NOVARTIS

Novartis Research and Development

KJX839/Inclisiran

Clinical Trial Protocol MDCO-PCS-16-01 (CKJX839A12201E1) / NCT03060577

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

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2016-003815-37
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Clinical Trial Phase:	II
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Protocol Synopsis

Name of Sponsor/Company: Novartis

Name of Finished Product: Inclisiran (also referred to as KJX 839) for Injection

Name of Active Ingredient: Inclisiran sodium

Title of Study: An open label, active comparator extension trial to assess the effect of long term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C (ORION-3 also referred to as CKJX839A12201E1)

Phase of Development: II

Study Centers: Multicenter study in North America and Europe (approximately 60 sites)

Principal Investigator: Professor [redacted]

Study Period:

The estimated study period for the study will be 4.5 years from first subject enrolled in this extension study to the last subject completed, or if the sponsor recommends discontinuation of the study, or until an administrative decision is made to end the study.

Objectives:

Primary:

- To evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 210 compared to Baseline of ORION-1 in Group 1 (inclisiran only arm).

Secondary:

- To evaluate the effects of inclisiran on the following (Group 1; inclisiran only arm):
- LDL-C levels over time
- PCSK9 levels over time
- Other lipids, lipoproteins, and apolipoproteins over time
- Proportion of subjects achieving target levels pre-specified in global lipid guidelines
- Proportion of subjects who have at least 50% LDL-C reduction from Baseline of ORION-1
- Individual responsiveness to inclisiran treatment
- To evaluate the long term safety and tolerability of inclisiran treatment (Group 1; inclisiran only arm)

[redacted]

Methodology: This study will be an open label, long term extension study with two arms: Group 1 (inclisiran only arm) will receive inclisiran only and Group 2 (switching arm) will receive an active comparator (evolocumab) for one year followed by inclisiran. The study will be conducted in up to 490 subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies who have completed study MDCO-PCS-15-01 (CKJX839A12201; ORION-1), 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.

Subjects completing study MDCO-PCS-15-01(CKJX839A12201) and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran or evolocumab, based on the treatment received in the feeder study MDCO-PCS-15-01 (CKJX839A12201). In countries where applicable, on signing consent and being entered into this study, the investigator will be informed by the IXRS(Interactive Voice/ Web Response System) regarding the treatment allocation, and therefore, whether placebo or inclisiran was administered in study MDCO-PCS-15-01 (CKJX839A12201) and the subject will be informed accordingly. Those subjects who received inclisiran in MDCO-PCS-15-01 (CKJX839A12201) will receive inclisiran sodium 300 mg throughout this study (Group 1; inclisiran only arm), and those subjects who received placebo in MDCO-PCS-15-01 (CKJX839A12201) will receive evolocumab as comparator for approximately 1 year, and then transition to inclisiran for the remainder of the study (Group 2; switching arm).

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

Group 1 (Inclisiran Only Arm):

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

The subsequent visit schedule is as follows:

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

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

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

Group 2 (Switching Arm):

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

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

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

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

The subsequent visit schedule is as follows:

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

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

End of Study (EOS)

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

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

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

[redacted]

A Data Monitoring Committee will review safety data on a regular schedule until the end of the study. A recommendation may be taken to stop or amend the study at any of these reviews.

Subjects enrolled into this extension study will receive study drug for approximately 4 years (or until the investigator's recommendation of discontinuation, sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to end the study). If subjects,

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

An interim analysis of lipids and PCSK9 will be conducted upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran. [redacted]

Number of Subjects: Maximum 490 planned

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 study MDCO-PCS-15-01 (CKJX839A12201) and no contraindications to receiving inclisiran or evolocumab.
2. Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.
3. Willing to self-inject of evolucumab.

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. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses).
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 >2x the upper limit of normal (ULN), or total bilirubin elevation >1.5x ULN at Study Entry visit, confirmed by a repeat abnormal measurement at least 1 week apart.
5. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of 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
    d. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
    e. Treatment with investigational medicinal products other than inclisiran or devices within 30 days or five half-lives, whichever is longer.
6. Planned use of other investigational medicinal products other than inclisiran or devices during the course of the study.
7. Subjects with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients.
8. Previous or current treatment (within 90 days of Study Entry) with monoclonal antibodies directed towards PCSK9.
9. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    a. Inappropriate for this study, including 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. Involved with, or a relative of, someone directly involved in the conduct of the study.
e. Any known cognitive impairment (eg, Alzheimer's disease).

Test Product, Dose and Mode of Administration:

Inclisiran will be administered as a single SC injection of 300 mg sodium (equivalent to 284 mg inclisiran)/ 1.5 mL. For those subjects that transition from evolocumab to inclisiran at Day 360, inclisiran sodium 300mg (equivalent to 284 mg inclisiran)/ 1.5 mL will be administered on Day 360 and a second inclisiran dose will be administered on Day 450, then every 180 days thereafter.

Duration of Treatment:

The expected duration of the subjects' involvement in the study will be 4 years.

