NOVARTIS

Clinical Development

KJX839/Inclisiran

CKJX839A12306B (MDCO-PCS-17-05) / NCT03814187

A long-term extension trial of the phase III lipid-lowering trials to assess the effect of long-term dosing of inclisiran given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C (ORION-8)

Statistical Analysis Plan (SAP)

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[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CS	Clinically significant
CVD	Cerebrovascular Disease
CRF	Case Report Form
CSR	Clinical Study Report
DBL	Database Lock
EAIR	Exposure-adjusted Incidence Rate
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
GGT	Gamma Glutamyl Transferase
HbA1c	Glycated Hemoglobin A1C
HDL-C	High-density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HLGT	High-level Group Term
HLT	High-level Term
hsCRP	High Sensitivity C-reactive Protein
IA	Interim Analyses
LDL-C	Low-density Lipoprotein Cholesterol
LLN	Lower Limit of the Normal range
LLQ	Lower Limit of Quantification
LMT	Lipid Modifying Therapy
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PAD	Peripheral Artery Disease
PCS	Potentially Clinically Significant
PPC	Post-Production Change
PT	Preferred Term
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBIL	Total Bilirubin
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TFLs	Tables, Figures, Listings
ULN	Upper Limit of the Normal range
WHO	World Health Organization

1 Introduction

This document contains details of the planned statistical methods and analyses that will be used for the final clinical study report (CSR) of the Phase III long-term extension trial CKJX839A12306B (ORION-8; MDCO-PCS-17-05). The purpose of this extension study is to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran in subjects with atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents (e.g., diabetes and familial hypercholesterolemia), or heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated dose of LDL-C lowering therapies. This statistical analysis plan (SAP) has been prepared based on clinical trial protocol CKJX839A12306B global amendment 2, content final dated 06-Oct-2020, and ORION-8 eCRF Post-Production Change (PPC) 1 (also called Revision 2 or R2) implemented on 23-Sep-2021.

1.1 Study design

This study will be a long-term extension of the Phase II lipid lowering trial CKJX839A12201E1 (ORION-3; MDCO-PCS-16-01), which is the extension study of CKJX839A12201 (ORION-1; MDCO-PCS-15-01), and Phase III lipid-lowering studies CKJX839A12303 (ORION-9; MDCO-PCS-17-03), CKJX839A12304 (ORION-10; MDCO-PCS-17-04), and CKJX839A12305 (ORION-11; MDCO-PCS-17-08). This trial will be a global, multicenter study in approximately 300 centers. Up to 3300 subjects with atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents (e.g., diabetes and familial hypercholesterolemia), or heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-C despite treatment with LDL-C lowering therapies who are eligible and willing to participate may be enrolled. The objective of the study is to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. Informed consent will be obtained from subjects before the initiation of any study-specific procedures. The End of Study (EOS) visit in the previous feeder studies will be Day 1 in this extension trial except for subjects enrolled in Sweden. Sweden Specific Protocol Amendment 1 (to Global Amendment 1 version, dated 1 Nov 2018) was implemented to allow limited lab tests to be done on Day 1 and to collect any safety information during the gap between feeder's EOS and Day 1 of this study until ethics committee approval was granted in that country.

Subjects rolled over from the Phase III studies (ORION-9/10/11) will receive blinded inclisiran sodium 300 mg which is equivalent to 284 mg inclisiran, or blinded placebo on Day 1 in this trial. Subjects who received placebo in the previous Phase III feeder studies will receive blinded inclisiran and subjects who received inclisiran in the previous Phase III feeder studies will receive blinded placebo at this visit, in order to

- maintain the blinding of the feeder studies until database lock of those studies,
- maintain the semi-annual dosing schedule for subjects who received inclisiran in the previous Phase III feeder studies,

- administer the first two doses of inclisiran on the three-monthly initial dosing schedule for subjects who received placebo in the previous Phase III feeder studies.

All subjects will return at Day 90 for the next visit and will receive open label inclisiran sodium 300 mg.

Subjects moving over from the open-label ORION-3 study will not receive study drug at Day 1. Their first dose of study drug in this trial will be at Day 90. This is to maintain their semi-annual dosing schedule on inclisiran treatment.

After the Day 90 dosing, subjects rolled over from all feeder trials (ORION-3/9/10/11) will return for open-label drug administration of inclisiran sodium 300 mg every 180 days until Day 990. The EOS visit will be on Day 1080. For subjects who discontinued early, the EOS visit should be completed ≥ 90 days following the last inclisiran injection whenever possible.

