

The number of participants in the FAS will be summarized by country, center, and treatment group for Part 1 analysis.

Number of participants with protocol deviations will be tabulated by category (e.g., selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other), deviation and Part. Listing of participants with protocol deviation will be provided.

The number of participants included in each analysis set will be tabulated using SCR.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including age, race, gender, ethnicity, country, region (North America, Europe, Other), baseline characteristics such as body height, weight, BMI, waist circumference, smoking status, number of pack years, alcohol history; baseline disease characteristics including HeFH underlying genetic mutation(s), LDL-C, TC (total cholesterol), TG (triglycerides), PCSK9, baseline use of statins or other lipid-modifying therapies (yes, no), status of statin intolerance, baseline diabetes status as determined by fasting plasma glucose and HbA_{1C}, baseline kidney function based on eGFR, baseline measurements of SBP, DBP, and pulse, will be summarized descriptively by treatment group. Listings will also be provided.

Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, non-missing observations, mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum will be presented. For Part 1 analysis, these data will be summarized using RAN.

No inferential statistics will be provided for baseline comparability among the treatment groups.

2.3.3 Medical history/current medical condition

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. Medical history/conditions will be summarized by primary system organ class, preferred term, and treatment group. Pre-specified solicited events selected Familial Hypercholesterolemia History and other targeted family history will be summarized separately by treatment.

For Part 1 analysis, this data will be summarized using RAN.

2.4 Treatments (study treatment, prior and concomitant therapies)

In general, all summaries of treatments of Part 1 will be performed on the SAF, and All summaries of treatments of Part 2 will be performed on the OAS.

2.4.1 Study treatment

The number of study doses administered, duration on study, duration of exposure, patient year of exposure will be summarized by treatment group and Part. The analysis of exposure will also be provided for overall i.e., Part 1 and 2 data combined. Listings will be provided.

The number of participants dosed, and the injection site location will also be summarized by study visit and treatment group.

Duration of exposure will be calculated as: minimum of (Date of last dose of treatment – Date of first dose of treatment + 180 + 1, Date of last known visit – Date of first dose of treatment + 1). For Part 1 data analysis, duration of exposure will be truncated at data cut-off date.

Patient-year of exposure will be calculated as duration of exposure/365.25.

Duration on study is defined as: date of last known visit on study – date of first dose of treatment + 1. For Part 1 data analysis, duration on study will be truncated at data cut-off date.

The patients who will discontinue the treatment prematurely before discontinuing the treatment period will be summarized by treatment group and Part, including the reason of treatment discontinuation. Listing will also be provided.

2.4.2 Prior and concomitant therapies

Prior (pre-baseline) therapies are defined as any medication that was stopped ≥1 day before the first dose date of study medication. They will be summarized by treatment group.

Concomitant therapies (any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit, including those which were started pre-baseline and continued into the period when study treatment is administered) will be summarized by treatment group and Part. Listings will be provided.

Lipid-modifying therapy (LMT) use, [redacted] will be summarized separately at screening and at the baseline/Randomization visit (Day 1) by treatment group using the following categories:

- Any LMT

- No LMT
- Statins
- Statins only
- Other LMT
- Other LMT only
- Ezetimibe
- Ezetimibe only
- [redacted]

New or changed lipid-modifying therapy, [redacted] after baseline will be summarized by treatment group and Part.

Significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and preferred term, by treatment group and Part. Significant non-drug therapies will be summarized similarly by primary system organ class, preferred term, treatment group and Part.

2.5 Analysis of the primary objective

The primary objective is to demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C.

2.5.1 Primary endpoint

The primary endpoint, i.e., primary analysis variable, is the percentage change in LDL-C from the baseline measurement to the Day 330 visit.

The primary clinical question of interest is: What is the effect of the test treatment versus placebo on change in LDL-C after 330 days of treatment in adolescents with HeFH and elevated LDL-C who are on stable, optimal standard of care (SoC) lipid-lowering therapy, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid-lowering therapy.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of changes in additional medication(s) used for HeFH, if they occur, as would be the case in clinical practice.