Reference Therapy, Dose, and Mode of Administration:

Evolocumab (REPATHA®) will be administered as an SC injection at 140 mg every 2 weeks up to Day 336. A subgroup of subjects will receive their final evolocumab dose at Day 360 (an approved dose and frequency as per the prescribing information) and will then be transitioned to inclisiran.

Criteria for Evaluation:

Primary Endpoint (Group 1; Inclisiran Only Arm):

- Percentage change from Baseline of ORION-1 in LDL-C at Day 210 in this study (Group 1; inclisiran only arm)

Secondary Endpoints (Group 1; Inclisiran Only Arm):

- Change and percentage change from Baseline of ORION-1 in LDL-C over time in this study
- Change and percentage change from Baseline of ORION-1 in PCSK9 levels over time in this study
- Change and percentage change from Baseline of ORION-1 in other lipids, lipoproteins, and apolipoproteins over time in this study
- Proportion of subjects with ≥50% LDL-C reduction from Baseline of ORION-1 at each time point
- Individual responsiveness to inclisiran defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at any time point
- Change and percentage change in LDL-C at Day 210 compared to Day 870 of ORION-3
- Long term safety and tolerability of inclisiran treatment

[redacted]

Safety: AEs, SAEs, vital signs, clinical laboratory values (hematology, coagulation testing, chemistry, and urinalysis), and electrocardiograms (ECGs) will be collected at specified visits through the EOS visit.

Statistical Methods:

Sample Size and Power

This is an extension of the MDCO-PCS-15-01 (CKJX839A12201) study (ORION-1). All eligible and willing subjects who have completed the ORION-1 study (to at least Day 210) and whose LDL-C has returned to within 20% of the Baseline of ORION-1 value or who have reached Day 360 in ORION-1 can be enrolled into the ORION-3 study. Subjects withdrawn from the ORION-1 study at any time are not eligible for the ORION-3 study.

Primary Endpoint Analysis: Confidence intervals will be provided.

Secondary [redacted] Endpoint Analysis: The analysis of the secondary [redacted] endpoints will be descriptive.

Interim Analysis: An interim analysis of lipids and PCSK9 will be conducted upon completion of Day 210 for subjects in Group 1 (inclisiran only arm).A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran. [redacted]

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List of Abbreviations

[redacted]	[redacted]
AE	adverse event
AESIs	Adverse Events of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo-A1	apolipoprotein A1
Apo-B	apolipoprotein B
aPTT	activated partial thromboplastin
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BUN	total protein urea
CHD	coronary heart disease
CK	creatine kinase
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DCF	data clarification forms
dL	deciliter(s)
DMC	Data Monitoring Committee
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 Department
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN-γ	interferon-gamma
IL6	interleukin 6
INR	International normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent-to-treat

IXRS	Interactive Voice/ Web Response System
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LNP	lipid nanoparticles
Lp(a)	lipoprotein(a)
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mITT	Modified intent-to-treat
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	millimole
mRNA	messenger ribonucleic acid
PCSK9	proprotein convertase subtilisin/kexin type 9
PEF	peak expiratory flow
[redacted]	[redacted]
PT	prothrombin time
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
siRNA	small interfering ribonucleic acid
TBIL	total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse event
TNF-α	tumor necrosis factor-alpha
TSQM	Treatment Satisfaction Questionnaire for Medication
TTR	target transthyretin
ULN	upper limit of normal
USA	United States of America
VLDL-C	very low density lipoprotein cholesterol
WHO	World Health Organization

Amendment 5 (07-Oct-2020)

Amendment rationale

The first subject for this trial was randomized in March 2017 and enrollment was completed in Nov 2017 with 382 subjects enrolled.

This amendment is written to address the sponsorship change from The Medicines Company to Novartis after acquisition of The Medicine Company by Novartis in Jan 2020. 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 study and IMP number. Additional minor changes to correct typos and provide clarifications were only incorporated directly into the protocol.

Wording in consideration of the COVID-19 pandemic was implemented and additionally following changes were implemented in the protocol.

- Introduce Novartis protocol number and IMP code – CKJX839A12201E1 and KJX839
- Contacts and process changes for NVS
    - Removal from protocol specific contact information of employees of the The Medicine Company – provided to the sites outside of the protocol
    - Update of section 12.3 on handling of protocol deviations (including PDs for COVID-19 related issues and any others considered relevant and not listed in the protocol)
    - Introduction of section 5.1.6 Reporting of product deficiencies (complaints) to ensure any deficiency observed to the product can be captured and reported within the trial.
    - Introduction of COVID-19 considerations – remote visits, extended visit windows
    - Update of Section 8.4.3.2 – Pregnancy, to include follow up on newborns for 12 months
    - Deletion of Secondary objective “Duration of lipid-lowering effect” in section 2.2 as this will no longer be evaluated.
    - Deletion of Secondary endpoint “Duration of lipid-lowering effect (LDL-C beta quantification over time)” in section 3.4 as this will no longer be evaluated.
    - Update in the section 10.3.3.4 –Interim Analysis. A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran.
    - Subjects in the trial who have completed the EOS will be given the opportunity to enroll into ORION-8 (open-label extension trial).

