NOVARTIS

Clinical Development

KJX839/inclisiran

CKJX839A12201E1 (MDCO-PCS-16-01) / NCT03060577

An open label, active comparator extension trial to assess the effect of long term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C (ORION-3)

Statistical Analysis Plan (SAP)

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24-Jan-2022	Prior to DB lock	Creation of amendment v03.	Removed "on-treatment" wording from diabetes analyses.	Section 2.7.4.2 and 2.7.4.3

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███	██████████
ATC	Anatomical Therapeutic Chemical classification system
AE	Adverse Event
ALT	Alanine Aminotransferase
Apo-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CK	Creatine Kinase
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive Protein
CS	Clinically Significant
CSR	Clinical Study Report
███	█████████
DBL	Database Lock
DMC	Data Monitoring Committee
DMS	Document Management System
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
HbA1c	Hemoglobin A1C
HDL-C	High-Density Lipoprotein Cholesterol
HLGT	High Level Group Term
HLT	High Level Term
IA	Interim Analyses
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density Lipoprotein Cholesterol
LLN	Lower Limit of the Normal range
LMT	Lipid Modifying Therapy
Lp(a)	Lipoprotein(a)
███	████████████████
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
PCS	Potentially Clinically Significant
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9

PK	Pharmacokinetics
PPS	Per-Protocol Set
███	████████████████
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standardized MedDRA queries
SOC	System Organ Class
PT	Preferred Term
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
VLDL-C	Very Low-Density Lipoprotein Cholesterol
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 Phase II open label extension trial CKJX839A12201E1. The purpose of this study is to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents 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 CKJX839A12201E1 (MDCO-PCS-16-01) global amendment 5, content final dated 07-Oct-2020.

1.1 Study design

This study will be an open label, long term extension study with two arms. Group 1 (inclisiran only arm) will receive inclisiran only and Group 2 (switching arm) will receive an active comparator (evolocumab) for one year followed by inclisiran. The study will be conducted in subjects with ASCVD or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies who have completed study MDCO-PCS-15-01 (ORION-1/ CKJX839A12201), to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. All eligible and willing subjects who have completed the ORION-1 study to at least Day 210, and subjects whose LDL-C has returned to within 20% of the Baseline of ORION-1 value or who have reached Day 360 can be enrolled into the ORION-3 study. The study will be a multi-national, multi-center study (approximately 60 centers). Informed consent will be obtained from subjects before the initiation of any study-specific procedures.

Subjects completing study MDCO-PCS-15-01 and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran or evolocumab, based on the treatment received in study MDCO-PCS-15-01. In countries where applicable, on signing consent and being entered into this study, the investigator will be informed by the Interactive Voice/Web Response System (IXRS) regarding the treatment allocation, and therefore, whether placebo or inclisiran was administered in study MDCO-PCS-15-01 (CKJX839A12201) and the subject will be informed accordingly. Those subjects who received inclisiran in MDCO-PCS-15-01 will receive inclisiran sodium throughout this study (Group 1; inclisiran only arm), and those subjects who received placebo in MDCO-PCS-15-01 (CKJX839A12201) will receive evolocumab as comparator for 1 year, and then transition to inclisiran for the remainder of the study (Group 2; switching arm). Until study drug is available, subjects will have monthly observation visits until study drug administration commences.

Day 1 of ORION-3 is the day when eligible subjects will receive the first subcutaneous (SC) administration of inclisiran or evolocumab.

Group 1 (Inclisiran Only Arm):

After first study drug administration of inclisiran, all subjects will be observed in the clinic for at least 4 hours post injection before being discharged.

The subsequent visit schedule is as follows:

- Dosing visits: Every 180 days until Day 720, an additional dose on Day 810, then back to every 180 day dosing until end of study (EOS). Therefore, dosing after Day 1 (ORION-3) will occur on Days 180, 360, 540, 720, 810*, 990, 1170 and 1350.

  *Day 810 dose added to assess the effect of giving 2 doses 90 days apart (at Days 720 and 810).