The primary estimand is described by the following attributes:

1. **Population**: Adolescents with the HeFH condition of interest and elevated LDL-C on stable optimal SoC lipid-lowering therapy. Further details about the population are provided in Section 5 of the study protocol.
2. **Endpoint**: Percentage change in LDL-C from baseline to Day 330 (Year 1)
3. **Treatment of interest**: The randomized treatment (the investigational treatment inclisiran or the control treatment placebo) as add-on to optimal SoC lipid-lowering therapy for HeFH.

The type and dose of the concomitant lipid-lowering therapy for HeFH must remain stable during Part 1 (Year 1) of the study. Further details about the investigational treatment and control treatment are provided in Section 6 of the study protocol. Data collected regardless of treatment discontinuation for any reason, regardless of unforeseen change in the concomitant lipid-lowering therapy will be used for analysis [Treatment policy].

4. **The summary measure**: difference between treatments in mean percentage change from baseline to Day 330.

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypotheses that will be tested are as follows:

- H0: The difference between inclisiran and placebo in the least squares mean percentage change from baseline to the Day 330 visit in LDL-C= 0
- Ha: The difference (inclisiran minus placebo) between participants treated with inclisiran and placebo in the least squares mean percentage change from baseline to the Day 330 visit in LDL-C < 0

The primary objective will be achieved if the null hypothesis is rejected at significance level of 0.025 (One-sided test).

The primary analysis will use an analysis of covariance (ANCOVA) model. Due to probable heterogeneity of variances between treatment groups, ANCOVA model which assumes unequal variances for treatment group will be used. The model will include the fixed effects of treatment group and baseline age group (≥12-<15 or ≥15-<18 years of age), with baseline LDL-C as a covariate. Multiple imputation will be used to impute missing data using a washout model specified in Section 5.7.1. A total of 100 imputed datasets will be created. The ANCOVA model will be fit to each imputed dataset, and results will be combined using Rubin's combination rules. The estimate and corresponding 2-sided 95% confidence intervals of mean difference between treatment groups will be calculated. P-value for hypothesis test for mean difference will also be provided. The FAS will be used for this analysis.

2.5.3 Handling of remaining intercurrent events of primary estimand

No remaining inter-current events are expected.

2.5.4 Handling of missing values not related to intercurrent event

Other missing data are expected to be intermittent missing data and will be assumed to be missing at random. Imputation details for data missing at random in the washout model has been provided in Section 5.7.1.

2.5.5 Sensitivity analyses for primary endpoint/estimand

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

- Linear mixed-effect model for repeated measures (MMRM) analysis without multiple imputation
- MMRM analysis on the imputed datasets, and multiple imputation will be based on a control-based pattern mixture model
- ANCOVA using the washout model including the following fixed effects: baseline concomitant lipid-modifying therapies, baseline age group, region, and a treatment-by-region interaction.

Due to the limited sample size of some countries, pooled regions will be used as the fixed effect for ANCOVA model. Analyses using the MMRM will include fixed effects for treatment, baseline age group (≥12-<15 or ≥15-<18 years of age), visits, interaction between treatment and visits, baseline LDL-C. Day 90, 150, 270, 330 and 360 will be included as visit. The Restricted Maximum Likelihood (REML) estimation approach will be used with covariance structure set as "Unstructured". If the model does not converge with unstructured covariance matrix, the compound symmetry covariance matrix will be used in the mixed model.

The control-based pattern mixture model, as specified in Section 5.7.2, will be used to further explore the possibility of missing data being missing not at random. This approach will utilize placebo data for monotone missing inclisiran treatment data. Same MMRM as specified above will be used on analyze the imputed datasets.