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/IECs

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

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, Inclisiran (CKJX839) for Injection (subcutaneous [SC] use), formerly referred to as ALN-PCSSC, for the treatment of hypercholesterolemia. This protocol describes a study to evaluate and compare the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 210 with evolocumab (REPATHA®). 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

According to the World Health Organization (WHO), atherosclerotic cardiovascular disease (ASCVD), comprised mainly of coronary heart disease (CHD) and stroke, is the leading cause of death worldwide, resulting in 17 million deaths annually (WHO Cardiovascular Statistics, 2011). Data from the INTERHEART case-control study estimates that 45% of myocardial infarctions (MI) in Western Europe and 35% of myocardial infarctions in Central and Eastern Europe are due to abnormalities in blood lipids (Yusef et al, 2004). Hypercholesterolemia, specifically, elevated LDL-C, is one of the major risk factors for the development of CHD, the leading cause of death worldwide (Grundy et al, 2004; Go et al, 2014). The continuous and graded relationship between plasma LDL-C concentration and CHD risk is such, based upon data a large body of epidemiological and clinical studies, for every 0.78 mmol/L (30 mg/dL) change in LDL-C, the relative risk for CHD changes by approximately 30% (Grundy et al, 2004). In addition, multiple clinical trials have demonstrated a decreased risk of cardiovascular mortality and morbidity in patients on statin therapy of around 5 to 6% for every 10 mg/dL reduction in LDL-C (Delahoy et al, 2009; Baigent et al, 2010). High dose statin treatment has also been shown to result in additional clinical benefit compared to low or moderate dose statin treatment (Cannon et al, 2004; Pedersen et al, 2005). Despite the extensive use of statins, current therapies for the management of elevated LDL-C remain inadequate in some patients. 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 aggressive management (Davidson et al, 2005). Among these high risk subjects, less than 50% achieved the target LDL-C goal of <2.6 mmol/L (100 mg/dL) following 6 months of statin treatment, despite close monitoring and drug regimen optimization (Foley et al, 2003; Baigent et al, 2005; Kearney et al, 2008; Foody et al, 2010). Thus, there is a clear unmet medical need for new drugs to lower LDL-C, especially in certain patient populations such as FH.

1.1.2 PCSK9 Biology and Target Rationale

Proprotein convertase subtilisin kexin type 9 (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 low-density lipoprotein receptor (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 cardiovascular (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). Thus, the overall scientific and clinical data suggests that PCSK9 is a well-validated drug target whose inhibition results in significant LDL-C lowering without otherwise negatively impacting overall health most recently culminating in the approval (in Europe and North America) of two monoclonal agents to inhibit PCSK9.

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 delivery of siRNA in lipid nanoparticle (LNP) 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 RNAi Therapeutic for Hypercholesterolemia

Inclisiran for Injection (SC use) is comprised of the PCSK9 siRNA, ALN-60212, formulated in phosphate buffer. The PCSK9 siRNA is a chemically synthesized double stranded oligonucleotide covalently linked to a ligand containing GalNAc residues. This synthetic investigational RNAi therapeutic has been designed to suppress the liver production of PCSK9 when administered via SC injection. Inhibition of PCSK9 synthesis through an RNAi mechanism has the potential to lower tissue and circulating plasma PCSK9 protein levels, resulting in higher expression of LDLR in the liver, and consequently lower LDL-C levels in the blood stream. The initial proposed indication for inclisiran is the treatment of subjects with hypercholesterolemia who are not achieving therapeutic LDL-C goals despite maximally tolerated lipid-lowering therapy, or for subjects who are intolerant of statins.

1.2.1 Preclinical Studies

The pharmacology, metabolism, pharmacokinetics (PK), and toxicology of inclisiran were evaluated in a series of in vitro and in vivo nonclinical studies. Development and reproductive toxicology studies have not been conducted.

The results of the pharmacology studies show that inclisiran exhibited dose-dependent sustainable suppression of PCSK9 protein that was paralleled by lowering of serum LDL-C with the same kinetics. The time to reach PCSK9 nadir was approximately 20 days and the mean maximal PCSK9 and LDL-C inhibition was 93% and 74%, respectively.

Off-target analysis encompassing bioinformatics and tissue culture assays indicate a very low likelihood of inclisiran affecting heterologous gene transcription, thereby decreasing the potential of untoward side effects. In a cardiovascular and respiratory study in telemetered conscious cynomolgus monkeys, inclisiran had no immediate or delayed effects on clinical observations, qualitative or quantitative electrocardiogram (ECG) parameters, hemodynamic parameters, respiration rate, or body temperature at any dose level.

Pharmacokinetic studies showed that inclisiran is very well absorbed following SC administration. Inclisiran has a short plasma half-life (range: 1 to 4 hours) and preferentially distributes to the liver, its target organ, achieving T_{max} levels within 8 hours of administration. With the exception of the kidney which is the main route of elimination, liver concentrations of inclisiran are many fold higher than other tissues examined, thereby reducing the potential for off-target toxicity. In addition, studies with heart tissue showed that very low levels of inclisiran are internalized and it does not associate with the ribonucleic acid-induced silencing complex indicating a low likelihood of activity in heterologous tissues.