- Safety follow-up visits: Days 30, 90, 210, 270, 390, 450, 570, 630, 870, 1080, 1260, and EOS (Day 1440).

- The primary analysis time point is Day 210.

Group 2 (Switching Arm):

Subjects receiving evolocumab will receive the first dose on Day 1 (ORION-3), administered by the investigator at the site, and will then self-administer evolocumab at home every 14 days until Day 336. Sites will then be assigned to have their evolocumab treated subjects placed into one of two transition groups.

- Transition 1 (staged): Day 336 will be the final dose of evolocumab therapy and the first dose of inclisiran will be administered at the Day 360 visit.

- Transition 2 (concurrent): Day 336 will be the final dose of evolocumab therapy at home. At the Day 360 visit subjects will receive an additional dose of evolocumab and their first dose of inclisiran, both administered by the investigator.

After first study drug administration of inclisiran on Day 360, all subjects in Group 2 (switching arm) will be observed in the clinic for at least 4 hours post injection before being discharged.

The subsequent visit schedule is as follows:

- Dosing visits: Day 450 (2nd dose), then every 180 days until end of study (Days 630, 810, 990, 1170 and 1350).

- Safety follow-up visits: Days 390, 510, 540, 720, 900, 1080, 1260, and EOS (Day 1440).

End of Study (EOS)

EOS visit will occur at Day 1440, 90 days after the final administration of study drug (at Day 1350). However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

Efficacy assessments will measure the effects of inclisiran on levels of LDL-C, lipids and lipoproteins including total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) (Lp(a)), C-reactive protein (CRP), and proprotein convertase subtilisin/kexin type 9 (PCSK9).

At each visit, adverse events (AE), serious adverse events (SAE), concomitant medications, and safety laboratory assessments will be collected.

A Data Monitoring Committee (DMC) will review on a regular schedule the safety data. A recommendation may be taken to stop the study at any of these reviews.

Subjects enrolled into this extension study will receive study drug for approximately 4 years or

- until the investigator's recommendation of discontinuation,

- until the sponsor's recommendation of discontinuation,

- until the subject's decision to discontinue for any reason,

- until an administrative decision is made to end the study

If subjects, who have completed EOS visit (90 days after last dose administration), wish to continue treatment with inclisiran (and none of the above listed decisions or recommendations to discontinue the trial are in place) they will be given the opportunity to enroll into ORION-8 (open-label extension trial).

The protocol described the conduct of an interim analysis of lipids and PCSK9 upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). Although there was a review of data upon completion of Day 210 for subjects in Group 1, no formal interim analysis report was generated. An interim analysis was conducted to evaluate Group 1 safety and tolerability data after all Group 1 subjects completed 24 months of treatment with inclisiran.

A schematic diagram of the study design is presented in Figure 1-1.

Figure 1-1   Study design

1.2   Study objectives, endpoints and estimands

This study is designed to evaluate the efficacy, safety, and tolerability of inclisiran injection(s). The objectives and the corresponding endpoints are listed in Table 1-1.

Table 1-1   Objectives and related endpoints

Objectives	Endpoints
Primary objective The primary objective of this study is: To evaluate • The effect of inclisiran treatment on LDL-C levels at Day 210 compared to Baseline of ORION-1 in Group 1 (inclisiran only arm).	**Endpoint for primary objective** • The percentage change from Baseline of ORION-1 in LDL-C at Day 210 in this study (Group 1; inclisiran only arm).

Secondary objectives
The secondary objectives of this study are:
• To evaluate the effect of inclisiran on the following (Group 1; inclisiran only arm):
  - LDL-C levels over time
 	
  - PCSK9 levels over time
 	
  - Other lipids, lipoproteins, and apolipoproteins over time
	Endpoints for secondary objectives
	(all for Group 1; inclisiran only arm)
	
	• Observed value, absolute change and percentage change from Baseline of ORION-1 in LDL-C over time in this study
	• Change and percentage change in LDL-C at Day 210 compared to Day 870 of ORION-3
	• Observed value, absolute change and percentage change from Baseline of ORION-1 in PCSK9 levels over time in this study
	• Observed value, absolute change and percentage change from Baseline of ORION-1 in other lipids, lipoproteins, and apolipoproteins, over time in this study