2.5.6 Supplementary analysis

Supplementary analyses of LDL-C percent change from baseline to Day 330 will be performed in subgroups as specified in Section 2.2.1. The MMRM model (using control-based pattern mixture model for missing value imputation) will be used to evaluate the difference between inclisiran and placebo groups in each subgroup. Forest plot will be provided for sub-group analyses.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoints

The following are key secondary efficacy endpoints:

- Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1), defined as the average of percent changes from baseline to day 150, 270, and 330.
- Absolute change in LDL-C from baseline to Day 330 (Year 1)
- Percent change in Apo B from baseline to Day 330 (Year 1)
- Percent change in Lp(a) from baseline to Day 330 (Year 1)
- Percent change in non-HDL-C from baseline to Day 330 (Year 1)
- Percent change in total cholesterol from baseline to Day 330 (Year 1)

Secondary estimands corresponding to key secondary efficacy endpoints are defined similarly to the primary estimand. These endpoints, and the corresponding summary measures, are listed

below. Population, treatment of interest, endpoints, and intercurrent events are defined similarly as for the primary estimand.

- Endpoint: time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1). Summary measure: difference between treatment groups in mean time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1).
- Endpoint: absolute change in LDL-C from baseline to Day 330 (Year 1). Summary measure: difference between treatment groups in mean absolute change in LDL-C from baseline to Day 330 (Year 1).
- Endpoint: percent change in Apo B from baseline to Day 330 (Year 1). Summary measure: difference between treatment groups in mean percent change in Apo B from baseline to Day 330 (Year 1).
- Endpoint: percent change in Lp(a) from baseline to Day 330 (Year 1). Summary measure: difference between treatment groups in mean percent change in Lp(a) from baseline to Day 330 (Year 1).
- Endpoint: percent change in non-HDL-C from baseline to Day 330 (Year 1). Summary measure: difference between treatment groups in mean percent change in non-HDL-C from baseline to Day 330 (Year 1).
- Endpoint: percent change in total cholesterol from baseline to Day 330 (Year 1). Summary measure: difference between treatment groups in mean percent change in total cholesterol from baseline to Day 330 (Year 1).

2.6.2 Statistical hypothesis, model, and method of analysis

The key secondary endpoints will be analyzed using the same ANCOVA with multiple imputation using wash-out model as mentioned for primary endpoint except the time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330. In the model baseline LDL-C will be replaced by baseline of respective endpoint. The estimate and corresponding 2-sided 95% confidence intervals of mean difference between treatment groups will be calculated. P-value for hypothesis test for mean difference will also be provided.

The time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 will be estimated using MMRM model. MMRM analysis (using control-based pattern mixture model for missing value imputation) will be performed on the percentage change in LDL-C from baseline over visits (Day 150, 270, 330) as specified for primary endpoint on each of the 100 imputed dataset. Then, linear combinations of the estimated means from visits Day 150, 270 and 330 will be used to compare treatment effects in terms of time-adjusted percent change in LDL-C. Treatment effects from these 100 MMRM analyses will then be combined using Rubin's Method. The estimate and corresponding 2-sided 95% confidence intervals of mean difference between treatment groups will be calculated. P-value for hypothesis test for mean difference will also be provided.

2.6.3 Multiplicity adjustment

A hierarchical testing strategy will be applied to control the family-wise type I error rate at the one-sided significance level of alpha=0.025 to assess superiority of inclisiran over placebo.

Hypotheses associated with the key secondary endpoints will be tested in the order listed above in Section 2.6.1.

2.6.4 Sensitivity analyses

MMRM analysis using control-based pattern mixture model for missing value imputation will be performed for key secondary endpoints (except the time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330) as specified for primary endpoint in Section 2.5.5. In model corresponding baseline value will be used instead of baseline LDL-C.

For the time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, mixed model for repeated measurements (MMRM) analysis without multiple imputation, that assumes missing data are MAR, will be performed. The model will be same as MMRM model mentioned in Section 2.6.2. A linear combination of the estimated means from visits Day 150, 270 and 330 will be used to compare treatment groups.