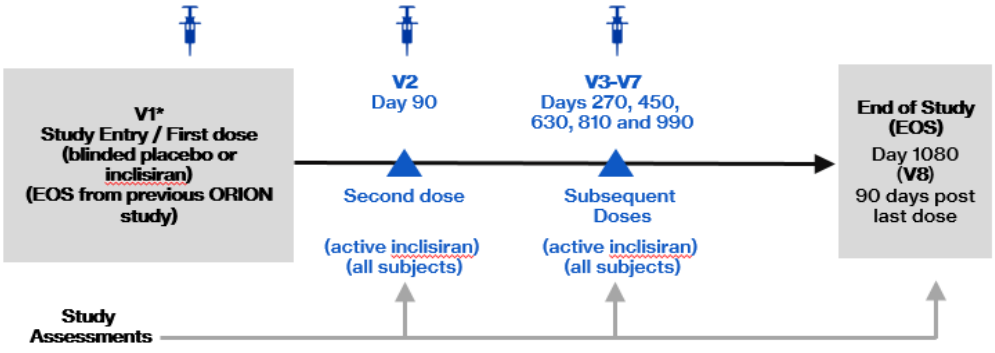
The duration that each subject is expected to participate in this study is a maximum of 3 years or the occurrence of one of the following events, whichever occurs first:

- a recommendation of discontinuation by the investigator or Sponsor,
- a decision by the subject to discontinue for any reason,
- an administrative decision is made to end the study. In particular, the decision has been made to end the study after the last subject from ORION-9/10/11 completes the 3-year treatment (or discontinued early). As a result, ORION-3 rollover subjects will have shorter than 3 years of participation in this study.

No formal interim analysis will be performed in this study.

A schematic diagram of the study design is presented in Figure 1-1. Note that the study duration for ORION-3 rollover subjects will be shorter than the three-year duration illustrated in the diagram.

Figure 1-1 Study design



* Subjects from the open label ORION-3 study will receive no drug administration on Day 1

1.2 Study objectives, endpoints and estimands

The purpose of the study is to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. The objectives and the corresponding endpoints are listed in Table 1-1.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives: The primary objectives of this study are to evaluate:	**Endpoints for primary objectives:**
• The effect of inclisiran treatment on the proportion of subjects achieving prespecified LDL-C targets at end of study (EOS)	• Proportion of subjects who attain global lipid targets (entry criterion from respective previous study) for their level of ASCVD risk at EOS
• The safety and tolerability profile of long-term use of inclisiran	• Adverse events (AE), clinical laboratory values, [redacted] vital signs, etc. (See Section 2.7 for all the safety analyses)
Secondary objectives: The secondary objectives of this study are to evaluate the effect of inclisiran on:	**Endpoints for secondary objectives:**
• LDL-C levels	• Absolute change and percentage change in LDL-C from baseline (defined as baseline in feeder study) to EOS
• Other lipids and lipoproteins	• Absolute change and percentage change in other lipids and lipoprotein from baseline (defined as baseline in feeder study) to EOS

2 Statistical methods

The following sections contain important information on detailed statistical methodologies to be used in the analyses for the final CSR.

2.1 Data analysis general information

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

Study-collected data will be summarized by the actual treatment groups of the feeder studies (Phase III Inclisiran-Inclisiran, Phase III Placebo-Inclisiran, ORION-3 Rollover) 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. For selected categorical variables, the 95% confidence interval (CI) for the percentage will be calculated using Blaker's method. Continuous variables, including changes from baseline, will be summarized using

descriptive statistics (n (number of non-missing observations), mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum). For selected continuous variables, the CI for the mean will be provided.

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

- Absolute change from baseline to Day X =Value at Day X – Baseline value.
- Percent change from baseline to Day X = (Absolute change/Baseline value)*100%.

For laboratory measurements below the lower limit of quantification (LLQ), LLQ/2 will be used as the numeric value for the measurement. For example, if numeric result is missing in the database and character result is "< 3", the numeric result should be treated as 3/2 = 1.5 during analysis.

Analyses for the final CSR will be conducted after the final database lock (DBL) of the study. The final DBL will be performed after ORION-9/10/11 rollover subjects either complete the Day 1080 visit or discontinue early and will not wait until ORION-3 rollover subjects complete Day 1080 visit. The ORION-3 rollover subjects will have shorter than 3 years of participation in this study, and their EOS visit will be scheduled 90 days after their last dosing visit.

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

2.1.1 General definitions

Study drugs

The study drugs in this trial are the following:

- Investigational drug: Inclisiran will be administered as a single subcutaneous (SC) injection of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran)/1.5 mL pre-filled syringe.
- Placebo: Placebo pre-filled syringes will contain saline solution and will be blinded and look identical to the inclisiran pre-filled syringes. Placebo will be administered as a 1.5 mL SC injection to match the dose of inclisiran.

Study day

Study day will be defined as the number of days since ORION-8 Day 1, which is defined as the date of first study drug administration in ORION-8 for ORION-9/10/11 rollover subjects and the date of ORION-8 consent for ORION-3 rollover subjects.

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

For dates on or after ORION-8 Day 1,

Study day = Assessment date – Date of ORION-8 Day 1 + 1;

For dates prior to ORION-8 Day 1,

Study day = Assessment date – Date of ORION-8 Day 1.