Objectives	Endpoints
- Individual responsiveness to inclisiran	• Individual responsiveness to inclisiran defined as the proportion of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL over time and at any time point
- Proportion of subjects achieving target levels prespecified in global lipid guidelines	• Proportion of subjects achieving global lipid targets for their level of ASCVD over time and at any time point
- Proportion of subjects with at least 50% LDL-C reduction from Baseline of ORION-1 over time	• Proportion of subjects with ≥50% LDL-C reduction from Baseline of ORION-1 over time and at any time point
• To evaluate the long term safety and tolerability of inclisiran (Group 1; inclisiran only arm)	• Long term safety and tolerability of inclisiran treatment (AEs, SAEs, and clinical laboratory values)

Objectives	Endpoints
███████████████████████	██████████████████

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis or a designated clinical research organization (CRO). The most recent version of SAS available in the statistical programming environment of Novartis or the designated CRO will be used for the analysis.

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Categorical variables will be summarized using counts and percentages. Percentages are based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including changes from Baseline of ORION-1 or ORION-3, will be summarized using descriptive statistics (n (number of non-missing observations), mean, standard deviation (SD), median, first and third quartiles, minimum and maximum). The precise definitions of the baselines are given in Table 2-1.

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%.

Analyses for the final CSR will be conducted after all participants complete the EOS visit or discontinued early. ██

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 SC injection of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran)/1.5 mL

- Comparator drug: Evolocumab (REPATHA®) will be administered as a single SC injection at 140 mg.

Date of first/last administration of study drug

Date of first/last administration of study drug is defined as the first/last date of administration of either inclisiran or evolocumab in ORION-3, unless otherwise specified.

Gap period

The time between the end of ORION-1 and the beginning (date of informed consent) of ORION-3 is called the gap period.

Study day

Study day will be defined as the number of days since the date of first administration of study drug. The date of first administration of study drug will be defined as Day 1 and the day before the first administration 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 date of first administration of study drug,

> Study day = Assessment date – Date of first administration of study drug + 1;

For dates prior to the date of first administration of study drug,

> Study day = Assessment date – Date of first administration of study drug.

Baselines

Depending on the specific analysis, either baseline of ORION-1 or baseline of ORION-3 is considered. The precise definitions of the baselines for each analysis are summarized in Table 2-1.

Table 2-1   Summary of baselines

Analysis category	Analysis	Baseline used	Explanation
Baseline Characteristics	Age*, weight, body mass index (BMI), country	Study entry of ORION-3	To provide a more accurate value of parameters that may change, baseline of ORION-3 is used.

	Estimated glomerular filtration rate (eGFR)	Last non-missing record prior to first study drug administration of ORION-3	To provide a more accurate value of parameters that may change, baseline of ORION-3 is used.
	Sex, race, ethnicity, height	Screening period of ORION-1	These values will not change or will not change significantly so baseline of ORION-1 is used.
	Medical history	Day 1 of ORION-1	Medical history is reported prior to the first treatment in ORION-1, after which any new medical conditions will be captured as AEs.
Prior and concomitant therapies	Concomitant Medications	Day 1 of ORION-3	Medications taken on or after Day 1 of ORION-3 will be considered as concomitant for ORION-3.**
Efficacy	Efficacy parameters in Group 1 (inclisiran only arm)	Baseline of ORION-1***	Due to residual efficacy from ORION-1, the true change from baseline should use baseline of ORION-1, i.e. prior to receiving any dose of inclisiran.
	Efficacy parameters in Group 2 (switching arm)	Baseline of ORION-3****	Placebo was given in ORION-1 and since treatment adjustments may have occurred during ORION-1 in lipid modifying therapies (LMT), baseline of ORION-3 will be used.
Safety	Adverse events	Day 1 of ORION-3	Previous AEs are collected in ORION-1, the gap period and the observation period so TEAEs in ORION-3 are collected from Day 1 (first dose) of ORION-3.
	Electrocardiograms (ECG)	Day 1 of ORION-3	To identify untoward change in ECG within ORION-3
	Safety laboratory parameters, vital signs	Baseline of ORION-3****	To identify untoward change in safety laboratory parameters and vital signs within ORION-3

* Since age will not be re-collected in ORION-3, the age at ORION-3 baseline is inferred using the ORION-1 baseline:

- If the difference between consent date in ORION-3 and ORION-1 is greater than 365 days for a subject then 1 year will be added to the age at ORION-1 baseline;
- Otherwise, ORION-1 baseline age will be used.