2.6.5 Supplementary analyses

Supplementary analyses of key secondary endpoints will be performed in subgroups as specified in Section 2.2.1. The MMRM model (using control-based pattern mixture model for missing value imputation) will be used to evaluate the difference between inclisiran and placebo groups in each subgroup.

Another supplementary analysis for Lp(a) will be applied in log-transformed scale using same MMRM without multiple imputation specified above.

2.7 Analysis of other secondary efficacy objective(s)

Other secondary efficacy endpoints include the percent change and absolute change from baseline throughout the time course up to Day 720 (Year 2) in the following:

- LDL-C
- Apo B
- Lp(a)
- non-HDL-C
- total cholesterol
- triglycerides
- HDL-C
- VLDL-C
- Apo A1
- PCSK9

Descriptive summaries by treatment group and Part and Line-Plot displaying mean will be provided by treatment group and Part for all above endpoints. The overall (Part 1 and Part 2 combined) descriptive summaries and Line-Plot of LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol and PCSK9 will additionally be provided.

Listings of all the above endpoints for all the available visits, including time-adjusted percent change in LDL-C will be provided. In addition, the absolute change in LDL-C and percent change in LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol and PCSK9 from baseline to Day 720 (Year 2) will be provided.

2.8 Safety analyses

In general, for Part 1 safety analyses, the SAF will be used; for Part 2 safety analysis, the OAS will be used.

Safety summaries will include only treatment emergent adverse events (TEAEs) by Part. For Part 1, TEAEs are defined as adverse events (AEs) starting on or after the first dose of double-blind treatment or AEs that were present prior to start of double-blind treatment but increased in severity in Part 1. For Part 2, TEAEs are defined as AEs starting after the Day 360 dosing time or AEs that were present prior to the Day 360 dosing time but increased in severity in Part 2. For Part 1, if the AE start date is the same as the date of the first dose of double-blind treatment but the time is not available for comparison, the AE will be considered as treatment emergent; for Part 2 if the AE start date is the same as the date of the Day 360 treatment but the time is not available for comparison, the AE will be considered as treatment emergent.

Vital signs values that have complete data and time values will be assigned to pre- or post-dose assessment (as per protocol) based on the actual date/time. For values with missing date/time, the scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for visit/time point summary.

2.8.1 Adverse events (AEs)

The number (and percentage) of participants with TEAEs will be summarized by Part in the following ways:

- Overall summary.
- By treatment, primary system organ class (SOC) and preferred term (PT).
- By treatment and PT.
- By treatment and PT for most common TEAEs (For Part 1: occurring in >= 3% of participants in total; for Part 2: threshold to be determined before final database lock).
- By treatment, SOC, PT and maximum severity.
- By treatment, SOC and PT for TEAEs leading to study drug discontinuation.
- By treatment, SOC and PT for TEAEs related to study drug.

The number (and percentage) of participants with treatment emergent serious adverse events (TESAEs) will be summarized by Part, in the following ways:

- By treatment, SOC and PT.
- By treatment and PT.
- By treatment, SOC and PT for TESAEs related to study drug.

Unless otherwise specified, SOCs will be sorted alphabetically and, within each SOC, the PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one AE with the same PT, the AE will be counted only once. A participant with multiple AEs within a SOC is only counted once towards the total of the SOC. In case of summary by severity or relationship to study drug, summary will be done using the most severe or related occurrence respectively. Listing of all AEs and SAEs will be provided.

AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than X% (X will be selected prior to final database lock) and on TESAEs and TESAEs 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 AEs 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.

These summaries will be provided after full study completion.

Injection site reactions

The number and percentage of participants who reported injection site reaction TEAEs will be summarized in the following ways:

- SOC, PT, treatment group and Part.
- SOC, PT, severity, treatment group and Part.

Listing will be provided for participants with injection site reactions.

