NOVARTIS

Novartis Research and Development

KJX839/Inclisiran

Clinical Trial Protocol MDCO-PCS-17-05 (CKJX839A12306B) / 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)

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Protocol Synopsis

Name of Sponsor/Company: Novartis

Name of Finished Drug/Device: Inclisiran for Injection (also referred to as KJX839),

Name of Active Ingredient: Inclisiran sodium

Title of Study: 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 also referred to as CKJX839A12306B)

Phase of Development: III

Study Centers: Global Multicenter study (approximately 300 sites).

Central Facilities: This list is maintained by the Sponsor

Number of Subjects: Maximum of up to 3300 subjects

Study Period: The estimated study period for the study will be approximately 4 years from first subject enrolled in this extension study to last subject completed, or until the investigator's recommendation of discontinuation, sponsor's recommendation of discontinuation, until an administrative decision is made to end the study.

Objectives:

Primary :

The primary objectives are to evaluate:

- The effect of inclisiran treatment on the proportion of subjects achieving prespecified low density lipoprotein cholesterol (LDL-C) targets at end of study (EOS)
- The safety and tolerability profile of long-term use of inclisiran

Secondary:

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

- LDL-C levels
- Other lipids and lipoproteins

Methodology:

This study will be a long-term extension study in up to 3300 subjects with atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia), or heterozygous [redacted] familial hypercholesterolemia (HeFH [redacted]) and elevated low density lipoprotein cholesterol (LDL-C) despite treatment with LDL-C lowering therapies who have completed the Phase II trial MDCO-PCS-16-01 (ORION-3, also referred to as CKJX839A12201E1) or Phase III lipid lowering studies: MDCO-PCS-17-03(ORION-9 also referred to as CKJX839A12303), MDCO-PCS-17-04 (ORION-10, also referred to as CKJX839A12304, or MDCO-PCS-17-08(ORION-11, also referred to as CKJX839A12305). The purpose of this extension 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 EOS visit in the previous study will be Day 1 in ORION-8.

Subjects completing one of the previously mentioned inclisiran trials (the Phase II trial (ORION-3, Phase III inclisiran studies (ORION-9, ORION-10 or ORION-11 trial) and fulfilling all inclusion and exclusion criteria of this study will receive blinded inclisiran sodium 300 milligrams (mg) which is equivalent to 284 mg inclisiran, or blinded placebo on Day 1 in this tria,. except for subjects moving over from ORION-3. These subjects will receive the first study medication at day 90. Subjects who received placebo in the previous Phase III feeder study will receive blinded inclisiran and subjects who received inclisiran in the previous feeder study will receive blinded placebo at this visit, in order to maintain the blinding of the feeder study until database lock of those studies. 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 Day1of this study until ethics committee approval was granted in that country.

After first study drug administration, all subjects will be observed in the clinic for 30 minutes post injection before being discharged.

All subjects will return at Day 90 for the next visit and will receive open label inclisiran sodium 300 mg which is equivalent to 284 mg inclisiran. Subjects will then return for open label drug administration of inclisiran sodium 300 mg every 180 days until EOS and be observed for 30 minutes at each visit.

Efficacy assessments will measure the effects of inclisiran on levels of LDL-C.

At each visit, adverse events (AEs), serious adverse events (SAEs), concomitant medications, and safety laboratory parameters will be collected.

[redacted]

An Independent Data Monitoring Committee (IDMC) will review safety data on a regular schedule as specified in the IDMC charter from subject enrollment in the double-blind phase until the end of the open label phase of the study. A recommendation may be taken to stop or amend the study after any of these reviews.

The duration of each subject is expected to be a maximum of 3 years (or until the investigator's recommendation of discontinuation, sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, until an administrative decision is made to end the study.. At this time, EOS evaluations will be conducted at the EOS visit.

Diagnosis and Main Criteria for Selection:

Subjects may be included if they meet all of the following inclusion criteria prior to entry into this study:

1. Completion of a previously qualifying inclisiran Phase II trial MDCO-PCS-16-01 (ORION-3, or Phase III lipid-lowering ORION feeder study [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10) or MDCO-PCS-17-08 (ORION-11)], meaning the subject received the last dose of study drug and completed the final study visit per applicable protocol.
2. On current lipid-lowering therapies (such as a statin and/or ezetimibe) from previous study with no planned medication or dose change during study participation.
3. Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

Subjects will be excluded from the study if any of the following exclusion criteria apply immediately prior to entry into the study:

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate's] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 3 years.
4. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin (TBIL) elevation >2x ULN at last recorded visit in the feeder study prior to study entry visit.
5. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least one method of acceptable effective contraception (eg, oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions from this criterion:
    a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age
    b. Postmenopausal women (as defined above) and less than 55 years old with a negative pregnancy test within 24 hours of enrollment
    c. Women who are surgically sterilized at least 3 months prior to enrollment
6. Planned use of other investigational medicinal products other than inclisiran or devices during the course of the study.
7. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    a. Subjects who are unable to communicate or to cooperate with the investigator
    b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency)
    c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study)
    d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study
    e. Persons directly involved in the conduct of the study

Test Drug/Device, Dose and Mode of Administration: Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) will be administered as a single subcutaneous (SC) dose every 180 days from the last previous study dose until the end of the study. Visit 1 dose will be blinded; subsequent doses will be open label.

Duration of Treatment: The expected duration of each subjects' involvement in the study will be a maximum of 3 years.

Reference Therapy, Dose and Mode of Administration: The placebo pre-filled syringes will contain saline solution. Placebo pre-filled syringes 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 the inclisiran group.

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

- Proportion of subjects who attain global lipid targets (entry criterion from respective previous study) for their level of ASCVD risk at EOS

Secondary Endpoints:

- Absolute change and percentage change in LDL-C from baseline (defined as baseline in feeder study) to EOS
- Absolute change and percentage change in other lipids and lipoprotein from baseline (defined as baseline in feeder study) to EOS

Safety Endpoint:

The safety and tolerability profile of long-term use of inclisiran by evaluation of adverse events, SAEs, vital signs, and clinical laboratory values (hematology, coagulation testing, chemistry, and urinalysis) collected at specified visits through the EOS visit.

Cardiovascular events will be reported as AEs for the compilation of information on cardiovascular (CV) events such as CV death, resuscitated cardiac arrest, nonfatal myocardial infarction (MI), and nonfatal stroke (ischemic and hemorrhagic).

Pharmacology: N/A; not collected

Statistical Methods:

Sample Size and Power

This is a long-term open label extension of the Phase II trial MDCO-PCS-16-01 (ORION-3), and Phase III lipid-lowering studies [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10), or MDCO-PCS-17-08 (ORION-11)]. All eligible and willing subjects from these studies may be enrolled into this study.

The statistical analysis are noncomparative. Sample size considerations do not apply.

Efficacy Endpoint Analysis:

All analysis will be descriptive. Confidence intervals will be provided whenever necessary.

Safety Endpoint Analysis:

The analysis of the safety endpoints will be descriptive.

Interim Analysis:

No interim analysis is planned in this study.

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List Of Abbreviations

[redacted]	[redacted]
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
BUN	total protein urea
CFR	Code of Federal Regulations
CHD	coronary heart disease
CK	creatine kinase
C_{max}	maximum plasma concentration
CrCl	creatinine clearance
CV	cardiovascular
CVD	cerebrovascular disease
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GPV	Global Pharmacovigilance
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
IDMC	Independent Data Monitoring Committee
IL6	interleukin 6
INR	International normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
IV	intravenous
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
[redacted]	[redacted]

LS mean	least square mean
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	millimole
mRNA	messenger ribonucleic acid
PCS	potentially clinical significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PK	pharmacokinetic
PT	prothrombin time
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
siRNA	small interfering ribonucleic acid
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TBIL	total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse event
TTR	target transthyretin
ULN	upper limit of normal
US	United States
WHO	World Health Organization

Amendment 2 (06-Oct-2020)

Amendment rationale

The first subject for this trial was enrolled in April 2019 and enrollment was completed in February 2020 (with 2991 subjects enrolled).

This amendment is written to address the change in sponsorship from The Medicines Company to Novartis after acquisition of The Medicines Company by Novartis in January 2020. At the time of this amendment, all subjects in the trial are receiving open label treatment. Additional changes incorporate Novartis processes, language and change in sponsor contacts, allow for flexibility during the COVID-19 pandemic.