Treatment group of the feeder studies

For the rest of this document, "treatment group of the feeder studies" refers to the following three groups unless otherwise specified:

- Phase III Inclisiran-Inclisiran: subjects who received inclisiran (actual treatment) in ORION-9/10/11
- Phase III Placebo-Inclisiran: subjects who received placebo (actual treatment) in ORION-9/10/11
- ORION-3 Rollover: subjects enrolled from ORION-3

Reflexive LDL-C

The endpoints involving LDL-C will use a reflexive LDL-C approach. When both calculated and beta-quantified LDL-C are available for a sample, calculated LDL-C will be used unless triglycerides are greater than 400 mg/dL or calculated LDL-C is less than 40 mg/dL. When only calculated LDL-C or beta-quantified LDL-C is available for a sample but not both, the available one will be used.

Feeder study baseline

When it refers to a timepoint, feeder study baseline is defined as the date/time of first study drug administration in ORION-1/9/10/11.

When it refers to a laboratory parameter baseline, it is defined as the last available record with date/time ≤ date/time of feeder study baseline as defined above, unless otherwise specified. When time is not available for baseline or for the laboratory assessment, the comparison of date/time will be based on the date only. The same rule is applicable throughout this document to determination of chronological orders, unless otherwise specified.

ORION-8 baseline

When it refers to a timepoint, ORION-8 baseline is defined as follows:

- For ORION-9/10/11 rollover subjects, ORION-8 baseline is defined as the date/time of first study drug administration in ORION-8.
- For subjects rolled over from ORION-3, ORION-8 baseline is defined as the date (without time) of ORION-8 consent (Day 1).

When it refers to a laboratory parameter baseline, it is defined as the last available record with date/time ≤ date/time of ORION-8 baseline as defined above, unless otherwise specified. Note that according to the definition of ORION-8 baseline above, when ORION-8 consent date is used as baseline, the comparison should be based on the consent date only and consent time should not be considered in the comparison even if it is available.

For most subjects rolled over from ORION-9/10/11, the ORION-8 laboratory baseline will be the last available record in ORION-9/10/11, but for some subjects with a gap between feeder trial EOS and ORION-8 Day 1, this needs to be taken from ORION-8 laboratory data for certain

parameters. For subjects rolled over from ORION-3, the last available record up to ORION-8 Day 1 (ORION-8 consent date) will be used.

Last contact/participation date

The last contact/participation date for a subject is the last available date across all the data collected for that subject. For a subject with a death event, the date of death will be used.

2.1.2 Decimal places

The rules for decimal places in data presentation are the following:

- All percentages and their confidence intervals will be presented to one decimal place.
- Standard errors and standard deviations: data precision + 2 decimal places
- Means, medians and quartiles: data precision + 1 decimal place
- Minimums and maximums: same as data precision
- Data precision of BMI will be 1 decimal place.
- Total subject-years of exposure will keep one decimal place.

2.2 Analysis sets

The safety population will be used for data analyses and/or presentation.

Safety Population

All ORION-3 rollover subjects who signed the informed consent to ORION-8, and all ORION-9/10/11 rollover subjects with at least one study drug administration in ORION-8 will comprise the Safety Population. Treatment classification will be based on the actual treatment groups of the feeder studies (Phase III Inclisiran-Inclisiran, Phase III Placebo-Inclisiran, ORION-3 Rollover). This will be the primary population for the efficacy and safety analyses.

2.2.1 Subgroup of interest

In general, no subgroup analysis will be performed. Selected analyses in Section 2.7.4 for diabetes will be subgrouped by baseline diabetes or glucose control status.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The following information will be summarized for the Safety Population overall and by treatment group of the feeder studies:

- The number of subjects in each analysis population
- The number of subjects by country and site

- The number of subjects who completed the study and discontinued early, with reasons for discontinuation
- The duration on study (days)
- Protocol deviations and violations of subject restrictions

Completers are defined as subjects indicated in the EOS page of eCRF to have completed the study. This will include ORION-9/10/11 rollover subjects who have completed the Day 1080 visit, and ORION-3 rollover subjects whose study duration is shortened to < 3 years by the administrative decision only.

The duration on study is defined as the number of days from Day 1 of ORION-8 to the date of last recorded contact/participation date in the database.

2.3.2 Demographics and other baseline characteristics

The following demographics and baseline characteristics will be summarized for the Safety Population overall and by treatment group of the feeder studies:

- Age (years) using descriptive statistics
- Age categories: ≥18 - <65, ≥65
- Age categories: ≥18 - <50, ≥50 - < 65, ≥65 - < 75, ≥75
- Gender
- Child-bearing potential of females
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m)
- Race
- Ethnicity
- Country
- Baseline estimated glomerular filtration rate (eGFR) (mL/min/1.73m)
- Baseline eGFR categories: ≥15 - < 30, ≥30 - <60, ≥60 - <90, ≥90
- Medical history (targeted and other medical history)

For categorical variables in the list above, the percentages will be calculated based on total number of subjects (N) in a particular treatment group including subjects with a missing value. Subjects with a missing value will be counted in "Missing" category.