The time to the first injection site reaction will also be summarized by treatment and Part using the following categories: ≤4h, 4h to ≤12h, >12h. The time (hours) to the event will be calculated from the most recent administration of study drug. The duration of the first and the longest injection site reaction will be summarized by treatment and Part using descriptive statistics. The outcome of the first and the longest injection site reaction will be summarized using the following categories: Resolved (≤4h, >4h to ≤7 days, >7 days to ≤14 days, >14 days), not resolved and unknown. The total number of injection site reactions per participant will be summarized in categories (e.g., 1, 2, 3, and >3 etc.). Symptoms of injection site reactions will be summarized by treatment group and Part.

Other safety topics

The number and percentage of participants who reported TEAEs of other safety topics will be summarized by PT, treatment group and Part. PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one AE with the same PT, the AE will be counted only once. If a participant reported more than one AE within the same safety topic, the participant will be counted only once at that safety topic. Listing of participants with AEs of other safety topics will be provided.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of other safety topics.

AEs of other safety topics will include the following:

- Hepatic events
- Renal events
- Hypersensitivity events
- Neurological events
- Psychiatric events
- Musculoskeletal events
- Cardiac events
- New onset diabetes and worsening of glycemic control

For search criteria of AE of other safety topics, refer to Appendix 5.4.

For detailed analysis of new onset diabetes and worsening of glycemic control, please see Section 2.8.4.

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

The percentage of participants with abnormal ECG findings reported as AEs will be summarized by treatment group and Part.

2.8.2 Deaths

Summary for deaths will be provided by SOC and PT of cause of death, treatment group, and Part. Listing of all deaths will be provided.

2.8.3 Laboratory data

Laboratory data consist of hematology, biochemistry, sexual hormones, urinalysis measurements and ADA (see Section 2.8.6) . Absolute values and change from baseline will be summarized for continuous laboratory parameters by visit and box plots will also be provided by visit. Frequency table of results for categorical laboratory parameters will be presented by visit. This analysis will be performed by treatment group and Part.

Shift tables using the low, normal, high/low, or high classification (except for eGFR and HbA_{1c} where the categories outlined below will be applied) will be used to compare baseline to the worst on-treatment value by treatment group and Part. All data collected after first dose of

double-blind treatment, from scheduled, unscheduled, and premature discontinuation visits in each part will be used to determine the worst on-treatment value.

The following categories will be used for eGFR and HbA1c:

- For eGFR, the categories will be <30 mL/min/1.73m^2; ≥ 30 to <60 mL/min/1.73m^2; ≥ 60 to <90 mL/min/1.73m^2; and ≥90 mL/min/1.73m^2.
- For HbA_{1c}, the categories will be <5.7%; ≥5.7% to <6.5%; and ≥6.5%.

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

For selected laboratory tests, the number and percentage of patients meeting the clinically notable criteria at any time, considering all data collected after first dose of double-blind treatment, from scheduled, unscheduled, and premature discontinuation visits, will be summarized by laboratory parameter and treatment group and Part. The worst post-baseline value will be used for this analysis. Notable criteria are defined in Appendix 5.5. Clinically notable criteria will be considered met when both of the following occur:

- Post-baseline value meets the clinically notable criteria.
- Baseline value does not meet the clinically notable criteria.

Furthermore, the number and percentage of participants meeting notable criteria in liver function tests (LFT) will be summarized by treatment and Part considering on-treatment data from scheduled, unscheduled, and premature discontinuation visit. LFT criteria are defined in Appendix 5.5.

The baseline value is the last value prior to the first dose of double-blind treatment.

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

2.8.4 Diabetes assessment

Diabetes will be assessed by the analysis of:

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

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

Unless otherwise specified, baseline of fasting plasma glucose will be defined as the average of Screening and Day 1 assessments. If one fasting plasma glucose value is missing (Screening or Day 1), the baseline will be based on the available data. For HbA1c, the Day 1 assessment will be considered as baseline. If missing, then the baseline will be based on the assessment at screening.