** Although all medications received 30 days prior to consent in ORION-1 through the EOS in ORION-3 will be reported, only medications taken on or after Day 1 of ORION-3 will be considered concomitant for ORION-3.

*** For PCSK9, lipids, lipoproteins and apolipoproteins, the last available record prior to first study drug administration in ORION-1 will be used as the baseline for Group 1.

**** The last available record in ORION-3 prior to first study drug administration will be used as the baseline for safety laboratory parameters, vital signs and Group 2 efficacy parameters, unless otherwise specified.

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, 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 but not both, the available one will be used.

2.2 Analysis sets

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

Intent-to-treat (ITT) population

The ITT Population will include all subjects who entered into the study. Treatment classification will be based on the allocated treatment.

Modified intent-to-treat (mITT) population

The mITT Population will include all subjects who receive at least one dose of study drug and have both the ORION-3 baseline and the Day 210 follow-up LDL-C (reflexive) assessment. Treatment classification will be based on the allocated treatment. This will be the primary population for analysis of the primary and secondary endpoints.

Safety (SAF) population

The Safety Population will include all subjects who received at least one dose of study drug. Treatment classification will be based on the actual treatment received. This will be the primary population for the safety analyses.

2.2.1 Subgroup of interest

No subgroup analyses will be performed.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Subject disposition will be summarized for the ITT population as follows:

- The number of subjects who were randomized for ORION-1 broken down by eligibility and consent status, who had a gap period, and who were treated will be summarized. The days from last dose in ORION-1 to first dose of study drug in ORION-3 will also be summarized.

- The number of subjects who consented and the number of subjects who were treated will be summarized by group and overall.

- The number of subjects in each analysis population will be summarized by group and overall.

- The number of subjects who completed the study or who discontinued early along with reasons for early discontinuation will be summarized by group and overall.

- The duration on study (number of days from the first date of study drug administration to the date of last recorded visit/contact date in the database) will be summarized by group and overall.

- Protocol deviations and violations of subject restrictions will be summarized by group and overall.

Select tables for Group 2 will be broken down by transition group (Transition 1 (staged) and Transition 2 (concurrent)).

Completers are defined as a subject who completes the Day 1440 visit.

2.3.2 Demographics and other baseline characteristics

Subject demographics and background characteristics including age, sex, weight, height, BMI, race, ethnicity, country (country of participation), baseline eGFR and re-evaluation of child-bearing potential will be summarized using the ITT population. The following categorizations of quantitative variables will be performed:

- Age into ≥ 18 - < 65 and ≥ 65

- Age into ≥ 18 - < 50, ≥ 50 - < 65, ≥ 65 - < 75, ≥ 75

- Baseline eGFR into ≥ 15 - < 30, ≥ 30 - < 60, ≥ 60 - < 90, ≥ 90

Age collected in ORION-1 will be used but if the difference between consent date in ORION-3 and ORION-1 is greater than 365 days for a subject then 1 year will be added to the age for this subject.

Medical history (targeted and other medical history) will be summarized using the safety population. 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 and preferred term.

Summaries will be presented overall and by group (Group 1 and Group 2). Select tables for Group 2 will be broken down by transition group (Transition 1 (staged) and Transition 2 (concurrent)).

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

2.4.1 Study treatment / compliance

Study drug administration will be summarized for inclisiran and evolocumab separately, overall and by visit. For inclisiran, the summary will include number of doses, actual dose for each injection, injection volume received, location for each injection, and occurrence of any medication errors. For subjects in Group 2 (switching arm), inclisiran administration after transitioning to inclisiran will be summarized by transition groups.