The results of repeat dose toxicology studies in rats and monkeys show that inclisiran was well tolerated. The most consistent findings were the presence of vacuolation in hepatocytes of rats and lymph node macrophages of monkeys and basophilic granules in hepatocytes of monkeys and renal tubule epithelium of rats. The presence of vacuolation, particularly in the liver, and basophilic granules in the kidney are not associated with changes in clinical pathology parameters including liver function enzymes and urinalysis parameters signifying that the vacuolation and basophilic granules are not adverse toxicological findings. In addition, there are indications that these findings are reversible.

Inclisiran was tested in a series of in vitro and in vivo genetic toxicology studies, including a bacterial mutagenicity assay, an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assays in rats. There were no gene mutations or chromosomal damage observed in any study. Therefore, inclisiran is not genotoxic.

Further information is in the Investigator's Brochure (IB).

1.2.2 Clinical Studies

One Phase I study has been conducted to date (Study ALN-PCSSC-001). This was a randomized, single-blind, placebo-controlled, single-dose escalation and multiple-dose study of inclisiran administered SC to subjects with elevated LDL-C. The study was conducted in two phases: a single ascending dose (SAD) phase and a multiple dose (MD) phase. During the SAD phase, 24 subjects were assigned to either receive placebo or one of five doses of inclisiran ranging from 25 mg to 800 mg. Those who received doses of at least 100 mg saw their LDL-C drop at least 40%; at the 500 mg dose, LDL-C levels dropped as much as 78%. At 140 days after the treatment was given, subjects still had an average LDL-C reduction of about 40%.

In the MD phase, 45 subjects received multiple doses of either inclisiran (125mg weekly x4, 250 mg biweekly x2, 300 mg and 500 mg twice given 1 month apart) or placebo. These subjects had maximal LDL-C reductions of 80% and average LDL-C reductions of 50% to 60%. To date, the drug appears to be generally safe and well tolerated. One subject on statin comedication had elevated liver enzymes with alanine aminotransferase (ALT) >4x the upper limit of normal (ULN), which resolved on stopping the statin.

One Phase II dose finding study CKJX839A12201 (MDCO-PCS-15-01; ORION-1) was conducted and is complete. This study was a placebo-controlled, double-blind, randomized trial to compare the effect of inclisiran administered SC as either a single dose (200 mg, 300 mg, or 500 mg) on Day 1 or as two doses (100 mg, 200 mg, or 300 mg) on Day 1 and Day 90 in subjects with high cardiovascular risk and elevated LDL-C. A total of 501 subjects were randomized (placebo=127 and inclisiran=374) and 497 received at least one dose of study drug (placebo=127 and inclisiran=370). After administration of dosing, all subjects were followed until Day 210. Subjects whose LDL-C values had not returned to within 20% of the change from their baseline value were followed up to Day 360. Regular reviews of safety were performed by an independent Data Monitoring Committee and no safety concerns were reported and no changes to the protocol were requested during conduct of the study.

An interim analysis was performed after all subjects had completed the Day 90 visit in order to select the dose for subsequent studies. Inclisiran was generally well tolerated following single and multiple dosing. There was no imbalance observed in the incidence or type of AEs and serious adverse events (SAEs) across the dose range of inclisiran groups with a similar incidence to placebo. The majority of adverse events (AEs) were mild or moderate in severity. The most common AEs observed after the first injection until Day 90 were myalgia, back pain, fatigue, headache, dizziness, nasopharyngitis, diarrhea and hypertension. A low incidence of mild, localized, injection site reactions (ISRs) was reported with no clear dose dependent or cumulative effect observed following first or second injection. No subjects developed treatment emergent liver findings that met the laboratory definition of Hy's Law. One subject developed clinically significant changes in liver function tests reported as an SAE which was attributed to concomitant statin therapy and a recent statin dose increase and resolved on discontinuation of statin. All doses

of inclisiran inhibited PCSK9 synthesis and lowered LDL-C significantly. One dose of 300 mg inclisiran achieved a mean 51% LDL-C reduction. Two doses of 300 mg inclisiran achieved a mean 57% LDL-C reduction in LDL-C. The LDL-C reduction was significant and durable out to 180 days following either one or two injections of inclisiran. No additional LDL-C reduction was observed with 500 mg as a single dose. Potentially favorable changes were also observed in the overall atherogenic lipid profile.

The end of trial evaluation confirmed the data observed at the interim analysis. Inclisiran, at all tested doses, was safe and well-tolerated in subjects at high cardiovascular risk who had elevated LDL-C levels. A single dose of 300 mg inclisiran sodium achieved a maximum mean LDL-C reduction of 50.9% at Day 60. Two 300 mg inclisiran sodium doses administered at Day 1 and Day 90 achieved a maximum mean LDL-C reduction of 55.5% at Day 150. The LDL-C reduction was clinically significant and durable out to 360 days following either one or two injections of inclisiran. Maximum PCSK9 reduction was observed at the 300 mg dose level. A similar reduction observed in LDL-C at Day 270 compared to Day 90 along with the time adjusted mean LDL-C reduction of 50.5% over this time interval further support a dose regimen of 300 mg inclisiran sodium given at Day 1, Day 90, and every 6 months thereafter as the optimal dose and dose regimen to investigate further in subsequent Phase III clinical studies. Modeling and simulation analyses provide further support for the proposed 6 monthly maintenance regimen.