Diabetes TEAE

New onset/worsening of diabetes will be identified by the search criteria specified in Appendix 5.4. The analysis will be performed for all subjects and then by baseline diabetes status. A participant will be identified as being diabetic at baseline if the medical history notes that the subject is diabetic or the baseline HbA_{1c} value is ≥ 6.5% or the baseline fasting plasma glucose is ≥126 mg/dL. This summary will be provided by treatment and Part.

Change in Glucose-related Laboratory Values over Time

This analysis only utilizes laboratory data (fasting plasma glucose and HbA_{1c}). The change from baseline to the last on-treatment observation and the worst on-treatment observation will be summarized by treatment and Part, separately for fasting plasma glucose and HbA_{1c} for all participants and then by baseline glucose control status. Baseline glucose control status will be identified separately for fasting plasma glucose and HbA_{1c} using the values provided in the table below (note that medical history will not be considered for this analysis). Figures will also be created showing change in mean fasting plasma glucose and HbA_{1c} values over time by baseline glucose control status.

Parameter	**Baseline Glucose Control Status (Laboratory Values)**
Fasting Plasma Glucose	<100 mg/dL
	≥100 to <126 mg/dL
	≥126 mg/dL
HbA1c	<5.7%
	≥5.7 to <6.5%
	≥6.5%

Shifts from Baseline in Glucose Control Category

Shifts from baseline in glucose control category will be summarized by treatment and Part in two different ways. The change from baseline to the worst-on-treatment and the last-on-treatment laboratory values will be used to classify the on-treatment glucose control category. Medical history will not be considered for this analysis.

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

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

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

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

Incidence of Post-baseline New-Onset of Diabetes

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

The participants with no diabetes at baseline are those who had no medical history of diabetes in the medical history CRFs, had baseline HbA1c <6.5%, and had baseline fasting plasma glucose <126 mg/dL prior to the start of study treatment.

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

- Diabetic TEAEs identified by the SMQ search (see Section 5.4), or
- Post-baseline fasting plasma 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 participants who have any of the 4 components will be summarized (post-baseline new onset of diabetes) by treatment and Part.

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

- Subjects with normal glucose control status at baseline are those with all the following:

- No medical history of diabetes.
- HbA1c < 5.7% and fasting plasma glucose < 100 mg/dL at baseline.

- Subjects with impaired glucose control status at baseline are those with all the following:
  - No medical history of diabetes.
  - HbA1c ≥5.7% and <6.5% (and fasting plasma glucose<126 mg/dL) or fasting plasma glucose ≥100 mg/dL and <126 mg/dL (and HbA1c <6.5%) at baseline.

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

2.8.5 Vital signs

Absolute values and change from baseline will be summarized for vital sign parameters by visit, time point, treatment group and Part. For SBP and DBP, average of 3 readings will be used for analysis while all 3 readings will be provided in the listing. Baseline and change from baseline in height, weight, and BMI will be assessed with/without using age- and sex-adjusted z-scores and summarized by visit treatment group and Part.

The number and percentage of patients meeting clinically notable criteria at any time, considering all data collected after first dose of double-blind treatment, from scheduled, unscheduled, and premature discontinuation visits will be summarized by treatment group and Part. The worst post-baseline value in each part will be used for this analysis. Notable criteria are defined in Appendix 5.6. Clinically notable criteria will be met when both of the following occur:

- Post-baseline value meets the clinically notable criteria.
- Baseline value does not meet the clinically notable criteria.

The baseline value is the last value prior to and up to Day 1 of the double-blind treatment.

All vital signs data will be listed by treatment group, participant, and visit/time and if clinically notable criteria are met, abnormalities will be flagged.

2.8.6 Immunogenicity

Number and percentage of subjects with treatment-induced transient and persistent ADA and no treatment-induced ADA will be summarized. Listing will be provided.