Age at ORION-8 baseline will be calculated by (age collected at ORION-1/9/10/11 screening) + floor[(ORION-8 consent date – ORION-1/9/10/11 consent date)/365.25], where floor(x) is the largest integer less than or equal to x.

Gender, race, and ethnicity will be taken from the data collected at ORION-1/9/10/11 screening.

Country will be based on the subject's participation site in ORION-8.

For child-bearing potential of females, the percentages are out of the number of female subjects. If a female was determined not to have child-bearing potential in the feeder study, the subject will also have no child-bearing potential in ORION-8. If a female was determined to have child-bearing potential in the feeder study, the subject's child-bearing potential will be re-evaluated at ORION-8 Day 1 and the result of the re-evaluation will be used.

The height collected at ORION-1/9/10/11 screening will be used as the baseline value for ORION-8, as no significant change in adult subjects' height is expected.

The last available weight in ORION-3/9/10/11 will be used as the baseline value for ORION-8. The BMI, which equals to weight in kilogram divided by (height in meter)^2, will be calculated based on this weight.

The baseline eGFR will use ORION-8 baseline data.

Medical History

Medical history (targeted and other medical history) from the initial feeder studies (ORION-1/9/10/11) will be summarized for the Safety Population overall and by treatment group of the feeder studies. For other medical history, the sites are allowed to report in ORION-8 eCRF any relevant medical or surgical issues that occurred prior to consent in the initial feeder study but were not recorded in the feeder study, and such information added in ORION-8 eCRF should be combined with other medical history from feeder trial databases. Other medical history will be coded into Medical Dictionary for Regulatory Activities (MedDRA) terminology using the most recent MedDRA version before database lock (DBL), and will be summarized by primary system organ class (SOC) and preferred term (PT).

For targeted medical history, the following data will be summarized:

- Smoking status: Current, Former, Never, Unknown
- Hypertension: Yes, No, Unknown
- Hyperlipidemia: Yes, No, Unknown
- Congestive heart failure: Yes, No, Unknown
- Diabetes mellitus: Yes, No, Unknown
- ASCVD status: ASCVD, ASCVD risk equivalent
- Prior or current CHD (Coronary Heart Disease): Yes, No, Unknown
- Prior or current CVD (Cerebrovascular Disease): Yes, No, Unknown
- Prior or current PAD (Peripheral Artery Disease): Yes, No, Unknown
- Family history of coronary artery disease: Yes, No, Unknown
- Family history of dyslipidemia: Yes, No, Unknown

A subject is classified as ASCVD if CHD = Yes or CVD = Yes or PAD = Yes. Otherwise, the subject is ASCVD risk equivalent.

In ORION-11, the questions for CHD, CVD and PAD are asked only when the subject is indicated as ASCVD in the subject type CRF question (only ORION-11 CRF has this question). Therefore, for ORION-11 subjects who are indicated as ASCVD risk equivalent, their answers to CHD, CVD and PAD questions are all implicitly "No".

For ORION-3 rollover subjects, CHD and CVD are derived as follows:

- CHD:
    - If prior PCI (Percutaneous Coronary Intervention) = Yes or prior MI (Myocardial Infarction) = Yes or prior CABG (Cardiovascular Arterial Bypass Graft) = Yes, then CHD = Yes.
    - Else if prior PCI = Unknown or prior MI = Unknown or prior CABG = Unknown, then CHD = Unknown.
    - Else CHD = No.
- CVD:
    - If prior stroke = Yes or prior TIA (Transient Ischaemic Attack) = Yes, then CVD = Yes.
    - Else if prior stroke = Unknown or prior TIA = Unknown, then CVD = Unknown.
    - Else CVD = No.

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

2.4.1 Study treatment / compliance

Study drug administration will be summarized for the Safety Population overall and by treatment group of the feeder studies. The summary will include

- The number and percentage of subjects dosed at each visit
- The number and percentage of subjects administered 0, 1, 2, ... doses, and total number of doses administered
- The number and percentage of injections at each injection site location (with total number of administered doses as the denominator for the percentage)
- The number and percentage of injections with each injection volume (with total number of administered doses as the denominator for the percentage)
- The number and percentage of subjects who missed 0, 1, 2, ... doses, and total number of missed doses. As per protocol, ORION-3 rollover subjects do not receive study medication on Day 1, thus ORION-3 rollover subjects who did not receive study medication on Day 1 do not count toward missed doses.

- The number and percentage of missed injections with each reason of not administering study drug (with total number of missed doses as the denominator for the percentage)

The duration of exposure (days) to inclisiran and the total subject-years of exposure in ORION-8 will be summarized for the Safety Population overall and by treatment group of the feeder studies.