Additional changes include:

- Introduction of Novartis protocol number and IMP code: CKJX83906 and KJX839 respectively
- Handling of protocol deviations including those for COVID-19 related issues
- COVID-19 considerations: remote visits and extended visit windows.
- Update of section 5.1.5 about reporting of drug and device deficiencies when using pre filled syringe
- Incorporation of language about Sweden Specific Protocol Amendment in Section 3.1
- Remove section 7.3 Assessment of Pharmacodynamics as deem not relevant
- Amending Section 8.4.3.2 – Pregnancy, to include follow up on newborns for 12 months
- Additional feeder trial to ORION-8 was added: ORION-3 (also referred to as CKJX839A12201E1) subjects can move over to ORION-8 after completing the treatment in the Phase II trial.
- ORION-5 was deleted as feeder trial to ORION-8

Administrative changes were made to the title page, the footer and headers and throughout the protocol to reflect the change in sponsorship and adding the Novartis protocol number and IMP code. Additional minor changes to correct typos and provide clarifications were incorporated directly into the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/ECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Ethics Committee (ECs) and Health Authorities as appropriate.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Introduction

Inclisiran (also referred to as KJX839) is a novel synthetic ribonucleic acid (RNA) interference (RNAi) therapeutic used for the treatment of hypercholesterolemia. This protocol describes a study to evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels. This study is sponsored by Novartis and will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1 Background

1.1.1 Disease Overview

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually (WHO 2016). Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated LDL-C is a major risk factor for the development of CVD (Grundy et al, 2004; Go et al, 2014). Lowering LDL-C has been shown to reduce the risk of death or heart attack and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005).

Approximately 100 million people worldwide are treated with lipid lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death nonfatal myocardial infarction (MI) and nonfatal stroke or associated events (Decision Resources Group, 2015). Yet residual risk for cardiovascular (CV) events remains and statins are associated with well-known limitations. First, not all patients reach LDL-C levels associated with optimal protection against clinical events (Foley et al, 2003; Baigent et al 2005; Davidson et al, 2005; CTT Collaborators et al, 2008; Foody et al, 2010). Second, not all patients tolerate statins or are able to take statins at sufficiently intensive doses. And third, observational studies have demonstrated that >50% of patients do not adhere to statin therapy for more than 6 months (Poluzzi et al, 2008; Mann et al, 2010).

There is an unmet need for additional treatment options beyond currently available treatments for lowering of the LDL-C level to reduce cardiovascular risk.

Despite statins alone or in combination with other lipid lowering medications, current therapies for the management of elevated LDL-C remain insufficient in some patients (Jones et al, 2012; Jameson et al, 2014; Barkas et al 2015; Fitzgerald et al, 2017). This is particularly true in patients with pre-existing CHD and/or diabetes or a history of familial hypercholesterolemia (FH), who are at the highest risk and require the most intensive management (Davidson et al, 2005).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in controlling the levels of low-density lipoprotein receptors (LDLR) on the surface of hepatocytes (Khorova, 2017). PCSK9 is expressed and secreted into the bloodstream predominantly by the liver, binds LDLR both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, (Lakoski et al, 2009; Mousavi et al, 2009) thereby increasing the circulating LDL-C levels. Loss of function mutations in PCSK9 have been found to lead to increased LDLR in liver, reduced serum LDL-C, and a lower risk for CHD (Berge et al, 2006; Cohen et al, 2006; Kotowski et al, 2006; Zhao et al, 2006) with no apparent negative health consequences. (Zhao et al, 2006; Hooper et al, 2007; Horton et al, 2009).

Recently developed and approved PCSK9-blocking monoclonal antibodies reduce circulating PCSK9 levels and lower LDL-C levels. Preliminary reports indicate that treatment with such antibodies can lead to reduction of cardiovascular events compared with placebo (Hooper et al, 2005; Navarese et al, 2015; Robinson et al, 2015; Zhang et al, 2015; Sabatine et al, 2017). Results from the first completed large CV outcomes trial (FOURIER) were reported in March 2017. Repatha® (evolocumab) significantly reduced the risk of cardiovascular events. The study in approximately 27,000 patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) met its primary composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, nonfatal MI or nonfatal stroke) (Sabatine et al, 2017).

The data from PCSK9 blocking antibodies such as Repatha® (evolocumab) and Praluent® (arilocumab) are very encouraging. However, these products are dosed SC every 2 to 4 weeks necessitating up to 26 injections per year (Hooper et al, 2005; Navarese et al, 2015; Zhang et al, 2015). In contrast, one injection of inclisiran is anticipated to be given three times in the first year and every 6 months thereafter.

1.1.2 PCSK9 Biology and Target Rationale

PCSK9 is a member of the subtilisin serine protease family. Proprotein convertase subtilisin kexin type 9 is predominantly expressed by the liver and is critical for the down regulation of hepatocyte LDLR expression (Mousavi et al, 2009). LDL-C levels in plasma are markedly elevated in humans with gain of function mutations in PCSK9, classifying them as having severe familial hypercholesterolemia (Abifadel et al, 2003). Data from genetic association studies have identified loss of function alleles in human PCSK9 that result in lower PCSK9 protein levels and lower LDL-C levels (Zhao et al, 2006; Hooper et al, 2007; Horton et al, 2009). In one published study, heterozygous individuals (carrying a single copy of a loss of function PCSK9 mutation) had significantly lower LDL-C with median levels of approximately 70 mg/dL (1.81 mmol/L) (Cohen et al, 2006). Over a 15-year period of retrospective data analysis, this sustained lowering in LDL-C levels translated to an 88% lower risk of risk for CHD. Follow-up publications describe two adult individuals that are compound heterozygous for loss of function alleles of PCSK9. These individuals lack detectable plasma PCSK9 protein, have LDL-C levels ≤20 mg/dL, and yet are otherwise healthy (Zhao et al, 2006; Hooper et al, 2007). Additionally, recent human clinical trials with PCSK9 blocking antibodies have shown significant lowering of LDL-C in healthy volunteers and across a range of high CV-risk populations and with elevated LDL-C both with and without statins (Banerjee et al, 2012; Dias et al, 2012; Milazzo et al, 2012; Raal et al, 2012; Roth et al, 2012; Stein et al, 2012; Sullivan et al, 2012; Hooper et al, 2013). Two monoclonal agents to inhibit PCSK9 are currently approved in Europe and North America. Recent cardiovascular outcomes trials have further confirmed that PCSK9 is a validated drug target whose inhibition results in LDL-C lowering and significant outcomes benefit without otherwise negatively impacting overall health (Ridker et al, 2017; Sabatine et al, 2017).

1.1.3 Mechanism of RNA Interference

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering RNAs (siRNAs). Typically, synthetic siRNAs are 19-base to 25-base pair double-stranded oligonucleotides in a staggered duplex with a two- to four-nucleotide overhang at one or both of the 3’ ends. Such siRNAs can be designed to

target an endogenous messenger RNA (mRNA) transcript of a given gene. When introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-Induced Silencing Complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the target mRNA and the suppression of the target protein encoded by the mRNA (Elbashir et al, 2001).

Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration (Soutschek et al, 2004), various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo, in animal models (including in rodents and nonhuman primates) and humans employs intravenous (IV) delivery of siRNA in lipid nanoparticle formulations (Soutschek et al, 2004; Morrissey et al, 2005; Geisbert et al, 2006; Judge et al, 2006; Zimmermann et al, 2006; Coelho et al, 2013; Tabernero et al, 2013). Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a N-acetylgalactosamine (GalNAc) carbohydrate ligand (Ashwell and Morell, 1974). Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and down regulation of hepatic proteins. Single and multiple doses of subcutaneously administered siRNA-GalNAc conjugates have been used to target transthyretin (TTR) mRNA for the treatment of TTR-mediated amyloidosis. ALN-TTRCSC has been found to be generally safe and well tolerated in Phase I and Phase II clinical trials in over 40 healthy volunteers and 18 subjects with familial amyloidotic cardiomyopathy and senile systemic amyloidosis (ALN-TTRSC-001; EudraCT 2012-004203-12; and ALN-TTRSC-002; EudraCT 2013-002856-33).

1.2 Inclisiran, an siRNA Therapeutic for Hypercholesterolemia

Inclisiran sodium is a chemically synthesized siRNA double-stranded oligonucleotide, covalently linked to a ligand containing three GalNAc residues.

Inclisiran is a long-acting, subcutaneously delivered, synthetic siRNA directed against PCSK9 that is conjugated to triantennary GalNAc carbohydrates. These carbohydrates bind to abundant liver-expressed asialoglycoprotein receptor, leading to inclisiran uptake specifically into hepatocytes.