Treatment-induced ADA will be defined as a negative ADA sample at baseline and at least one positive ADA sample post-baseline. Persistent will be defined as negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample. Transient will be defined as treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

In addition, further ADA details will be assessed and will be listed in a separate ADA report. If applicable, additional analyses may be conducted.

2.8.7 Other safety evaluation

Shift from baseline in Tanner stage will be summarized by sex, treatment, visit and Part. Additionally, shift in menarche status from baseline will be summarized by visit and treatment group and Part. Mean and SD of age of the participants in each of category of shift table will be provided. Listing will be provided.

In cases where following a Tanner stage 5 the data of the next visit are missing, they will be imputed as Tanner stage 5 (as the protocol does not mandate to repeat the Tanner stage assessment once Tanner stage 5 has been reached). Similarly, menarche data will be imputed as yes if the previous assessment was yes for menarche and data are missing at the next visit.

[redacted]

2.10 Biomarkers

Analyses of PCSK9 and lipids/lipoproteins are discussed in Section 2.7. No additional biomarkers will be evaluated in this study.

[redacted]

[redacted]

2.12 Interim analysis

Interim safety analyses are planned for the monitoring of participants' safety and will be performed as determined by the DMC (see DMC charter). Interim safety analyses before the unblinding for the analysis of Part 1 of the study will be performed by an independent statistician/programmer who will not be involved in the trial conduct. The interim results will be reviewed by the independent DMC.

[redacted]

3 Sample size calculation

The sample size was calculated based on detecting a reduction of at least [redacted] in the inclisiran group compared to the placebo group in percent change of LDL-C from baseline to day 330. The primary efficacy variable is assumed to have a standard deviation of [redacted] in the control group and [redacted] in the inclisiran group. These assumptions are based on observed results from adult inclisiran studies.

The sample size of at least [redacted] total participants will provide more than [redacted] power to detect a [redacted] reduction at significance level of [redacted] in a 2:1 (Inclisiran vs placebo) randomization ratio.

Furthermore, in the adult HeFH inclisiran study (ORION-9), a SD of [redacted] in the control group and [redacted] in the inclisiran group was observed. With a more conservative assumption of a SD of [redacted] in the control group and [redacted] in the inclisiran group, the sample size of at least [redacted] total

participants will still provide more than [redacted] power to detect a [redacted] with a [redacted] significance level of [redacted]

[redacted]

The revised sample size requires a minimum of [redacted] articipants; however, the actual enrollment is [redacted] participants. [redacted]

4 Change to protocol specified analyses

[redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of treatment will not be imputed.

5.1.2 AE date imputation

Partial AE start and end dates will be imputed. If there is uncertainty whether an AE occurred on-treatment or not, imputation will be performed, such that AE will be considered as on-treatment. Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Analyses to be performed in Part 1 analysis (ANA1) and Part 2 analysis (ANA2)

	Data to be included (ANA1 and ANA2 analysis)			Comment
	Part 1	Part 2	Part 1 & Part 2 combined	
Disposition	ANA1	ANA2		
Protocol Deviations	ANA1	ANA2		
Demography and baseline characteristics	ANA1			
[redacted]				
Concomitant therapies (Including lipid modifying therapy [redacted])	ANA1	ANA2		SAF for ANA1; OAS for ANA2. CM will be counted in both parts when starting from part 1 and continuing to part 2.
New or changed lipid-modifying therapy [redacted]	ANA1	ANA2		
Doses, Duration on study, Exposure	ANA1	ANA2	For exposure	
Efficacy (Primary & key secondary endpoints)	ANA1			
Efficacy (other Secondary [redacted] endpoints)	ANA1	ANA2	For selected efficacy parameters	
AEs	ANA1	ANA2		SAF for ANA1; OAS forANA2
Diabetes assessment	ANA1	ANA2		SAF for ANA1; OAS for ANA2
Lab and Vital signs	ANA1	ANA2		SAF for ANA1;

				OAS for ANA2

5.4 Search criteria for AE of other safety topics

The most recent eCRS available during database lock will be used.