The duration of exposure to inclisiran is defined as the number of days from Day 1 of ORION-8 to the earliest of the following:

- Last recorded contact/participation date of ORION-8
- Last study drug administration date in ORION-8 (if any) + 180 days

2.4.2 Prior and concomitant therapies

Concomitant medications new or changed since ORION-8 baseline will be summarized by 3rd level Anatomical Therapeutic Chemical (ATC) classification and preferred name. Medications will be coded using the World Health Organization (WHO) drug dictionary.

ORION-8 baseline concomitant lipid modifying therapies (LMT) and LMTs new or changed since ORION-8 baseline will be summarized by preferred name with dose and frequency. LMTs are medications with 2nd level ATC classification being C10 (lipid modifying agents) according to the coding by the WHO drug dictionary. LMTs will be grouped into statins and other LMT. Statins will be further grouped by intensity (low, moderate, high) according to American College of Cardiology/American Heart Association (ACC/AHA) classification of statin intensity and based on the specific statin drug name, dose, and frequency recorded in the data.

ORION-8 baseline concomitant LMT is defined as any LMT started before or on ORION-8 Day 1 and either still ongoing or stopped on ORION-8 Day 1 or later. Any medications/LMT with start date > ORION-8 Day 1 are considered as new or changed concomitant medications/LMT.

2.5 Analysis supporting primary objective(s)

The primary objective of the study is to evaluate:

- The effect of inclisiran treatment on the proportion of subjects achieving prespecified LDL-C targets at EOS.
- The safety and tolerability profile of long-term use of inclisiran. This objective will be addressed in Section 2.7.

2.5.1 Primary endpoint

The primary efficacy analysis of this study is to assess the proportion of subjects who attain global lipid targets for their level of ASCVD at EOS. Summaries will include the number and percentage of subjects who attain global lipid targets for their level of ASCVD, along with the 95% CI for the percentage. In addition, the proportion of subjects who attain global lipid targets for their level of ASCVD at ORION-8 baseline and at each scheduled visit from Day 90 to Day

1080 will be provided. The analysis will be performed for the Safety Population overall and by treatment group of the feeder studies.

2.5.2 Handling of missing values/censoring/discontinuations

Missing data will not be imputed. Subjects missing any required data for computing the endpoint will be excluded from the analysis.

2.6 Analysis supporting secondary objectives

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

- LDL-C levels
- Other lipids and lipoproteins

2.6.1 Secondary endpoint(s)

The actual value, absolute and percentage change in LDL-C and other efficacy parameters from feeder study baseline will be summarized over time using descriptive statistics. The 95% CI for the mean absolute and percentage change will also be provided. Other efficacy parameters include total cholesterol (TC), triglycerides, high density lipoprotein cholesterol (HDL-C), and high sensitivity C-reactive protein (hsCRP).

All the parameters will be summarized at feeder trial baseline, at ORION-8 baseline, at each scheduled visit from Day 90 to Day 1080, and at EOS. The exception is that post-baseline hsCRP will be summarized at Day 1080 and EOS only because hsCRP in ORION-8 is only assessed at EOS per protocol.

The analysis will be performed for the Safety Population overall and by treatment group of the feeder studies.

2.6.2 Handling of missing values/censoring/discontinuations

Missing data will not be imputed. Subjects missing any required data for computing an endpoint will be excluded from its analysis.

2.7 Safety analyses

The safety objectives of this study are to evaluate the safety and tolerability profile of long-term use of inclisiran.

Unless otherwise specified, safety evaluations will be performed for the Safety Population overall and by treatment group of the feeder studies.

Safety analyses are based on observed values and missing data will not be imputed.

2.7.1 Adverse events (AEs)

The most recent version of MedDRA before DBL will be used for coding AEs. An AE will be counted as an ORION-8 treatment emergent AE (TEAE) if the AE started on or after ORION-8 baseline or the AE was present prior to ORION-8 baseline but increased in severity on or after

ORION-8 baseline. Since the investigators are required to enter any worsened AE as a separate record, implementation-wise an AE is a TEAE as long as its onset date/time ≥ date/time of ORION-8 baseline.

The following summaries will be presented for ORION-8 TEAEs using number and percentage of subjects with the event:

- Overall Summary of TEAEs
- TEAEs by primary SOC and PT
- TEAEs by PT
- TEAEs by primary SOC, PT, and maximum severity
- TEAEs possibly related to study drug by primary SOC and PT
- Treatment Emergent Serious AEs (TESAEs) by primary SOC and PT
- TESAEs by PT
- TESAEs possibly related to study drug by primary SOC and PT
- TEAEs leading to withdrawal of study treatment by primary SOC and PT
- TEAEs with a fatal outcome by primary SOC and PT

Subject data listings will be presented for AEs with a fatal outcome, SAEs, and AEs leading to drug discontinuation. Those listings will include all AEs in ORION-8 database, regardless of whether they are ORION-8 TEAE.