When introduced into the hepatocyte, inclisiran engages the natural pathway of RNAi by binding intracellularly to the RNA-induced silencing complex (RISC), enabling it to cleave mRNA molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein. A single siRNA-bound RISC is catalytic and cleaves many transcripts and the duration of action is anticipated to be longer than other mechanisms.

1.2.1 Nonclinical Studies

Inclisiran was specifically designed with molecular and biochemical characteristics to minimize untoward side effects which are reflected by the absence of dose limiting toxicities in preclinical models. For example, GalNAc ligands were added to the RNA strands in order to target inclisiran to receptors on hepatocytes, thereby greatly reducing uptake by heterologous tissue. This is highlighted by tissue distribution studies in rats showing that compared to liver, inclisiran exposure in other tissues was 36-fold to 1076-fold lower than liver. [redacted]

Inclisiran was well tolerated in all studies. The most common findings were related to the expected pharmacological effects of inclisiran on lipid profiles and histopathological findings of vacuolation in hepatocytes of rats and lymph node macrophages of monkeys and the presence of basophilic granules in hepatocytes of monkeys and kidneys of rats. These microscopic findings are not considered adverse because they are not associated with changes in clinical pathology parameters. Liver function enzymes were only minimally to mildly increased, and were reversible following treatment-free periods, and there were no changes in urinalysis or urine chemistry parameters.

Additional non-clinical studies are ongoing or planned.

1.2.2 Clinical Studies

1.2.2.1 Clinical pharmacology

Inclisiran is inactive in plasma and acts directly in the hepatocytes leading to inhibition of PCSK9 protein synthesis. After SC administration of inclisiran, peak plasma concentrations were observed by 4 hours and became undetectable in plasma in 24 hours to 48 hours with an elimination terminal half-life ($t_{1/2}$) of 7.3 hours and dose-proportional increase in exposure parameters of maximum plasma concentration (C_{max}) and area under the curve (AUC). There was no accumulation of inclisiran plasma concentrations following multiple weekly, biweekly or monthly dosing. Mean fraction excreted unchanged in the urine was around 25%. In vitro studies using hepatic P450 metabolic enzymes showed that inclisiran neither inhibited nor induced common hepatic metabolic pathways.

In a Phase I study in subjects with renal impairment (ORION-7, also referred to as CKJX839A12103) (Section 1.2.2.2.4), a single 300 mg SC dose of inclisiran sodium which is equivalent to 284 mg inclisiran was observed to increase C_{max} and AUC up to approximately two-fold in subjects with mild and moderate renal impairment, and increased C_{max} up to four-fold and AUC up to three-fold in subjects with severe renal impairment compared to subjects with normal renal function. However, by 48 hours plasma levels of inclisiran were below the level of quantification in all groups.

Despite the differences observed in pharmacokinetic (PK) parameters over the first 48 hours following injection of inclisiran, there were generally no relevant differences between the groups with respect to PCSK9 reduction and LDL-C reduction. In addition, there was no difference in the overall safety profile between subjects with normal renal function and those with mild, moderate, or severe renal impairment.

This finding is consistent with that observed in the previous Phase I (ALN-PCSSC-001, also referred to as CKJX839A12101.) study (Section 1.2.2.2.1) where doses above 300 mg, which is

equivalent to 284 mg inclisiran, led to a dose related increase in PK parameters. A single 500 mg dose increased AUC two to three fold and Cmax four to five fold compared to a single 300 mg dose, which is similar to the increase observed in subjects with severe renal impairment compared to those with normal renal function in this study. In both the Phase I (ALN-PCSSC-001) and Phase II (ORION-1 also referred to as CKJX839A12201) studies single doses above 300 mg did not lead to greater reductions in PCSK9 or LDL-C levels over time or differences in the safety profile.

These data support the administration of inclisiran to subjects with mild, moderate, or severe renal impairment in future and ongoing clinical studies with inclisiran.

Additional clinical pharmacology studies are ongoing or planned.

1.2.2.2 Clinical

Results are presented from four clinical studies:

1.2.2.2.1 Study ALN-PCSSC-001 (also referred to as CKJX839A12101)

ALN-PCSSC-001 (completed) was a Phase I study in which single (25 mg, 100 mg, 300 mg, 500 mg and 800 mg) and multiple [125 mg once weekly (four doses), 250 mg every 2 weeks (two doses), 300 mg every 4 weeks (two doses) and 500 mg every four weeks (two doses)] doses of inclisiran sodium were evaluated. Subjects in this study were followed until their LDL-C levels returned to ≥80% of the baseline value or until 180 days after the last dose was given, whichever occurred first. At cumulative doses of 100 mg or greater, the majority of subjects reached 180 days of follow-up after the last dose, confirming the extended duration of action of inclisiran. No further follow-up occurred beyond this time point in this Phase I study. All adverse events (AEs) were mild or moderate (Grade 1 or 2) in severity with no differences relative to placebo other than skin reactions which were infrequent, mild and reversible following inclisiran.

The Phase I study demonstrated that the 300 mg dose of inclisiran sodium administered as a single or multiple dose is the lowest dose to achieve near-maximal reductions in PCSK9 and LDL-C levels. Two 300 mg doses of inclisiran sodium given 30 days apart achieved an additional 10% LDL-C reduction compared to a single 300 mg dose. PK parameters of inclisiran demonstrated a short plasma half-life ($t_{1/2}$ = ~6 hours) and did not correlate with the observed pharmacodynamic (PD) effects of inclisiran.

1.2.2.2.2 Study ORION-1 (MDCO-PCS-15-01 also referred to as CKJX839A12201

ORION-1 (MDCO-PCS-15-01, completed study) was a Phase II, double-blind, randomized, multi-national, multi-center study in subjects with ASCVD or ASCVD-risk equivalents (eg, diabetes and FH) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of inclisiran injection(s).

A total of 501 subjects were randomized to a single dose regimen of placebo, 200 mg inclisiran sodium, or 300 mg inclisiran sodium, 500 mg inclisiran sodium (on Day 1) or a double-dose regimen of placebo, 100 mg inclisiran sodium, 200 mg inclisiran sodium, or 300 mg inclisiran sodium (on Day 1 and Day 90).

The 300 mg dose provided near maximal PCSK9 and LDL-C reductions. The 500 mg dose did not provide a meaningful further increase in PD effect. The double-dose regimen of 300 mg regimen led to reduced LDL-C of 52.6% (LS mean) compared to a 1.8% increase in the placebo

group ($p<0.0001$) at Day 180. Similarly, this regimen led to reduced PCSK9 of 69.1% (mean) compared to a 1.2% decrease in the placebo group at Day 180. At Day 360 (9 months after the second 300 mg dose), LDL-C reduction was 33.8%.

There were no clinically significant safety observations other than mild-moderate, short-lived skin reactions at the injection site in approximately 5% of subjects. Local injection site reactions were not dose-related.

1.2.2.2.3 Study ORION-2 (MDCO-PCS-16-02, also referred to as CKJX839A12202)

ORION-2 (MDCO-PCS-16-02 completed study) was a Phase II, open label, single arm, multicenter pilot study in subjects with homozygous familial hypercholesterolemia (HoFH). Four subjects were randomized and received open-label inclisiran sodium 300 mg SC on Day 1. The subsequent dosing interval was determined by PCSK9 level at Day 60 or 90 or rate of change of PCSK9 between Days 60 and 90. In three subjects mean serum PCSK9 levels were not suppressed by >70% at Day 60 or 90, as compared to baseline and received a second injection on Day 90.

Inclisiran treatment resulted in robust and durable reductions in PCSK9 levels in all four subjects treated at a dose of 300 mg SC. Three of the four subjects also had significantly reduced levels of LDL-C. One subject had a significant reduction in PCSK9 but not a concomitant reduction in LDL-C. The mean percentage LDL-C reduction from baseline was 12.3% and 21.0% at Day 90 and Day 180, respectively. The maximum reductions in LDL-C were at Day 120 for two subjects and at Day 150 for a third subject. Therefore, the second dose achieved a greater reduction in LDL-C than after the first dose.

The mean percentage PCSK9 reduction from baseline was 59.0% and 62.9% at Day 90 and Day 180, respectively. Decreases in other lipids, lipoproteins, and apolipoproteins were commensurate with the decreases in LDL-C.

No safety observations were noted and inclisiran was generally well tolerated. Three of the four subjects reported adverse events. None were considered related to study drug and the majority have resolved. One adverse event of leg pain was not resolved at the most recent visit. There were no deaths and one SAE (unstable angina, which was not considered related to study drug). No subjects withdrew due to an adverse event and no adverse events at the injection site were reported.