Duration of exposure to inclisiran in ORION-3 and cumulative exposure to inclisiran from ORION-1 through ORION-3 will be summarized. Duration of exposure to inclisiran will be calculated as: minimum of (Date of last dose of inclisiran – Date of first dose of inclisiran + 180) and (Date of last known visit/contact – Date of first dose of inclisiran). Patient years exposure (ORION-3 and cumulative) to inclisiran will also be summarized, which is calculated as (sum of duration of exposure to inclisiran)/365.25.

For evolocumab, the number and percent of subjects who have evolocumab administrations will be summarized for each planned time point of injection. Number of injections and number of missed injections will also be summarized.

Summaries will be presented for the safety population by treatment group (Group 1 and Group 2). Select tables for Group 2 will be broken down by transition group (Transition 1 (staged) and Transition 2 (concurrent)).

2.4.2 Prior and concomitant therapies

Prior medications, baseline (Day 1 of ORION-3) concomitant medications, new or changed concomitant medications, and all prior and concomitant medications combined 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.

Prior lipid modifying therapies (LMT), baseline (Day 1 of ORION-3) concomitant LMTs, new or changed concomitant LMTs, and all prior and concomitant LMTs combined will be

summarized by preferred name with dose and frequency. LMTs are medications with 3rd level ATC classification being either C10A (lipid modifying agents, plain) or C10B (Lipid modifying agents, combinations) according to the coding by the WHO drug dictionary. LMTs will be grouped into statins and other LMT. Statins will be furthered 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.

Prior medication/LMT is defined as the medication stopped before Day 1 of ORION-3. Concomitant medication/LMT at Baseline (Day 1 of ORION-3), is defined as any medication onset before or on Day 1 (Day 1 of ORION-3) and either still ongoing or stopped on Day 1 (Day 1 of ORION-3) or later. Any medications with start date after study Day 1 (Day 1 of ORION-3) are considered as new or changed concomitant medications/LMT.

Summaries will be presented by group (Group 1 and Group 2). Select tables for Group 2 will be broken down by transition group (Transition 1 (staged) and Transition 2 (concurrent)). Analyses will be performed on the safety population.

2.5 Analysis supporting primary objective(s)

The primary objective of this study is to evaluate the effect of inclisiran treatment on LDL-C levels at Day 210 compared to Baseline of ORION-1 in Group 1 (inclisiran only arm).

2.5.1 Primary endpoint(s)

The primary efficacy endpoint is the percentage change from Baseline of ORION-1 in LDL-C at Day 210 in this study (Group 1; inclisiran only arm).

Summary statistics (n, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum) for the percentage change in LDL-C and 95% confidence interval for the mean will be provided. One sample t-test will also be utilized to assess if the mean percent change from baseline to Day 210 is 0 or not. P-value (two-sided test) will be provided.

Analyses will be performed on the ITT and mITT populations.

2.5.2 Handling of missing values

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 efficacy objective of this study is to evaluate the effect of inclisiran on the following for Group 1 (inclisiran only arm):

- LDL-C levels over time
- PCSK9 levels over time
- Other lipids, lipoproteins, and apolipoproteins over time

- Individual responsiveness to inclisiran

- Proportion of subjects achieving target levels prespecified in global lipid guidelines

- Proportion of subjects with at least 50% LDL-C reduction from Baseline of ORION-1 over time

2.6.1   Secondary endpoint(s)

The secondary efficacy endpoints of this study are:

- Observed value, absolute change and percentage change from Baseline of ORION-1 in LDL-C over time in this study

- Observed value, absolute change and percentage change from Baseline of ORION-1 in PCSK9 levels over time in this study

- Change and percentage change in LDL-C at Day 210 compared to Day 870 of ORION-3

- Observed value, absolute change and percentage change from Baseline of ORION-1 in other lipids, lipoproteins, and apolipoproteins, over time in this study

- Individual responsiveness to inclisiran defined as the proportion of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL over time and at any time point

- Proportion of subjects achieving global lipid targets for their level of ASCVD over time and at any time point

- Proportion of subjects with ≥50% LDL-C reduction from Baseline of ORION-1 over time and at any time point

The global lipid target is LDL-C level of < 70 mg/dL for ASCVD subjects and LDL-C level of < 100 mg/dL for ASCVD risk equivalent subjects.