If more than one event occurred with the same SOC/PT for the same subject, the subject will be counted only once for that SOC/PT, using the most severe occurrence for the summary by severity.

2.7.1.1 AEs of special interest (AESI) and additional safety topics

2.7.1.1.1 AEs at the injection site

TEAEs at the injection site, which is an AESI, include all TEAEs identified as being an AE at the injection site on the AE page of eCRF or with “injection site reactions” as the high-level term (HLT).

The number of injection site TEAEs per subject will be summarized using descriptive statistics as well as the number of subjects with 0, 1, 2, 3, ... injection site TEAEs.

The following summaries will be presented for ORION-8 injection site TEAEs using number and percentage of subjects with the event:

- Overall Summary of TEAEs
- TEAEs by PT
- TEAEs by PT and maximum severity

- TESAEs by PT
- Signs and symptoms of TEAEs (only applicable to the events identified as AEs at the injection site on eCRF)
- TEAEs by PT and worst outcome

Outcomes of TEAEs ordered from worst to best will be:

1) Fatal
2) Not resolved
3) Resolved with sequelae
4) Unknown
5) Resolving
6) Resolved

For subjects whose injection site TEAEs are all resolved (i.e. the worst outcome for the subject is "Resolved"), the duration (in days) of injection site TEAEs will be summarized using descriptive statistics. If a subject has multiple durations, the median time will be used for that subject.

A subject data listing will be provided for injection site AEs. Such listing will include all AEs in ORION-8 database, regardless of whether they are ORION-8 TEAE.

2.7.1.1.2 Other AESIs and AEs of additional safety topics

Other AESIs include:

- Hepatic events
- Diabetes mellitus (see Section 2.7.4 for additional analyses for diabetes)

Additional safety topics include:

- Renal events
- Hypersensitivity
- Neurological events and neurocognitive disorders
- Ophthalmological events
- Cardiac safety: Major adverse cardiovascular events (MACE) and each of the MACE components

See Appendix 5.2 for the search criteria of each safety topic.

The following summaries of ORION-8 TEAEs will be presented for other AESIs and AEs of additional safety topics using number and percentage of subjects with the event:

- Overall Summary of TEAEs
- TEAEs by PT

- TEAEs by PT and maximum severity
- TEAEs possibly related to study drug by PT
- TESAEs by PT
- TEAEs leading to study drug withdrawal

Subject data listings will be provided for hepatic and diabetic AEs. Such listings will include all AEs in ORION-8 database, regardless of whether they are ORION-8 TEAE.

2.7.2 Deaths

As mentioned in Section 2.7.1, TEAEs with a fatal outcome will be summarized by SOC and PT, and a subject data listing for AEs in ORION-8 database with a fatal outcome will be generated.

2.7.3 Laboratory data

Fasting glucose parameter, when used in any analysis, will require the lab sample to be taken while fasting. Glucose values recorded at non-fasting state will not be used.

2.7.3.1 Summary tables using descriptive statistics

Summaries for safety laboratory values will include observed value, changes and percent changes from ORION-8 baseline over time:

- Hematology and coagulation parameters will be summarized at ORION-8 baseline (for observed value only), at Day 1080, and at EOS.
- Safety chemistry parameters in the full serum chemistry panel but not in limited serum chemistry panel will be summarized at ORION-8 baseline (for observed value only), at Day 1080, and at EOS.
    - These include direct and indirect bilirubin, lactate, bicarbonate, uric acid, urea (blood urea nitrogen; BUN), sodium, potassium, calcium, inorganic phosphorus, chloride, albumin, total protein, fasting glucose.
- Safety chemistry parameters in limited chemistry panel, which is a subset of the full chemistry panel, will be summarized at ORION-8 baseline (for observed value only), at each scheduled visit from Day 90 to Day 1080, and at EOS.
    - These include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), creatine kinase (CK), creatinine, eGFR, glycated hemoglobin A1C (HbA1c).

2.7.3.2 Shift analysis

A shift analysis from baseline to EOS will be performed for eGFR and HbA1c using the following categories:

- For eGFR, the categories will be Severe = < 30 mL/min/1.73m^2; Moderate = ≥ 30 to < 60 mL/min/1.73m^2; Mild = ≥ 60 to < 90 mL/min/1.73m^2; and Normal = ≥ 90 mL/min/1.73m^2.
- For HbA1c, the categories will be < 5.7%, ≥ 5.7% to < 6.5%, and ≥ 6.5%.

2.7.3.3 Clinically significant laboratory values

The number and percentage of subjects with potentially clinically significant (PCS) laboratory values or clinically significant (CS) laboratory values (refer to Appendix 5.3 for the criteria) will be summarized. For AST, ALT and CK, the most severe result for each subject will be used. For creatinine, the following two categories will also be presented in addition to the CS criterion:

1) Subjects with the baseline value ≤ 2 mg/dL and any post-baseline value > 2 mg/dL.
2) Subjects who are not in the first category but has ≥ 50% increase from baseline.