No persistent and clinically relevant treatment related abnormalities were reported in any laboratory parameter. A low incidence of AST, ALT and CK rises were reported, although some of these subjects also had elevated baseline value or underlying medical conditions contributing to these elevations. There were no treatment emergent increases in bilirubin from a normal baseline and no case met the definition of Hy's Law. One subject had a rise in ALT on Day 104 following the second injection of 300 mg inclisiran sodium as reported in the interim analysis. This was considered related to a recent increase in the dose of statin and resolved immediately on stopping the statin. There were no clinically relevant or persistent changes in the inclisiran dose groups observed in any other laboratory parameters including renal function, hemoglobin, platelets, HbA1c and coagulation parameters and no clinically relevant differences from placebo.

Subjects participating in MDCO-PCS-15-01 (CKJX839A12201) were asked to consent to the ORION-3 trial described in this protocol (MDCO-PCS-16-01 (CKJX839A12201E1)) once their lipid levels have returned to within 20% of the baseline levels or after they reached the Day 360 visit in study MDCO-PCS-15-01, whichever occured first.

1.2.3 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 or comparator. 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. Evolocumab is an approved drug with a good safety profile, but may cause allergic reactions.

An expanded risk-benefit summary is provided in the current/approved version of the Investigator's Brochure.

1.3 Study Rationale

1.3.1 Study Rationale

The overall safety data from inclisiran in nonclinical studies and clinical data from the Phase I ALN-PCSSC-001 study, the ALN-PCS02-001 study (ALN-PCS02 2014), 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 II extension study. A switching arm has been added to this long-term extension to evaluate safety, tolerability and patient reported outcomes (PRO) compared to an active comparator (evolocumab) and [redacted]

1.3.2 Dose Rationale

For this extension study a single dose of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran)/ 1.5 mL or evolocumab (approved active comparator) will be used. The 300 mg dose of inclisiran was selected based on the interim analysis of the Phase II MDCO-PCS-15-01 study, which was performed after all subjects had completed the Day 90 visit. Inclisiran was generally well tolerated following single and multiple dosing. There was no imbalance observed in the incidence or type of AEs and SAEs across the dose range (200 mg, 300 mg or 500 mg single dose or 100 mg, 200 mg or 300 mg double dose) of inclisiran groups with a similar incidence of AEs to placebo. The majority of AEs were mild or moderate in severity. The most common AEs observed after the first injection until Day 90 were myalgia, back pain, fatigue, headache, dizziness, nasopharyngitis, diarrhea and hypertension. A low incidence of mild, localized, ISRs was reported with no clear dose dependent or cumulative effect observed following first or second injection. All doses of inclisiran inhibited PCSK9 synthesis and lowered LDL-C significantly after one or two injections. One dose of 300 mg inclisiran achieved a mean 51% LDL-C reduction. Two doses of 300 mg inclisiran achieved a mean 57% LDL-C reduction in LDL-C. The LDL-C reduction was significant and durable out to 180 days following either one or two injections of inclisiran. No additional LDL-C reduction was observed with 500 mg as a single dose compared to the 300 mg dose. Potentially favorable changes were also observed in the overall atherogenic lipid profile. These efficacy and safety data support the 300 mg dose as the dose for subsequent clinical trials and a biannual dosing for this study.

Therefore, the 300 mg dose selected for this study is based on the safety and efficacy findings from the Phase II study where this dose provides maximal LDL-C reduction.

In this extension study, the 300 mg dose of inclisiran sodium with a biannual dosing will be used for the first two years for subjects in Group 1 (inclisiran only arm). Following the dose at Day 720, an additional dose will be administered at Day 810. This dose will allow the assessment of the effect of inclisiran dosed at 90 days apart, rather than 180 days apart. Following the dose at Day 810, a biannual dosing will be used for the remainder of study. The additional dose at Day 810, which is similar to the initial dosing regimen selected for other inclisiran studies, will evaluate the effect of an alternative dosing regimen in the third and fourth years of this study.

Subjects in Group 2 (switching arm) will be transitioned to inclisiran therapy at Day 360 in one of two ways; one transition group (Transition 1) will self administer the final dose of evolocumab therapy at Day 336 and the first dose of inclisiran will be administered at the Day 360 visit. The second transition group (Transition 2) will self administer evolocumab through Day 336, then

receive their final evolocumab injection and their first inclisiran injection at the Day 360 Visit in the clinic. Administration of the two treatments on the same day is supported by the following:

- Distinct pharmacological mechanisms; although both drugs reduce PCSK9 levels they work very differently. Evolocumab is a monoclonal antibody that works by binding to circulating plasma PCSK9, and inclisiran is an siRNA that has a short plasma half life and its mode of action is in the liver, inhibiting the synthesis of PCSK9. Both products have limited potential to interact with each other or other treatments. No clinically relevant safety issues are expected from concurrent administration.
- Concurrent administration of evolocumab and inclisiran may optimally maintain PCSK9 reduction during the transition period from evolocumab to inclisiran as the maximal effect of evolocumab on PCSK9 levels is observed over 14-30 days from the time of administration, then the PD effect tails off. Inclisiran's effect on PCSK9 inhibition is at its peak between 30 and 60 days after administration. [redacted] A follow up visit will occur for all subjects 30 days later.