Elevations in chemistry parameters were observed. One subject with an elevated total bilirubin (>1x ULN) at screening experienced a single elevation of total bilirubin >2x ULN on Day 120. There were no ALT or AST elevations >3 x ULN or CK elevations >5x ULN. [redacted]

The results from this pilot study support the 300mg dose and dose regimen for the ongoing Phase III ORION-5 study in HoFH.

1.2.2.2.4 Study ORION-7 (MDCO-PCS-16-03, also referred to as CKJX839A12103)

ORION-7 (MDCO-PCS-16-03); completed study) was a Phase I, single-dose, open-label study to evaluate the PK, safety, and PD of a single dose of inclisiran sodium 300 mg, SC injection in subjects with renal impairment compared to subjects with normal renal function. Subjects were classified into one of four renal function groups (normal, mild, moderate, and severe), as defined

by creatinine clearance (CrCl) which was calculated using the Cockcroft and Gault estimation from a spot serum creatinine level (Table 1-1).

Table 1-1 Renal Function Categories by Estimated CrCl Ranges

Group	Description	Estimated CrCl (mL/min)
1	Normal renal function	≥ 90
2	Mild renal impairment	60 to 89
3	Moderate renal impairment	30 to 59
4	Severe renal impairment	15 to 29

CrCl=creatinine clearance

These subjects were matched for age (+/- 10 years), body weight (+/- 20%), and proportional race and gender in order to ensure that the normal renal function group was comparable to the renal impairment groups for average demographics. Thirty-one subjects were randomized into the study, eight subjects in each of the normal renal function and the mild and moderate renal impairment groups and seven in the severe renal impairment group. All subjects completed the study to Day 60.

In individuals with mild, moderate and severe renal impairment, inclisiran C_{max} was 2.33, 1.97 and 3.31 fold higher, respectively; AUC_{0-24} was 1.75, 1.91 and 2.50 fold higher, respectively; AUC_{0-48} was 1.58, 1.83 and 2.33 fold higher, respectively; AUC_{0-t} was 1.53, 1.73 and 2.35 fold higher, respectively; AUC_{0-inf} was 1.44, 1.39 and 2.23 fold higher, respectively, relative to subjects with normal renal function. However, inclisiran was not detectable in plasma 48 hours after administration of a single 300 mg dose in any group irrespective of renal impairment.

At Day 60, LDL-C (beta-quantification) was reduced by 57.56%, 35.11%, 53.09%, and 49.20%, in the normal renal function group and the mild, moderate, and severe renal impairment groups respectively. Mean LDL-C reduction was less in the mild renal impairment group compared to the other three groups. Overall, LDL-C reduction was generally similar between groups with no impact of renal function on LDL-C response.

A single injection of 300 mg inclisiran was generally well tolerated in all study groups with no clinically significant safety findings to date. There was no difference in the overall safety profile between subjects with normal renal function and those with mild, moderate, or severe renal impairment and therefore no dose adjustment of inclisiran is considered necessary in subjects with renal impairment.

1.3 Known and Potential Risks and Benefits

Subjects taking part in this clinical study will receive guideline recommended standard of care as background therapy (including maximally-tolerated statin therapy and/or other LDL-C lowering therapies) when administered inclisiran. Reduction of LDL-C has been associated with reduced CV risk both by epidemiology and in controlled clinical trials. Injection site reaction is the only event known to be attributed to inclisiran treatment. The safety profile of inclisiran observed to date is considered acceptable for this clinical trial.

An expanded risk-benefit summary is provided in the current/approved version of the investigator brochure (IB).

1.4 Study Rationale

1.4.1 Study Rationale

The overall safety data from inclisiran in nonclinical studies and clinical data from the Phase I and Phase II study (ORION-1 also referred to as CKJX839A12201), and multiple PCSK9 antibody studies demonstrated that potent lowering of PCSK9 is well tolerated in human subjects and support the dose and dosing schedule proposed in this Phase III extension study. This extension study allows subjects continued access to inclisiran treatment and to allow the collection of additional efficacy and safety beyond the end of the original studies.

1.4.2 Dose Rationale

Previous studies have shown that a 300 mg dose of inclisiran sodium is well tolerated and provides maximum efficacy (ie, doses higher than 300 mg did not provide additional efficacy in LDL-C lowering). Subjects completing the Phase II trial MDCO-PCS-16-01 (ORION-3, also referred to as CKJX839A12201E1) or one of the Phase III lipid lowering studies [MDCO-PCS-17-03 (ORION-9, also referred to as CKJX839A12303), MDCO-PCS-17-04 (ORION-10, also referred to as CKJX839A12304) or MDCO-PCS-17-08 (ORION-11, also referred to as CKJX839A12305)] and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran sodium 300mg at the next time point they are scheduled as per the previous study to receive inclisiran i.e. 180 days after the last injection in the previous study. Modelling and simulation has demonstrated that this regimen will allow for the necessary robust and sustained reduction in PCSK9 (and LDL-C) and has the potential to tackle the lack of adherence generally seen in the chronic management of subjects with hypercholesterolemia. The 300 mg dose of inclisiran sodium will be used for the entire duration of this study for subjects receiving inclisiran.

1.5 Study Population

This study will include male or female subjects who have completed a previous qualifying Phase II lipid lowering trial [MDCO-PCS-16-01 (ORION-3)] or Phase III lipid-lowering ORION feeder study [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10) or MDCO-PCS-17-08 (ORION-11),], and fulfill the study entry criteria.

2 Study Objectives and Purpose

2.1 Primary Objectives

The primary objectives of the study are to evaluate:

- The effect of inclisiran treatment on the proportion of subjects achieving prespecified LDL-C targets at end of study (EOS)
- The safety and tolerability profile of long-term use of inclisiran

2.2 Secondary Objectives

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

- LDL-C levels
- Other lipids and lipoproteins

3 Study Design

3.1 Type/Design of Study

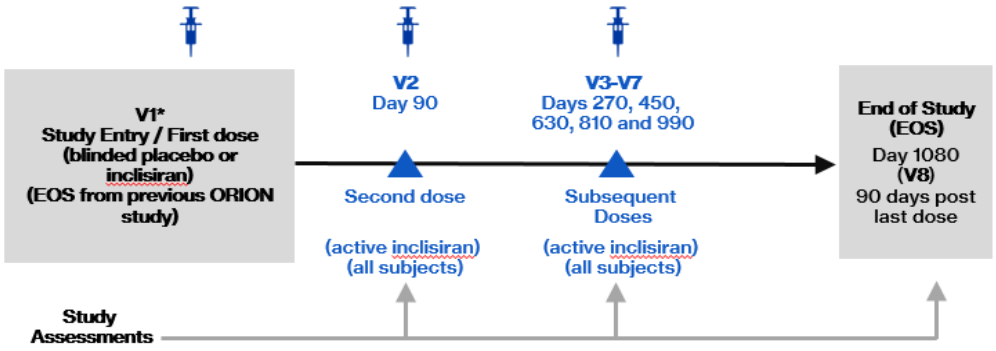
This study will be a long-term extension of the Phase II lipid lowering trial [MDCO-PCS-16-01 (ORION-3)] and Phase III lipid-lowering studies [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10), or MDCO-PCS-17-08 (ORION-11) . Up to 3300 subjects with atherosclerotic cardiovascular disease (ASCVD), ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia), heterozygous [redacted] familial hypercholesterolemia (HeFH [redacted]) and elevated LDL-C despite treatment with LDL-C lowering therapies who are eligible and willing to participate may be enrolled. The objectives 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 EOS visit in the previous feeder studies will be Day 1 in the 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 Day1of this study until ethics committee approval was granted in that country. Subjects moving over from the open label ORION-3 study will not receive study medication at Day 1. Their first dose of study medication in this trial will be at day 90. This is to maintain their 6 months dosing schedule on inclisiran treatment. This trial will be a global, multicenter study in approximately 300 centers.

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

3.2 Schematic Diagram of Study Design

Figure 3-1 Study Design



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

3.3 Primary Efficacy Endpoint

The primary endpoint of this study is:

Proportion of subjects who attain global lipid targets (entry criterion from respective previous study) for their level of ASCVD risk at EOS.