Summary statistics (n, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum) along with 95% confidence intervals for the mean will be provided for the continuous endpoints. The categorical variables will be summarized using the number and percentage of subjects who achieve each response level. 95% confidence intervals for the proportions will be provided.

Analyses will be performed on the ITT and mITT populations (Group 1; inclisiran only arm).

2.6.2   Handling of missing values

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

2.7   Safety analyses

All safety evaluations will be performed for the following groups unless otherwise specified:

- Subjects on evolocumab from the switching arm (Group 2) for the period between Day 1 (Day 1 of ORION-3) and Day 360.

- Subjects from the inclisiran only arm (Group 1), for the period from Day 1 (Day 1 of ORION-3) until EOS.

All the safety analyses will be performed on the safety population unless otherwise specified. Safety analyses are based on observed values. Any missing safety data including laboratory data will not be imputed.

2.7.1 Adverse events (AEs)

Adverse events will be summarized for every group specified above in Section 2.7.

The most recent version of MedDRA before DBL will be used for coding AEs. An AE (classified as preferred term) will be counted as a treatment emergent AE (TEAE) if the AE started after the first treatment in ORION-3 or the AE was present prior to the first treatment in ORION-3 but increased in severity after initiation of study drug in ORION-3. Only TEAEs will be summarized in the tables, but the subject data listings will include all AEs.

The following summary tables will be presented:

- Overall Summary of TEAEs
- TEAEs by primary system organ class (SOC) and preferred term (PT)
- TEAEs by PT
- TEAEs by primary SOC, PT, and severity
- TEAEs related to study drug by primary SOC, PT
- Treatment Emergent Serious AEs (TESAEs) by primary SOC and PT
- TESAEs by PT
- TESAEs related to study drug by primary SOC, PT
- TEAEs leading to withdrawal of study treatment by primary SOC and PT
- TEAEs with a fatal outcome by primary SOC and PT
- TEAEs at the injection site by primary SOC and PT
- Clinically relevant TEAEs at the injection site (listed in Appendix 5.3) by PT

- TEAEs at the injection site by primary SOC, PT and severity
- Prespecified signs and symptoms at the injection site

If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term, using the most severe occurrence for the summary by severity. For select tables, exposure-adjusted incidence rate (EAIR) will be calculated for subjects from the inclisiran only arm (Group 1), for the period from Day 1 (Day 1 of ORION-3) until EOS, ██
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EAIR is defined as the total number of subjects with the event / total exposure (years) * 100%, where total exposure = sum of duration from start date of inclisiran injection in ORION-3 to the onset date of the event (the last visit/contact date will be used for the patients without the event).

TEAEs at the injection site include all TEAEs identified as being an injection site reaction on AE Case Report Form (CRF) or with "injection site reactions" as the high level term (HLT).

The following additional adverse events will be assessed (Refer to Appendix 5.2 for the detailed definitions):

1. Hepatic events
2. Renal events
3. Hypersensitivity
4. Neurological events and Neurocognitive disorders
5. Ophthalmological events

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Listings will be presented for subjects with death, SAEs, and AEs leading to a discontinuation.

2.7.2   Deaths

As mentioned in Section 2.7.1, TEAEs with a fatal outcome will be summarized by SOC and PT.

2.7.3   Laboratory data

Summaries for laboratory values will include observed value, changes and percent changes from ORION-3 baseline at each time point.

A shift analysis using the normal range (except for eGFR and HbA1c) will be done which counts the number of subjects with a low, normal or high value at ORION-3 baseline and a low, normal or high value post baseline.

The following ranges will be used for eGFR and HbA1c:

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

- For HbA1c, the categories will be < 5.7%, ≥ 5.7% to < 6.5%, and ≥ 6.5%.