All subjects in Group 2 (switching arm) will receive their first administration of inclisiran sodium 300mg on Day 360 and a second 300mg dose 90 days later (Day 450 visit) and then every 180 days until the EOS. Modelling and simulation analyses have 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. This is also the dosage regimen being implemented in the ongoing Phase III program.

1.4 Study Population

This study will include male or female subjects ≥18 years of age with a history of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia), or a >20% 10-year risk of a CV event assessed by Framingham Risk Score or equivalent and receiving maximum-tolerated lipid-lowering therapy who have completed study MDCO-PCS-15-01 (ORION-1).

2 Study Objectives and Purpose

This study is designed to evaluate the efficacy, safety, and tolerability of inclisiran injection(s).

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effects of inclisiran on the following (Group 1; inclisiran only arm):
  - LDL-C levels over time
  - PCSK9 levels over time

- Other lipids, lipoproteins, and apolipoproteins over time
- Proportion of subjects achieving target levels prespecified in global lipid guidelines
- Proportion of subjects with at least 50% LDL-C reduction from Baseline of ORION-1 over time
- Individual responsiveness to inclisiran

- To evaluate the long term safety and tolerability of inclisiran (Group 1; inclisiran only arm)

3 Study Design

3.1 Type/Design of Study

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

Subjects completing study MDCO-PCS-15-01 and fulfilling all inclusion and exclusion criteria of this study will receive inclisiran or evolocumab, based on the treatment received in study

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

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

Group 1 (Inclisiran Only Arm):

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

The subsequent visit schedule is as follows:

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

  *Day 810 dose added to assess the effect of giving 2 doses 90 days apart (at Days 720 and 810).
- Safety follow-up visits: Days 30, 90, 210, 270, 390, 450, 570, 630, 870, 1080, 1260, and EOS (Day 1440).

Group 2 (Switching Arm):

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

- Transition 1 (staged): Day 336 will be the final dose of evolocumab therapy and the first dose of inclisiran will be administered at the Day 360 visit.
- Transition 2 (concurrent): Day 336 will be the final dose of evolocumab therapy at home. At the Day 360 visit subjects will receive an additional dose of evolocumab and their first dose of inclisiran, both administered by the investigator.

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

The subsequent visit schedule is as follows:

- Dosing visits: Day 450 (2^{nd} dose), then every 180 days until end of study (Days 630, 810, 990, 1170 and 1350).
- Safety follow-up visits: Days 390, 510, 540, 720, 900, 1080, 1260, and EOS (Day 1440).

End of Study (EOS)

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

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

At each visit, AEs, SAEs, concomitant medications, and safety laboratory assessments will be collected.

[redacted]

An interim analysis of lipids and PCSK9 will be conducted upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran. [redacted]

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

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

- until the investigator's recommendation of discontinuation,

- until the sponsor's recommendation of discontinuation,

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

- until an administrative decision is made to end the study

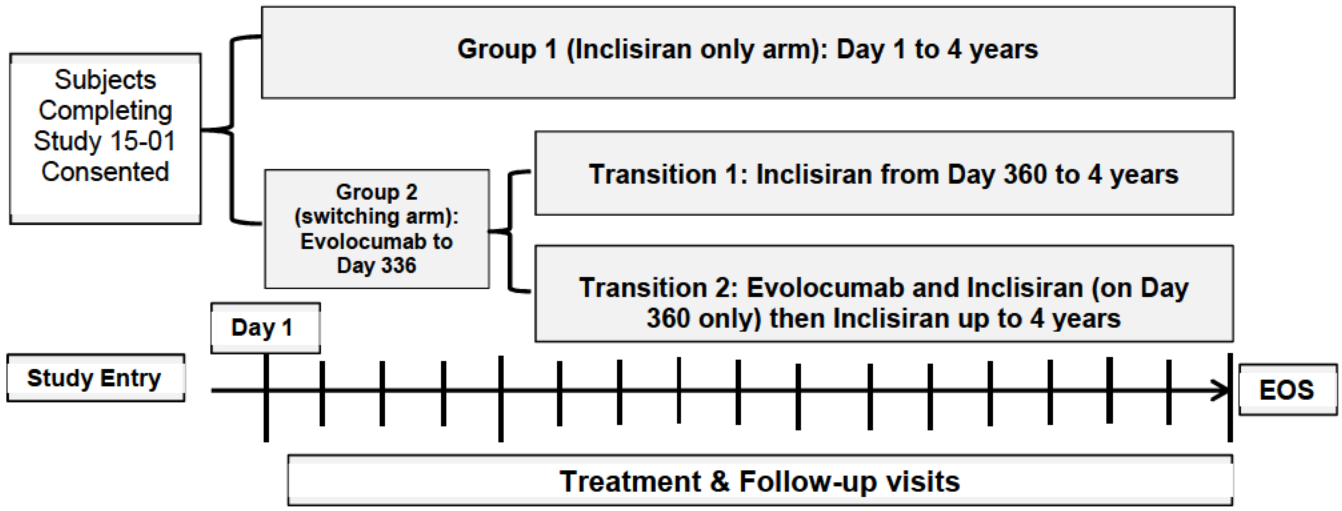
If subjects, who have completed EOS visit (90 days after last dose administration), wish to continue treatment with inclisiran (and none of the above listed decisions or recommendations to discontinue the trial are in place) they will be given the opportunity to enroll into ORION-8 (open-label extension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