3.4 Secondary Efficacy Endpoints

The secondary endpoints of this study are:

- Absolute change and percentage change in LDL-C from baseline (defined as baseline in feeder study) to EOS
- Absolute change and percentage change in other lipids and lipoprotein from baseline (defined as baseline in feeder study) to EOS

3.5 Safety Endpoints

The safety endpoint of this study is:

- To evaluate the safety and tolerability profile of long-term use of inclisiran

3.6 Measures to Minimize/Avoid Bias

This is a long-termextension study. Subject enrollment will be based on completion of one of the Phase III lipid-lowering feeder studies [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10) or MDCO-PCS-17-08 (ORION-11)] or Phase II trial [MDCO-PCS-16-01 (ORION-3)]. To minimize bias, laboratory tests related to efficacy and safety will continue to be conducted via a central laboratory.

4 Subject Population

4.1 Number of Subjects

Approximately 3300 subjects will be studied at centers globally (approximately 300 sites).

4.2 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Completion of a previously qualifying Phase II lipid lowering trial [MDCO-PCS-16-01 (ORION-3)] or Phase III lipid-lowering ORION feeder study [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10), or MDCO-PCS-17-08 (ORION-11)] meaning the subject received the last dose of study drug and completed the final study visit per applicable protocol.
2. On current lipid-lowering therapies (such as a statin and/or ezetimibe) from previous study with no planned medication or dose change during study participation.
3. Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

4.3 Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to entry into the study:

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk [according to investigator's (or delegate's)judgment] if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 3 years.
4. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >3x the upper limit of normal (ULN), or total bilirubin (TBIL) elevation >2x ULN at the last recorded visit in the feeder study prior to study entry visit.
5. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least one method of acceptable effective contraception (eg, oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions from this criterion:
    a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age
    b. Postmenopausal women (as defined above) and less than 55 years old with a negative pregnancy test within 24 hours of enrollment
    c. Women who are surgically sterilized at least 3 months prior to enrollment

6. Planned use of other investigational medicinal products other than inclisiran or devices during the course of the study.
7. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
   a. Subjects who are unable to communicate or to cooperate with the investigator
   b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency)
   c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study)
   d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study
   e. Persons directly involved in the conduct of the study

4.4 Withdrawal Criteria

All subjects have the right to withdraw from the study at any point during treatment without prejudice. The investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completed the clinical study. If study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. The reasons that a subject may discontinue participation in a clinical study could be from one or more of the following:

- AE(s)
- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up
- Initiation of protocol-prohibited lipid-lowering therapy (eg, an approved PCSK9 inhibitor)

The applicable reason(s) above will be recorded in the eCRF and subjects should be encouraged to complete the EOS visit. All data collected up until the time of subject withdrawal is to be entered into the electronic case report form (eCRF). Any withdrawn subjects will not be replaced in this study. No further follow-up is allowed with the subject to collect additional information following discontinuation from the trial.

4.4.1 Individual Subject Dosing Stopping Criteria

During the study subjects will have clinic visits at regular intervals. Dosing with inclisiran should be temporarily discontinued or stopped in subjects with:

1. Intolerable AEs, or if the investigator believes that continuing dosing will be detrimental to the subject's mental or physical health. This includes severe or serious reactions at the injection site and any anaphylactic type reactions.
2. Unexplained increases in transaminases (ALT or AST) or total bilirubin as follows:
   a. ALT or AST >8xULN

b. ALT or AST >5xULN for more than 2 weeks
c. ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)
d. ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The investigator should evaluate to see if other causes for the laboratory abnormalities are immediately apparent, such as obstructive gall bladder or bile duct disease, viral or alcoholic hepatitis, malignancy involving the liver, congestive hepatopathy, other hepatotoxins or heritable disorders.

3. Unexplained creatine kinase (CK) values >5 x ULN confirmed by repeat test when the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction.

In the case that study medication is permanently discontinued the subject will be asked to return to complete an EOS visit, which should occur at least 90 days following the last dose of inclisiran.

All subjects should be followed until all clinically significant laboratory abnormalities return to normal or to the baseline state. Subjects discontinuing the trial due to withdrawal of consent or initiation of other PSCK9 lipid lowering therapies will not be followed up within the trial.

5 Treatment of Subjects

5.1 Study Medications

Investigational product (Inclisiran for Injection also referred to as KJX839) information is described in Table 5-1.

Table 5-1 Investigational Product

Product Name:	Inclisiran for Injection
Active ingredient	inclisiran sodium
Dosage Form:	Solution for Injection
Unit Dose	Inclisiran sodium 300 mg/1.5 milliliter (mL) pre-filled syringe (equivalent to 284 mg inclisiran) for injection
Route of Administration	SC use
Physical Description	Clear, colorless to pale yellow solution essentially free of particulates
Manufacturer	[redacted], Italy.

Investigational product preparation: The pharmacist or qualified designee will prepare the investigational product under aseptic conditions to be administered to the subject on that day.

The procedure for preparing investigational product is provided in the Pharmacy Manual.

Investigational product administration: Subjects will be administered a single SC injection of 300 mg Inclisiran for Injection at predefined time points as described in the Schedule of Assessments (Table 6-1). Investigational product injection will be administered by qualified clinical study site staff under the supervision of the investigator or designee. The site of injection is the abdomen, arm or thigh, alternating sites for each injection. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

5.1.1 Placebo

The placebo pre-filled syringes will contain saline solution. Placebo pre-filled syringes 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 the inclisiran group.

5.1.2 Packaging and Labeling

Investigational product (Inclisiran for Injection and matching placebo) will be provided by the sponsor. All pre-filled syringes, inclisiran or placebo, will look identical. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

The container closure system for the pre-filled syringe consists of a Type I glass syringe with a stainless steel 27G ½" staked needle covered by a removable rigid needle shield and Fluorotech coated bromobutyl plunger.

All inclisiran and placebo investigational product used for the Day 1 dose will have a yellow shroud to maintain the blind.

5.1.3 Storage

Investigational product (pre-filled syringes) will be stored at controlled room temperature (20°C to 25°C [68°F to 77°F] with allowable excursions between 15°C and 30°C [59°F to 86°F]) as specified in the Pharmacy Manual. Access should be strictly limited to the investigator, pharmacists, and their designees. No special procedures are required for the safe handling of Inclisiran for Injection.

5.1.4 Accountability

The investigator or designee must maintain an inventory record of the investigational product (inclisiran/placebo) received and all administered to assure the regulatory authorities and the Sponsor that the new investigational product will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Investigational product accountability forms and/or specific instructions can be found in the Pharmacy Manual.

The investigational product supplied for use in this study is to be prescribed only by the Principal Investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

Since used syringes must be discarded during the study, the box that the pre-filled syringes came in will be kept until the monitor has reviewed the accountability records.

All unused investigational product will be destroyed on site (or returned to the packaging and labeling facility for destruction) once the investigational product has been inventoried and the monitor has reviewed the accountability records. In the event that investigational product needs to be returned for any other reason, the site will receive a written request listing the investigational product lot number(s) to be returned and the reason for the return request.

5.1.5 Product and Device Deficiencies Reporting

Sites are required to report any product and device deficiency observed to Sponsor immediately but no later than 24 hours from the time of awareness All product and device deficiencies observed during the conduct of the trial and leading to a preference or Technical Quality Deficiency reporting must be recorded in the eCRF.

Product deficiency reporting (complaints): Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, durability, reliability, quality, safety, effectiveness or performance of a product, after it is released for distribution (European Union [EU] DIR 2001/83/EC). (Derived from Ref US 21 Code of Federal Regulations [CFR] 211.198) and Medical Device Regulation (EU) 2017/745).

There are two types of Product Deficiencies:

Preference complaints: A report of dissatisfaction with service, delivery, packaging or other preference.

Technical Quality Deficiency reporting (technical quality complaints): A report of dissatisfaction with the product with regard to its efficacy, strength, integrity, purity, or quality; thus a potential failure to meet product specifications. Examples include:

- An indication that there is an unexpected physical change in the drug product such as discoloration, change in shape of the drug product, presence of particulates or any other physical change that might indicate contamination, a manufacturing defect or any other event that might indicate a compromise in product quality
- An indication that the content does not meet its labeled volume, count, etc.
- An indication that there is an unexpected physical change in any part of the container closure or the label
- An indication that the product is mislabeled
- An indication that the product is falsified, tampered with or adulterated
- An indication that the product did not meet its pharmacologic effect, ie lack of efficacy
- Medical Device Incidents/deficiencies (such as failure to deliver the drug, breakage of a syringe tip, breakage of needleless connector, failure to securely lock the syringe to a needle, etc); in case the drug or device deficiency is leading to an Adverse Event or Serious Adverse Event these have to be recorded on the CRF and reported as specified in Section 8,4. and relationship to the device or drug deficiency must be indicated.