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

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

2.7.3.4 Hy's law

The number and percentage of subjects satisfying Hy's Law will be tabulated 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 subjects who meet all of the criteria listed above at the same time point without regard to the baseline lab parameter results. The baseline here refers to ORION-8 baseline.

2.7.4 Diabetes assessment

Diabetes will be assessed by the analysis of:

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

Fasting glucose parameter, when used in any analysis, will require the lab sample to be taken while fasting. Glucose values recorded at non-fasting state will not be used.

2.7.4.1 Diabetes TEAE

New onset/worsening of diabetes will be identified by the search criteria specified in Appendix 5.2. The analysis will be performed for all subjects and then by baseline diabetes status. A subject will be identified as being diabetic at ORION-8 baseline if any of the following is true:

- The targeted medical history notes that the subject is diabetic
- The subject has ORION-8 Day 1 concomitant anti-diabetic medication (ATC level 2 code: A10)
- The ORION-8 baseline HbA1c value is ≥ 6.5%
- Fasting glucose ≥126 mg/dL at ORION-8 baseline.

Baseline fasting glucose uses average of last two assessments at or prior to ORION-8 baseline.

A subject data listing will be provided for diabetic AEs. Such listing will include all AEs in ORION-8 database, regardless of whether they are ORION-8 TEAE.

2.7.4.2 Change in glucose-related laboratory values over time

This analysis only utilizes laboratory data (fasting glucose and HbA1c). The change from baseline to EOS will be summarized for fasting glucose for all subjects and then by baseline glucose control status. The change from baseline to the EOS and to the worst observation will be summarized for HbA1c for all subjects 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 HbA1c values over time by baseline glucose control status.

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

* Baseline uses average of last two fasting glucose assessments at or prior to ORION-8 baseline.

2.7.4.3 Shifts from baseline in glucose control category

Shifts from baseline in glucose control category will be summarized in two different ways: the change from ORION-8 baseline to the worst and then again for the change to last 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline	Fasting glucose < 100 mg/dL on two consecutive occasions AND

	OR HbA1c ≥ 6.5%	HbA1c < 5.7%
Diabetes to Impaired	Fasting glucose ≥ 126 mg/dL on the last two measurements at or prior to ORION-8 baseline 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 the last two measurements at or prior to ORION-8 baseline 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.

Diabetes takes precedence over impaired, i.e. if a subject satisfies the diabetes criteria, the subject cannot be in impaired category.

2.7.4.4 Incidence of post-baseline new onset of diabetes

The number of subjects who shift from no diabetes at baseline (see Section 2.7.4.1 for definition of baseline diabetes) to diabetes will be summarized. A 4-component definition of diabetes will be utilized. The 4 components are provided below.

1. Diabetic TEAEs identified by the search criteria in Appendix 5.2, or
2. Post-baseline fasting glucose ≥126 mg/dL on two consecutive occasions, or
3. Initiation of anti-diabetic medication (ATC level 2 code: A10) at any time post-baseline, or
4. At least one post-baseline HbA1c ≥6.5%.

The number of subjects who have any of the 4 components (post-baseline new-onset of diabetes) will be summarized 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. Baseline fasting glucose uses average of last two assessments at or prior to ORION-8 baseline.

The time to new-onset diabetes will also be summarized. Only subjects without diabetes at baseline will be included in the analysis. The time (weeks) to new-onset diabetes will be calculated from ORION-8 Day 1.

2.7.5 Other safety data

2.7.5.1 ECG and cardiac imaging data

Not applicable to this study.

2.7.5.2 Vital signs

Observed value, change, and percent change from ORION-8 baseline in vital signs (blood pressure and heart rate) will be summarized descriptively at ORION-8 baseline (for observed value only) and at each scheduled time point from Day 90 to Day 1080 and at EOS.

The change from ORION-8 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

[redacted]

2.8 Pharmacokinetic endpoints

Not applicable to this study.

2.9 PD and PK/PD analyses

Not applicable to this study.

2.10 Subject-reported outcomes

Not applicable to this study.

2.11 Biomarkers

Not applicable to this study.

2.12 Other Exploratory analyses

No exploratory analyses are planned for this study.

2.13 Interim analysis

No formal interim analysis will be performed in this study.

3 Sample size calculation

This study will be a long-term extension study of ORION-3/9/10/11 and all completers of those studies who fulfill ORION-8 entry criteria and willing to participate can be enrolled into this study.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

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

An AE with an unknown or partial onset date will be categorized as a TEAE unless there is sufficient information to determine that the event began before baseline. For example, if an AE's resolution date/time < baseline date/time, the AE's onset date/time is logically < baseline date/time and thus it is not a TEAE.

5.1.3 Concomitant medication date imputation

Any medication with both start and stop dates missing are considered as baseline concomitant medication. Any medication with only start date missing are considered as either prior or baseline concomitant medication depending on the stop date. Any medication with only stop date missing are considered as either baseline concomitant or new/changed concomitant medications depending on the start date.