The shift table for the fasting glucose will require the lab sample to be taken while fasting. Samples taken while the subject was not fasting will not be analyzed.

The number and percentage of subjects with potentially clinically significant (PCS) laboratory values and clinically significant (CS) laboratory values (refer to Appendix 5.4 for the criteria) will be summarized by treatment group. HbA1c criteria is explicitly stated in Appendix 5.4. All other PCS and CS criteria are met when both of the following occur:

- Worst post-baseline value meets the thresholds listed in Appendix 5.4

- Baseline value does not meet the thresholds in Appendix 5.4

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

The number and percentage of subjects satisfying Hy's Law will also be tabulated 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.

2.7.4 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

- incidence of post-baseline new onset of diabetes.

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

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 baseline if the targeted medical history notes that the subject is diabetic or the baseline HbA1c value is ≥ 6.5%.

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

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

* Baseline uses average of ORION-3 study entry and Day 1 fasting glucose values. If one fasting glucose value is missing, the assessment will be based on the available data.

** ORION-3 Day 1 assessment will be considered as baseline for HbA1c. If missing, then the baseline will be based on assessment at ORION-3 study entry.

2.7.4.3   Shifts from baseline in glucose control category

Shifts from baseline in glucose control category will be summarized two different ways: the change from ORION-3 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 ORION-3 study entry or Day 1 AND HbA1c < 5.7%	Fasting glucose < 100 mg/dL on two consecutive occasions AND HbA1c < 5.7%

Normal to Impaired	Fasting glucose < 100 mg/dL on ORION-3 study entry or Day 1 AND HbA1c < 5.7%	Fasting glucose ≥ 100 and < 126 mg/dL on two consecutive occasions OR HbA1c ≥ 5.7 and < 6.5%
Normal to Diabetes	Fasting glucose < 100 mg/dL on ORION-3 study entry or Day 1 AND HbA1c < 5.7%	Fasting glucose ≥ 126 mg/dL on two consecutive occasions OR HbA1c ≥ 6.5%
Impaired to Normal	Fasting glucose ≥ 100 and < 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 5.7 and < 6.5%	Fasting glucose < 100 mg/dL on two consecutive occasions AND HbA1c < 5.7%
Impaired to Impaired (no change)	Fasting glucose ≥ 100 and < 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 5.7 and < 6.5%	Fasting glucose ≥ 100 and < 126 mg/dL on two consecutive occasions OR HbA1c ≥ 5.7 and < 6.5%
Impaired to Diabetes	Fasting glucose ≥ 100 and < 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 5.7 and < 6.5%	Fasting glucose ≥ 126 mg/dL on two consecutive occasions OR HbA1c ≥ 6.5%
Diabetes to Normal	Fasting glucose ≥ 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 6.5%	Fasting glucose < 100 mg/dL on two consecutive occasions AND HbA1c < 5.7%
Diabetes to Impaired	Fasting glucose ≥ 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 6.5%	Fasting glucose ≥ 100 and < 126 mg/dL on two consecutive occasions OR HbA1c ≥ 5.7 and < 6.5%
Diabetes to Diabetes (no change)	Fasting glucose ≥ 126 mg/dL on ORION-3 study entry and Day 1 OR HbA1c ≥ 6.5%	Fasting glucose ≥ 126 mg/dL on two consecutive occasions OR HbA1c ≥ 6.5%

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

** If one fasting glucose value is missing (ORION-3 study entry or Day 1), the assessment will be based on the available data.

2.7.4.4 Incidence of post-baseline new-onset of diabetes

The number of subjects who shift from no diabetes at baseline (defined as no medical history of diabetes in the targeted medical history CRF, HbA1c <6.5% at baseline, and fasting glucose <126 mg/dL at baseline (note that baseline is defined as the average of study entry and Day 1

fasting glucose values. If one fasting glucose value is missing (study entry or Day 1), the assessment will be based on the available data) to diabetes will be summarized. A 4-component definition of diabetes will be utilized. The 4 components are provided below.