5.2 Concomitant Medications

5.2.1 Prohibited Concomitant Medications

The following medications/treatments are not permitted to be added during the study:

- Medications prescribed to lower LDL-C (eg, statins, ezetimibe, lomitapide, mipomersen, niacin, colesevelam, bile acid absorption inhibitors, monoclonal antibodies directed towards PCSK9)

- Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies

5.2.2 Permitted Concomitant Medications

The following medications/treatments are permitted during the study:

- Hormone replacement therapy
- Lipid-lowering medications; subjects already on a stable lipid-lowering medication at enrollment (such as statins and/or ezetimibe) should remain on the dose that they have received during participation in the previous feeder study protocol unless clinically indicated
- Prescription medications prescribed to treat preexisting medical conditions such as diabetes and hypertension
- Prescription or nonprescription medications, when necessary to treat an AE, and at the discretion of the investigator

5.3 Medical Management Guidelines

5.3.1 Adverse events

Adverse events or abnormal test findings must be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/Investigator and/or returns to baseline values.

5.3.2 Pregnancy

Pregnant women are excluded from the study. If a subject becomes pregnant during the course of the study, the investigational product administration must be discontinued and the pregnancy should be followed through to outcome. Follow-up information on newborns will be sought. Reporting of pregnancy and any associated AEs are specified in Section 8.4.3.2.

5.4 Restrictions

Subjects will have to comply with the following restrictions during the study:

- Fasted for at least 8 hours for all visits for fasting lipids and glucose blood samples
- Blood donation will not be allowed at any time during the study
- Must refrain from unaccustomed strenuous physical exercise for 48 hours before the screening and any study visit until the follow-up has been completed

6 Schedule and sequence of procedures

The Schedule of Events/Assessments (Table 6-1) summarizes the study assessments by time point.

This study will be a long-term extension study for subjects considered “completers” of the Phase II lipid lowering MDCO-PCS-16-01 (ORION-3) or Phase III lipid lowering ORION feeder studies [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10), or MDCO-PCS-17-08 (ORION-11)]. A “completer” of the previous study is defined as having received the final protocol dose of study drug and completing the final study visit/and being considered a successful completion during the EOS visit. The EOS visit in the previous feeder study will be Day 1 in

ORION-8 trial except for subjects enrolled in Sweden (Section 3.1 and Section 6.3). The expected duration of the subjects' involvement in the study will be a maximum of 3 years.

On Day 1 (EOS visit in the feeder study), subjects will receive blinded study medication except for subjects moving over from ORION-3. These subjects will receive the first study medication at day 90. Subjects who received placebo in the previous Phase III feeder study will receive blinded inclisiran and subjects who received inclisiran in the previous feeder study will receive blinded placebo at this visit, in order to maintain the blinding of the feeder study until database lock of those studies.

On Day 90, all subjects will receive inclisiran sodium 300 mg which is equivalent to 284 inclisiran. This is 180 days after the last injection in the previous feeder study for subjects that received inclisiran and will be the second dose of inclisiran for the subjects that received placebo in the feeder study.

The three study periods are:

- Study Entry (Day 1):
  - The EOS visit procedures from the previous ORION feeder study will be used as the Day 1 data for this study except for subjects enrolled in Sweden (Section 3.1 and Section 6.3). In addition, consent and eligibility assessment for this study will be completed.
- Treatment Phases:
  - Double Blind: Day 1 (blinded inclisiran or blinded placebo) to Day 90
  - Open Label: Day 90 (open label inclisiran for all subjects) and subsequent dosing visits with inclisiran every 180 days
- End of Study (EOS):
  - The EOS visit will occur at Day 1080 or 90 days following the last Inclisiran for Injection dose once one of the following criteria are met:
    - the investigator's recommendation of discontinuation
    - sponsor's recommendation of discontinuation
    - an administrative decision is made to end the study
  - NOTE: For subjects prematurely and permanently discontinued from study treatment, who are not willing to return within the 90 day timeframe, the EOS visit will be scheduled as soon as possible, or if decision to discontinue and not return is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

6.1 Schedule of Events/Assessments

The schedule of assessments is provided in Table 6-1.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or remote/virtual contacts (e.g. teleconsult) can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. Also, the visits window has been extended to +/-2 months during the pandemic.

Table 6-1 Schedule of Assessments

	Study Entry/ Double blind treatment	**Open Label Treatment Phase**		**EOS [1]**
Study Day **Visit window (± days)**	Day 1 [2] **(N/A)**	Day 90 (First Dose) **(±30)**	Subsequent dosing visits [3] (i.e. Days 270, 450, 630, 810, 990) **(±30)**	Final Follow-up Day 1080 **(≥ 90 days post final dose)**
Informed consent	x			
Inclusion/exclusion Criteria	x			
Physical examination				x
Vital signs [4]		x	x	x
Full serum chemistry [5]				x
Limited serum chemistry [5]		x	x	
Hematology and coagulation [6]				x
Urinalysis (local) [7]				x
Pregnancy test (local) [8]		x	x	x
Lipids and lipoproteins		x	x	x
[redacted]				
Double blinded inclisiran or placebo[10, 11]	x			
Open label Inclisiran administration [11]		x	x	
Concomitant medications [12]		x	x	x
AE/SAE reporting [12]		x	x	x
Drug and device deficiencies (including AE/SAEs related to the drug or device deficiency	x	x	x	x

AE = adverse event; EOS = end of study; SAE = serious adverse event

1. EOS visit should occur at least 90 days following the last inclisiran dose once a decision is made to end the study (either by the subject, investigator or sponsor). For subjects prematurely and permanently discontinued from study treatment, who are not willing to return within the 90 day timeframe, the EOS visit will be scheduled as soon as possible, or if decision to discontinue and not return is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

2. Day 1 visit is the same as EOS visit in the previous qualifying ORION study. Aside from informed consent and eligibility, procedures will not be repeated but will be those captured during feeder study EOS visit except for subjects enrolled in Sweden. See Section 3.1.and Section 6.3 Sweden Specific Protocol Amendment 1 (to Global Amendment 1 version), dated 1 Nov 2018.

3. Dosing visits will occur every 180 days until the study ends for each respective subject. Visit windows have been extended to +/-2 months due to COVID-19.

4. Vital signs: blood pressure and heart rate will be measured prior to injection on dosing days. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit.
5. See Section 7.1.6.3 for details of specific tests to be analyzed
6. See Section 7.1.6.1 and Section 7.1.6.2 for details of specific tests to be analyzed
7. Urinalysis collection is prior to the injection; supplies from the central laboratory must be used to perform the urinalysis
8. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies and with results prior to injection; urine pregnancy test). Results of the pregnancy test from Day 540 of the feeder study will be used on Day 1 in ORION-8

[redacted]

10. Subjects who received blinded placebo in the feeder study will receive blinded inclisiran and subjects who received blinded inclisiran in the feeder study will receive blinded placebo on Day 1 in ORION-8. Subjects moving over from the ORION-3 trial will not receive any treatment at Day 1; all subjects were on inclisiran in the feeder trial and will receive their first dose of inclisiran in this study at day 90
11. Subjects will be observed in the clinic for 30 minutes post injection in order to have additional vital and/or laboratory assessments completed if needed. For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as logically possible).
12. Concomitant medications (relevant) and AE/SAE collection for this study will begin at time of consent and continue through EOS. Ongoing concomitant medications and AEs/SAEs from the feeder study will continue to be followed in this study until resolution.

6.2 General Conduct of the Study

Discussion about participation and consent for the ORION-8 study should occur after conduct of the ORION feeder study EOS procedures and include discussion that the EOS visit data in the previous study will be considered for Day 1 in this trial. Written informed consent will be obtained for this study by the principal investigator or designee from all subjects before the performance of any protocol-specific procedure.

Please see the Schedule of Assessments (Table 6-1) for a detailed schedule and Section 7 for details of all tests required in each panel.