5.2 Standardized MedDRA queries (SMQ) and AE terms for additional AE investigations

1. Hepatic events
   - Drug related hepatic disorders - comprehensive search (SMQ, broad and narrow)
2. Renal events
   - Acute renal failure (SMQ, broad and narrow)
3. 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')
4. Neurological events and neurocognitive disorders
   - Neurological events
     - Demyelination, (SMQ, broad and narrow)
     - Peripheral neuropathy, (SMQ, broad and narrow)
   - Neurocognitive disorders
     - Deliria (incl confusion), (HLGT)
     - Cognitive and attention disorders and disturbances, (HLGT)
     - Dementia and amnestic conditions, (HLGT)
     - Disturbances in thinking and perception (HLGT)
     - Mental impairment disorders (HLGT)
5. Ophthalmologic events
   - Optic nerve disorders, (SMQ, broad and narrow)
   - Retinal disorders, (SMQ, narrow)
   - Corneal disorders, (SMQ, narrow)
6. Cardiac safety: Major adverse cardiovascular events (MACE)
   - CV death
     - Fatal SAEs in Cardiac disorders SOC
     - Fatal SAEs in General disorders and administration site conditions SOC: PTs ‘Death’, ‘Sudden cardiac death’, ‘Cardiac death’, ‘Apparent death’

- Central nervous system haemorrhages and cerebrovascular accidents (HLT), fatal events only

- Resuscitated cardiac arrest
  - Non-fatal AEs with PT 'Cardiac arrest'
- Non-fatal MI
  - Myocardial infarction (SMQ, broad and narrow), nonfatal events only
- Non-fatal stroke
  - Central Nervous System hemorrhages and cerebrovascular accidents (HLT), non-fatal events only

7. New onset/worsening of diabetes
   - Hyperglycaemia/new onset diabetes mellitus (SMQ, narrow)
   - Diabetic complications (HLGT)
   - Diabetes Mellitus (incl subtypes) (HLT)
   - Carbohydrate tolerance analyses (incl diabetes) HLT, excluding PT "Blood glucose decreased"

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

Hemoglobin A1c criteria is explicitly stated in the table below. For all other parameters, a PCS/CS criterion is met when both of the following occur (baseline refers to ORION-8 baseline):

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

Some examples are:

- For leukocytes, a subject satisfies "<= 2.8 x 10^9/L" criterion as long as the baseline value is > 2.8 x 10^9/L and any post-baseline value is <= 2.8 x 10^9/L; a subject satisfies ">=16 x 10^9/L" criterion as long as the baseline value is <16 x 10^9/L and any post-baseline value is >=16 x 10^9/L.
- For CK, a subject satisfies "> 3 and ≤ 5 × ULN" criterion as long as the baseline value is ≤ 3 x ULN and any post-baseline value is > 3 and ≤ 5 × ULN. A subject satisfies "> 5 and ≤ 10 × ULN" criterion as long as the baseline value is ≤ 5 x ULN and any post-baseline value is > 5 and ≤ 10 × ULN. If a subject satisfies both "> 3 and ≤ 5 × ULN" and "> 5 and ≤ 10 × ULN" criteria and does not satisfy the criteria of any more severe category, the subject will be presented under "> 5 and ≤ 10 × ULN" but not under "> 3 and ≤ 5 × ULN" because the most severe category will be used for CK.
- For serum creatinine, the CS criterion is satisfied if at least one of the following is true:

- The baseline value is ≤ 2 mg/dL and any post-baseline value is > 2 mg/dL.
- Any post-baseline value is ≥ 50% increase from baseline, regardless of whether the baseline value is ≤ 2 mg/dL.

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 (Leukocyte) Count	10^9/L	≤ 2.8	≥ 16
Serum Chemistry			
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 1 and ≤ 3 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 3 and ≤ 5 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 5 and ≤ 10 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 10 and ≤ 20 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 20 × ULN*
Alkaline Phosphatase	U/L	N/A	> 2 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 1 and ≤ 3 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 3 and ≤ 5 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 5 and ≤ 10 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 10 and ≤ 20 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 20 × ULN*
Creatine Kinase (CK)	U/L	N/A	> 1 and ≤ 3 × ULN
Creatine Kinase (CK)	U/L	N/A	> 3 and ≤ 5 × ULN
Creatine Kinase (CK)	U/L	N/A	> 5 × and ≤ 10 × ULN*
Creatine Kinase (CK)	U/L	N/A	> 10 and ≤ 20 × ULN*
Creatine Kinase (CK)	U/L	N/A	> 20 × ULN*
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.
For AST, ALT and CK, the most severe result for each subject will be used.
*Clinically significant laboratory boundaries.

6 Reference

CKJX839A12306B (MDCO-PCS-17-05) Protocol global amendment 2

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