1. Diabetic TEAEs identified by the 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.

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

2.7.5 Other safety data

2.7.5.1 Electrocardiograms (ECG)

The percentage of subjects with any changes from baseline ECG will be summarized over time.

2.7.5.2 Vital signs

Observed value, change, and percent change from ORION-3 baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group.

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

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

- o > -5 to ≤ -3
- o > -3 to < 3
- o ≥ 3 to < 5
- o ≥ 5 to < 10
- o ≥ 10

whose assessment date is closest to the start date of that visit will be used for analyses. If more

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2.8.1.1 Handling of missing values

For missing questionnaires no imputation will be undertaken.

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2.10   Interim analysis

The protocol described the conduct of an interim analysis of lipids and PCSK9 upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). Although there was a review of data upon completion of Day 210 for subjects in Group 1, no formal interim analysis report was generated. An interim analysis was conducted to evaluate Group 1 safety and tolerability data after all Group 1 subjects completed 24 months of treatment with inclisiran, ███████████ ██ ████████████████████████████ The interim analysis was not intended for hypothesis testing, hence no sequential testing boundaries were applied.

3   Sample size calculation

This is an extension of the Phase II ORION-1 (CKJX839A12201; MDCO-PCS-15-01) study. All eligible and willing subjects who have completed the ORION-1 study to at least Day 210 and whose LDL-C level returned to within 20% of the Baseline of ORION-1 value or who have reached Day 360 can be enrolled into this study. Subjects withdrawn from the ORION-1 study at any time will not be eligible for 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.

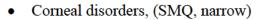#### 5.1.2   AE date imputation

Adverse events with incomplete dates will be categorized as treatment emergent unless there was sufficient specificity to the start/end dates to determine that the event began before the first dose of study drug.

5.1.3 Concomitant medication date imputation

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

       o Demyelination, (SMQ, broad and narrow)

       o Peripheral neuropathy, (SMQ, broad and narrow)

   • Neurocognitive disorders

       o Deliria (incl confusion), (HLGT)

       o Cognitive and attention disorders and disturbances, (HLGT)

       o Dementia and amnestic conditions, (HLGT)

       o Disturbances in thinking and perception (HLGT)

       o Mental impairment disorders (HLGT)

5. Ophthalmologic events

   • Optic nerve disorders, (SMQ, broad and narrow)

   • Retinal disorders, (SMQ, narrow)

- Corneal disorders, (SMQ, narrow)

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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 Clinically relevant adverse events at injection site preferred terms

Injection site atrophy
Injection site cellulitis
Injection site dermatitis
Injection site eczema
Injection site erythema
Injection site fibrosis
Injection site granuloma
Injection site hypersensitivity
Injection site infection
Injection site inflammation
Injection site ischaemia

Injection site lymphadenopathy
Injection site necrosis
Injection site nerve damage
Injection site photosensitivity reaction
Injection site pruritus
Injection site pustule
Injection site rash
Injection site reaction
Injection site recall reaction
Injection site scar
Injection site thrombosis
Injection site ulcer
Injection site urticaria
Injection site vasculitis
Injection site vesicles

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

Hemoglobin A1c criteria is explicitly stated in the table below.

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

- Post-baseline values meet the thresholds below

- Baseline value does not meet the thresholds below

Parameter	Unit	Lower Boundary	Upper Boundary
Hematology			
Hematocrit	%	≤ 0.8 × LLN	N/A
Hemoglobin	g/dL	≤ 10 g/dL	N/A
Platelet Count	10^9/L	≤ 75*	≥ 700*
White Blood Cell Count	10^9/L	≤ 2.8	≥ 16
Serum Chemistry			
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 1 and ≤ 3 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 3 and ≤ 5 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 5 and ≤ 10 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 10 and ≤ 20 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 20 × ULN*
Alkaline Phosphatase	U/L	N/A	> 2 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 1 and ≤ 3 × ULN

Parameter	Unit	Lower Boundary	Upper Boundary
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. *Clinically significant laboratory boundaries.			

6 Reference

1. MDCO-PCS-16-01 (CKJX839A12201E1) Protocol global amendment 5