6.3 Study Entry/Double-blind Treatment phase (Day 1)

The following procedures and laboratory assessments are conducted as part of the EOS visit from the feeder study and are not repeated for Day 1 of this trial. The same values/samples data will be used for Day 1 assessments in ORION-8 were applicable 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 Day1of this study until ethics committee approval was granted in that country

- Physical examination
- Vital signs (blood pressure and heart rate)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 7.1.6)
- Urinalysis (performed locally, using central laboratory supplies) (Section 7.1.6.4)
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only) (results of test must be reviewed prior to dosing)
- Fasting lipid and lipoprotein profile (Section 7.2)
- [redacted]
- Concomitant medication assessment (relevant ongoing concomitant medications from feeder study are reported at this visit)
- AE/SAE reporting (ongoing AEs/SAEs from feeder study are reported at this visit)

The following ORION-8 specific procedures will be performed on Day 1:

- Informed consent for the ORION-8 study
- Assessment of inclusion and exclusion criteria
- Administration of double-blinded placebo or inclisiran treatment (except for subjects moving over from ORION-3)

The following additional procedures were performed on Day 1 for subjects in Sweden only and data used for Day 1 assessments (the feeder study EOS data was not used for the following assessments):

- Central clinical laboratory (limited chemistry, hematology (no coagulation) (Section 7.1.6)
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only) (results of test must be reviewed prior to dosing)

- Fasting lipid, lipoprotein profile and PCSK9 (Section 7.2)

6.4 Open-label inclisiran Treatment Phase [Day 90 and Subsequent dosing visits]

Prior to the start of dosing of Inclisiran for Injection on Day 90, central laboratory blood results from Day 1 must be reviewed. If these results suggest any contraindication to treatment with Inclisiran for Injection, dosing should be delayed until repeat results at an interval agreed upon by the investigator and medical monitor have been conducted and returned to levels that deem dosing acceptable per investigator and medical monitor judgement (Section 4.2 and Section 4.3). The following procedures will be performed on Day 90 and every 180 days thereafter (see schedule of assessments):

- Vital signs (blood pressure and heart rate)
- Central clinical laboratory (limited serum chemistry) (Section 7.1.6.3)
- Pregnancy test (performed locally, using central laboratory supplies with results prior to dosing) (women of childbearing potential only)
- Fasting lipid and lipoprotein profile (Section 7.2)
- [redacted]
- Open-label inclisiran administration (all subjects)
- Relevant concomitant medications assessment
- AE/SAE reporting

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

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

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

6.5 End of Study Visit (Day 1080 or ≥ 90 days post final dose)

A subject's participation in the study is complete when the final visit (EOS) has occurred. The following assessments will be completed during this visit:

- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 7.1.6)
- Urinalysis (performed locally, using central laboratory supplies)
- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Fasting lipid and lipoprotein profile (Section 7.2)
- [redacted]
- Relevant concomitant medication assessment
- AE/SAE reporting

7 Protocol Assessments

7.1 Assessment of Safety

7.1.1 Adverse Events

Subjects will be carefully monitored for AEs by the investigator during the designated study period (see Section 8 for details).

7.1.2 Demographics and Medical History

Baseline demographic and medical history information from the previous ORION study will be used.

7.1.3 Vital Signs

Vital signs include heart rate and blood pressure.

7.1.4 Physical Examination

The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, neurological, abdominal, and extremities evaluations, and recording of weight.

7.1.5 Cardiovascular Events

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

7.1.6 Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1).

Subjects will be in a fasted state for all clinical laboratory assessments. Study entry laboratory tests (EOS tests from the original qualifying Phase II or Phase III lipid lowering ORION feeder study) will be performed by the central laboratory, with the exception of urinalysis and pregnancy test, which will be done in house at the participating institution's laboratory using testing materials supplied by the central laboratory. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual. Note: Efficacy laboratory assessments (eg, LDL-C) are described in Section 7.2.

7.1.6.1 Hematology

Blood draws for hematology will include:

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

7.1.6.2 Coagulation

Blood draws for coagulation will include:

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

7.1.6.3 Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments (Table 6-1). Analysis will vary based visit day as follows:

- **Full serum chemistry**
  AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, urea (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), glycated hemoglobin A1C (HbA1C), high sensitivity C-reactive protein (hsCRP) and tryptase (as required)
- **Limited serum chemistry**
  ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, HbA1C and tryptase (as required)

7.1.6.4 Urinalysis

Urinalysis will be performed at the time points defined in the Schedule of Assessments (Table 6-1) and evaluated by dipstick analyses at the investigational site (a standardized dipstick test will be supplied by the central laboratory). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

The following parameters will be assessed:

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

7.1.6.5 Urine Pregnancy

Urine pregnancy testing will be performed locally at the visits specified in the Schedule of Assessments (Table 6-1), using the supplies provided by the central laboratory.

7.1.6.6 Lipids / Lipoproteins

Lipids and lipoproteins assessments are described in Section 7.2.

[redacted]

7.1.7 Stored samples

The central laboratory will take aliquots of serum and plasma samples from the received routine blood sampling noted above and will store these [redacted]

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

7.2 Assessment of Efficacy

Subjects will be in a fasted state for all efficacy laboratory assessments of lipids and lipoproteins. Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1). Parameters to be assessed will include:

- Total cholesterol (TC), triglycerides, LDL-C, and high density lipoprotein cholesterol (HDL-C)

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

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

8.1.2 Serious Adverse Event

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life
- Requires in-subject hospitalization or prolongs hospitalization
- Is a congenital anomaly/birth defect
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected

transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction

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

8.1.3 Special Situations – Adverse Events

There are situations when information is not necessarily considered an adverse event but can possibly contribute to the overall knowledge concerning the safety of the investigational product.

Examples include, but are not limited to, reports of pregnancy/lactation exposures with or without any AEs related to the parent or child; medication errors – actual and potential; accidental exposure; suspected transmission via an investigational product of an infectious agent; drug interaction.

8.2 Collection and Assessment of Adverse Events

8.2.1 Adverse Event Severity

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

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

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

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

8.2.2 Relationship to Investigational Product

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

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

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

8.3 Requirements For Additional Safety Data Collection

8.3.1 Special Situations – Additional Safety Data Collection

Special Situations designated for this study include:

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

8.3.2 Other safety related information

Injection site reactions (ISR) including individual signs or symptoms at the injection site following investigational product administration should be recorded on specifically designed eCRF pages.

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

- Potential anaphylactic reactions assessed by Sampson criteria (APPENDIX A). If Sampson criteria are positive, confirm by elevation of tryptase in blood plasma measured within 30 minutes of symptoms
- Hyperglycemia-related AEs:

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

- HbA1C becomes ≥6.5% and/or
- If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected

Report 'Worsening of the glycemic control' or 'diabetic complications' in subjects with a medical history of disease (HbA1C ≥6.5% at baseline) when:

- HbA1C increases from baseline > 0.5% and/or
- New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level

8.4 Procedure for Adverse Event Reporting

8.4.1 Serious Adverse Events (SAEs)

All SAEs that occur from consent (Day1) through EOS must be reported to Novartis safety within 24 hours of awareness of the event using the provided study specific SAE Report Form. Each SAE must also be recorded on the source documents and on the appropriate page of the eCRF.

The investigator should provide any follow-up information for the event to the Sponsor on an updated SAE Report Form as soon as it becomes available. The Sponsor will contact the investigator, if necessary, to clarify any of the event information or request additional information.

If the investigator is notified of a SAE that occurs post-study period, that he or she wishes to report to the Sponsor (eg, an event suspected to be causally related to investigational product), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the investigator should report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority in addition to the Sponsor.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

8.4.2 Non-Serious AEs

All non-serious AEs that occur from consent through EOS must be assessed and recorded on the source documents and eCRF, regardless of causal relationship to the investigational product.

8.4.3 Special situations – Adverse Event Reporting

8.4.3.1 Medication Errors

All AEs (serious and non-serious) that occur in association with medication errors should be recorded in the AE page eCRF. Serious AEs should also be reported to Novartis safety as described in section 8.4.1. No record of Medication Error itself should be included on the AE eCRF page.

8.4.3.2 Pregnancy/Lactation Exposure

Occurrences of pregnancy/lactation exposure in a study subject from Day 1 through EOS must be reported to the Sponsor within 24 hours using the Pregnancy/Lactation Exposure Report Form.

In cases where a pregnancy/lactation exposure occurs with a SAE, the SAE Report Form should be used to report the SAE and the Pregnancy/Lactation Exposure Report Form should be used to report the pregnancy/lactation exposure.

When a pregnancy/lactation exposure occurs without any concurrent SAE, the Pregnancy/Lactation Exposure Report Form must be submitted alone.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Newborns should be followed for 12 months.

8.5 Expectedness

8.5.1 Expectedness Determination

Novartis safety department will be responsible for determining whether an AE is expected or unexpected for the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information previously described for the investigational product in the current/approved version of the Investigator's Brochure.

8.6 Study Stopping Criteria

8.6.1 Independent Data Monitoring Committee (IDMC) Stopping Rules

The IDMC will use all available evidence and their collective judgment in making a recommendation to stop or modify the ORION-8 study for safety. Any statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise. Details will be provided in the respective charter(s).