5.5 Laboratory parameters derivations

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined:

Table 5-1 Clinical notable criteria for selected laboratory tests

	Notable post-baseline value
Hematology	
Hemoglobin	≤10 g/dL
Hematocrit	≤ 0.8 x LLN
WBC count / Leukocytes	≤ 2.8 x 10ˆ9/L or ≥16 x 10ˆ9/L
Platelet count	≤ 75 x 10ˆ9/L or ≥700 x 10ˆ9/L
Clinical chemistry	
C(P)K	>5 x ULN >5 and ≤10 x ULN >10 and ≤20 x ULN >20 x ULN
Creatinine	≥50% increase from baseline (not >2 mg/dL) >2 mg/dL ≥50% increase from baseline or >2 mg/dL
eGFR	<30 mL/min/1.73m2 ≥ 30 to <60 mL/min/1.73m2 ≥ 60 to <90 mL/min/1.73m2
Glucose	≥100 to <126 mg/dL ≥126 mg/dL
HbA1C	≥5.7% to <6.5% ≥6.5%

Table 5-2 Notable liver function test values

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

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

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window.

5.6 Vital signs – definition of clinically notable values

The following table shows the clinical notable criteria for vital signs.

Table 5-3 Clinical notable criteria for vital signs

Age	SBP [mmHg]	DBP [mmHg]	Heart Rate [beats min-1]
>=12 years	< 90, > 145	< 55, > 90	< 45, > 95

5.7 Statistical models

5.7.1 Multiple Imputation Wash-out model

A multiple imputation washout model will be utilized for the primary efficacy analysis of the percentage change in LDL-C from baseline to Day 330 endpoint. The washout model can be thought of as a modified control-based PMM that will be used to explore the possibility of missing data being 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 330 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.

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 270 (continuous)
- Observed value of efficacy measurement at Day 330 (continuous)
- Observed value of efficacy measurement at Day 360 (continuous)

For the subjects in the inclisiran group who completed first 3 doses and have data available after Day 330 (considered to have completed the Study Part 1) 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 330 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 330 from the placebo group (continuous)

1. Intermittent missing data in the placebo treatment group will be imputed using Markov Chain Monte Carlo (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. Baseline age group will be included in the regression model. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed for the placebo treatment group. These datasets will be utilized in Step #4.
3. Subjects in the inclisiran group who received first 3 doses of study medication, have the Day 330 value missing, and have evaluable data after Day 330 will be included in this step. Missing values at Day 330 will be imputed assuming data are MAR. Only subjects in the inclisiran group will be included in this step. Observed Baseline data, Day 330 data and baseline age group will be utilized to impute missing Day 330 data utilizing SAS PROC MI. This will be performed 100 times to create 100 datasets that are fully imputed at Day 330.
4. The remaining missing values at Day 330 in the inclisiran group will be imputed in this step. Note that the subjects with imputed inclisiran Day 330 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 330. Baseline data and age group 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 effects of treatment group: baseline age group and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to Day 330 primary efficacy endpoint. PROC MIXED with (repeated / group=treatment) statement which allows separate variance to estimate for treatment groups will be used.

9. Treatment effects (difference in least squares (LS) means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

5.7.2 Control based Pattern-Mixture model

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

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

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 90 (continuous)
- Observed value of efficacy measurement at Day 150 (continuous)
- Observed value of efficacy measurement at Day 270 (continuous)
- Observed value of efficacy measurement at Day 330 (continuous)
- Observed value of efficacy measurement at Day 360 (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. Baseline age group will be included in the imputation model. 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 for the primary and key secondary efficacy endpoints.

6. Treatment effects (difference in LS means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

5.8 Rule of exclusion criteria of analysis sets

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