An interim analysis of lipids and PCSK9 will be conducted upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran. [redacted]

3.2 Schematic Diagram of Study Design

The study design is presented in Figure 3-1

Figure 3-1 Study Design



3.3 Primary Endpoint (Group 1; Inclisiran Only Arm)

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

3.4 Secondary Endpoints (Group 1; Inclisiran Only Arm)

The secondary endpoints of this study are:

- Change and percentage change from Baseline of ORION-1 in LDL-C over time in this study
- Change and percentage change from Baseline of ORION-1 in PCSK9 levels over time in this study
- Change and percentage change from Baseline of ORION-1 in other lipids, lipoproteins, and apolipoproteins, over time in this study
- Proportion of subjects with ≥50% LDL-C reduction from Baseline of ORION-1 at each time point
- Individual responsiveness to inclisiran defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at any time point
- Change and percentage change in LDL-C at Day 210 compared to Day 870 of ORION-3
- Long term safety and tolerability of inclisiran treatment

[redacted]

3.6 Measures to Minimize/Avoid Bias

3.6.1 Unblinded Study

This is an open label, nonrandomized study. The primary endpoint is based on an assessment of LDL-C, which is a measurement that is not likely to be subject to interpretation bias.

4 Subject Population

This will be a multicenter study conducted in North America and Europe (at approximately 60 sites) in subjects with ASCVD or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies who have completed study MDCO-PCS-15-01.

4.1 Number of Subjects

A maximum of 490 subjects can be included in the study.

4.2 Inclusion Criteria

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

1. Completion of study MDCO-PCS-15-01 and no contraindication to receiving inclisiran or evolocumab.

2. Willing and able to give written and informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.
3. Willing to self-inject.

4.3 Exclusion Criteria

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. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses).
4. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained ALT, aspartate aminotransferase (AST), elevation >2x ULN or total bilirubin elevation >1.5x ULN at Study Entry visit, confirmed by a repeat abnormal measurement at least 1 week apart.
5. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of 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. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
7. Treatment with investigational medicinal products other than inclisiran or devices within 30 days or five half-lives, whichever is longer.
8. Planned use of investigational medicinal products other than inclisiran or devices during the course of the study.
9. Subjects with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients.
10. Previous or current treatment (within 90 days of Study Entry) with monoclonal antibodies directed towards PCSK9.
11. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:

a. Inappropriate for this study, including 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. Involved with, or a relative of, someone directly involved in the conduct of the study.
e. Any known cognitive impairment (eg, Alzheimer Disease).

4.4 Withdrawal Criteria

All subjects have the right to withdraw 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 for any subject study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

- AE
- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up

It is especially important that all subjects be contacted to attend the Day 210 visit, as it is the primary endpoint of the study. .Subjects discontinuing participation in this trial should be encouraged to complete the EOS visit except for those subjects who specifically withdraw consent. 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.

4.4.1 Withdrawal from Study Medication

In the event a subject withdraws or is withdrawn from the study medication, the investigator will inform the Medical Monitor and the Sponsor immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator for protocol-specified safety follow up procedures.

4.4.2 Individual Subject Dosing Stopping Criteria

Subjects will have clinic visits at regular intervals. The following individual dosing stopping criteria will be followed:

1. Dosing with study medication (inclisiran or evolocumab) may be temporarily discontinued or stopped for 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. Subjects with persistent and unexplained increases in transaminases (ALT or AST) >3x ULN or with bilirubin increases >2x ULN from a normal baseline on two consecutive occasions at least 4-7 days apart by repeat test must be discontinued from study treatment

and asked to complete the remainder of the scheduled visits without receiving study medication (inclisiran or evolocumab).

3. Subjects with unexplained creatine kinase (CK) values >5 x ULN confirmed by repeat test, for whom the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction, must be discontinued from study treatment and asked to complete the remainder of the scheduled visits without receiving study medication (inclisiran or evolocumab).

5 Treatment of Subjects

5.1 Study Medications

Treatments will be assigned based on the treatment the subjects received in Study MDCO-PCS-15-01, as outlined in Table 5-1.