8.6.2 Sponsor Discontinuation Stopping Criteria

The Sponsor will review data on an ongoing basis and may, on discussion with the IDMC terminate the study for any clinically significant drug related safety signal (eg, serious hypersensitivity reactions or drug induced liver injury, etc).

Premature termination of a study may also occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of inclisiran at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days of the notification. Final study visits should occur within 30 days of subject contact. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

The Sponsor, or designee, will inform the health authorities and the IRBs/EC that the study has been stopped and the reasons for doing so, within the locally applicable timelines.

9 Data Collection

An electronic data capture (EDC) system which is 21 CFR Part 11 compliant will be used for this study. Certain data points from the previous protocol participation (ORION-3, ORION-9, ORION-10, or ORION-11) may be imported to the EDC system for this study. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A UserID/Password will be granted after training. This UserID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site 3 days after each visit. It is not expected that the eCRF will serve as source for any data collected in this study. If there is a reason for a site to do so, it must be approved by Sponsor and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic. After the end of the study, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification. For this study, the end of the study will be defined as the last visit of the last subject.

10 Statistical Plan

This study will be a long-term extension study in up to 3300 subjects with ASCVD, ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia), HeFH, [redacted] and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies who have completed one of the Phase III lipid lowering studies [MDCO-PCS-17-03(ORION-9), MDCO-PCS-17-04 (ORION-10), MDCO-PCS-17-08 (ORION-11), or Phase II ORION-3 trial (MDCO-PCS-16-01)] and fulfill the entry criteria for this study in order to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. Following completion of study procedure for the final visit in the feeder study, informed consent will be obtained from subjects before the initiation of any study-specific procedures. The EOS visit in the previous study will be Day 1 in ORION-8. This will be a global, multicenter study in approximately 300 centers.

The duration that a 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

A separate Statistical Analysis Plan (SAP) document will provide more detailed specifications in data analysis and presentation.

10.1 Sample Size

Up to 3300 subjects with atherosclerotic cardiovascular disease who have completed one of the Phase III lipid-lowering feeder studies [MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10), MDCO-PCS-17-08 (ORION-11) or Phase II ORION-3 trial (MDCO-PCS-16-01)] and fulfill the entry criteria for this study will participate in this study.

10.2 General Statistical Considerations and Definitions

10.2.1 General Statistical Methods

All study-collected data will be summarized using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage.

10.2.2 Analysis Population - Safety population

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

All subjects who received at least one dose of study drug will comprise the safety population. Treatment classification will be based on the actual treatment received. This will be the primary population for the efficacy and safety analyses.

10.2.3 Analysis Windows

The observational period for the study includes Day 1 (EOS visit in the previous study), the Treatment phase which consists of the first dose (Day 1), Day 90 dose, and subsequent dosing

visits every 180 days until Day 990 and EOS (Day 1080) visit. Any event occurring beyond the defined observational period, even if collected in the e-CRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

10.2.4 Missing Data Handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

10.3 Statistical Analyses

10.3.1 Demographic and Background Characteristics

Subject demographics and baseline characteristics except age collected from prior corresponding Phase III studies for each subject will be used for the summary using the safety population. For subjects moved over from the Phase II ORION-3 study, subject demographics and baseline characteristics collected at the ORION-3 study baseline will be used for this summary. Age will be recalculated by adding the duration that each subject spent in the prior corresponding Phase II or Phase III study

10.3.2 Study Drug and Concomitant Medications

Summary of each prior (prebaseline in the previous corresponding Phase II or Phase III study) medication and concomitant medication will be provided. Medication will be coded with World Health Organization (WHO) drug dictionary. Subjects will be counted only once within each period by medication.

10.3.3 Efficacy Analysis

10.3.3.1 Primary Efficacy Endpoints

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. Confidence interval will be provided.

10.3.3.2 Secondary Efficacy Endpoints

The actual value, absolute and percentage change in LDL-C and other lipids parameters from baseline (defined as baseline in the corresponding Phase II or Phase III feeder study) to EOS will be summarized over time. Descriptive statistics will be provided.

10.3.4 Safety Analysis

The safety objectives of this study are to evaluate the safety and tolerability profile of inclisiran. The safety analysis will be descriptive.

10.3.4.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified by preferred term) occurring during the study drug treatment period will

be counted as a treatment emergent AE (TEAE) either if it is not present at Day 1 of this study or if it is present at Day 1 of this study but increased in severity during the treatment period.

The number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to study drug. If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively.

10.3.4.2 Laboratory Tests

Laboratory values will be summarized at each time point. Analyses will also be performed for each lab parameter for incidence rates of potentially clinical significant (PCS) values for subjects without PCS value at baseline (defined as baseline in the corresponding Phase II or Phase III feeder study), as well as without PCS value at Day 1 of the study

10.3.4.3 Vital Signs

Vital signs will be summarized descriptively at each scheduled time point.

10.4 Interim Analysis

No formal interim analysis will be performed in this study.

10.4.1 Interim Safety Reviews

The IDMC will review safety data on a regular schedule as specified in the IDMC charter from first subject enrollment in the double-blind phase until the end of the open label phase of the study. A recommendation may be taken to stop or amend the study at any of these reviews.

11 Records Retention

The US Food and Drug Administration (FDA) regulations require all investigators participating in clinical study drug/device studies to maintain detailed clinical data for one of the following periods:

- At least two years following the date on which a New Drug Application is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA

Similarly, current EU Directives / Regulations and International Conference on Harmonization (ICH) guidelines collectively require that essential clinical study documents (including case report forms) other than patient's medical files must be retained for the following time period:

- For at least 15 years after completion or discontinuation of the study
- Or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community
- Or for at least two years after formal discontinuation of clinical development of the study drug/device

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs of the final data received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

12 Quality Control and Quality Assurance

12.1 Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his/her responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this study. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

12.2 Auditing

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, study drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must permit regulatory authority inspections.

12.3 Protocol Deviations

Deviations from the protocol identified during the conduct of the trial have to be recorded in the e-CRF and will be reviewed periodically:

- Informed Consent not signed prior to study entry in this study
- Inclusion criteria violation
- Exclusion criteria violation
- SAEs not reported to sponsor within 24 hours

Additional protocol deviations and associated actions depending on the nature and impact of the protocol deviation will be defined and periodically reviewed by standard automated and/or manual checks by the clinical team or monitors.

13 Ethics and Responsibility

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States FDA regulations, the ICH GCP guidelines, the Declaration of Helsinki, and other local regulations, as applicable.

13.1 Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legally authorized representative), and whenever possible, or as per IRB or EC guidelines before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form (ICF), which shall be approved by the same IRB or EC responsible for approval of this protocol. Each ICF shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor, or designee, of any written ICF used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB- or EC-approved written ICF. The subject shall be given a copy of the signed ICF, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2 Institutional Review Board (IRB)/Ethics Committee (EC)

This protocol, the written ICF and any materials presented to subjects shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated ICF were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such nonparticipation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

14 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

Sponsor commits to comply with all applicable data protection laws and regulations and take all appropriate measures to ensure that subjects' data is processed securely and appropriately. Sponsor adheres to the privacy principles of notice, choice, accountability for onward transfer, security, data integrity, purpose limitation, access, and enforcement regarding the collection, use, and retention of personal information from European Economic Area countries and Switzerland. In addition, Sponsor's Global Commercial General Liability with Umbrella Liability and Global Products / Clinical Trial Liability policy includes coverage for the processing of subjects' data

15 Investigator agreement

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the new study drug, inclisiran, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for such matters in the clinical study facility where inclisiran will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB or EC approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for subjects screened or randomized in the study.

I agree to provide all subjects with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11 and applicable local regulations.

Principal Investigator (Signature)	Date
Principal Investigator (Printed Name)	Protocol Version: Global Amendment 2
Institution Name	

16 References

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Appendix A: Sampson Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
  AND AT LEAST ONE OF THE FOLLOWING:
  a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, painful abdominal cramps, vomiting)
3. Reduced blood pressure after exposure to a *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure*
   b. Adults: systolic blood pressure <90 millimeters of mercury (mmHg) or >30% decrease from that person's Day 1 reading

*Low systolic blood pressure for children is age specific and defined as: <70 mmHg for age 1 month to 1 year; <70 mmHg + [2 x age] for age 1 to years; <90 mmHg for age 11 to 17 years.

Source: Sampson et al, 2005; Sampson et al, 2006.