Table 5-1 Treatment assignments

Study MDCO-PCS-15-01 (ORION-1)	Study MDCO-PCS-16-01 (ORION-3)
Inclisiran	Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran)/ 1.5 mL
Placebo	Evolocumab 140 mg every 2 weeks, as per the prescribing information of the approved therapy, until Day 336 or Day 360 (at Day 360, subjects will be transitioned to Inclisiran)

5.1.1 Inclisiran (also referred to as KJX839)

Study drug (inclisiran) information is described in Table 5-2.

Table 5-2 Investigational Product

	Investigational Product
Product Name	Inclisiran for Injection
Dosage Form:	Solution for Injection
Unit Dose	300 mg (equivalent to 284 mg inclisiran) /1.5 mL vial
Route of Administration	SC use
Physical Description	Clear, colorless to pale yellow solution essentially free of particulates
Manufacturer	Alcami Corporation, Charleston, South Carolina, USA.

Study drug preparation: The pharmacist or qualified designee will prepare the study drug under aseptic conditions to be administered to the subject on that day.

The procedure for preparing study drug is provided in the Pharmacy Manual.

Study drug administration: Subjects will be administered a single SC injection of 300 mg (equivalent to 284 mg inclisiran)/ 1.5 mL Inclisiran for Injection at predefined time points as described in the Schedule of Assessments (Section 6.1). Study drug 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. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

If a **local reaction around the injection site** occurs, photographs of the injection site should be obtained, if possible, at first presentation and at each of the follow-up visits until the injection site reaction resolves. Detailed instructions for study drug administration are found in the Pharmacy Manual.

5.1.2 Comparator Drug (evolocumab)

Evolocumab will be administered as a single SC injection at a dose and frequency as per the label of the approved therapy. Training for self administration will be provided by site personnel according to the label, and the first dose will be injected under supervision of the Investigator or designee. Subjects will be required to self administer evolocumab every 14 days until Day 336. For subjects in Transition 2, an additional dose of evolocumab, the final dose, will be administered at the Day 360 visit by the investigator and these subjects will also receive their first inclisiran injection at the same visit. The investigator (or designee) should use different sites of injection when administering these two products (evolocumab and inclisiran) at the same time. Do not inject into the same area of the skin.

Evolocumab, a monoclonal antibody directed towards PCSK9, is a sterile, clear to opalescent, colorless to pale yellow solution available as a 140 mg/mL solution in a single-use prefilled syringe or SureClick® autoinjector. Evolocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). The recommended subcutaneous dosage of evolocumab in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is 140 mg every 2 weeks.

5.1.3 Packaging and Labeling

Inclisiran for Injection will be provided by the sponsor. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

The Inclisiran for Injection (subcutaneous use) is packaged in a glass vial containing 300 mg (equivalent to 284 mg inclisiran) per 1.5 mL. The container closure system consists of a Type I glass vial, a Teflon-faced bromobutyl 13 millimeter stopper, and a flip off Truedge aluminum seal.

Evolocumab will be provided as prefilled pens, as locally approved.

5.1.4 Storage

Inclisiran for Injection will be stored at room temperature [up to 25°C (77°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.

Evolocumab will be used according to its approved label. Evolocumab should be kept in the refrigerator and allowed to warm to room temperature for at least 30 minutes before use.

Alternatively, evolocumab can be kept at room temperature [up to 25°C (77°F)] in the original carton, but under these conditions, it must be used within 30 days.

5.1.5 Accountability

The investigator or designee must maintain an inventory record of study drugs received and administered to assure the regulatory authorities and the Sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Drug accountability forms and/or specific instructions can be found in the Pharmacy and Comparator Manuals.

The study drug supplied for use in this study is to be prescribed only by the principal investigator or designated subinvestigators and may not be used for any purpose other than that outlined in this protocol.

During the study, all used study drug containers (eg, empty vials/bottles) will be kept until the monitor has reviewed the accountability records.

All unused study drug will be destroyed on site (or returned to the packaging and labeling facility for destruction if destruction on site is not possible) once the study drug has been inventoried and the monitor has reviewed the accountability records. In the event that study drug(s) needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.

5.1.6 Product Deficiencies Reporting

Sites are required to report any product deficiency observed for the study medications (inclisiran) to sponsor immediately but no later than 24 hours from the time of awareness.

In addition, any product deficiency observed for inclisiran,is required to be recorded in the eCRF. In case the drug deficiency is leading to an Adverse Event or Serious Adverse Event these have to be recorded and reported as specified in Section 8, Section 4, Section 2 and relationship to the drug deficiency must be indicated.

Product Deficiencies reporting: 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 United States [US] 21 CFR 211.198)

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 (this includes the bottle, any part of the seal, the cap or the label).
- An indication that the product is mislabeled.

- An indication that there is an unexpected physical change of the product or container once the product is diluted or reconstituted (the container includes the unit dose, bag, intravenous line, syringe or any other item that is in contact with the product).
- 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.

5.2 Concomitant Medications

5.2.1 Prohibited Concomitant Medications

Background lipid-lowering treatment should remain stable throughout the study duration. As a result, the following medications/treatments are not permitted to be added or changed 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 (with the exception of evolocumab for Group 2 during the first year).
- Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies.
- Any other investigational medicinal product(s) other than inclisiran during the course of the study.

5.2.2 Permitted Concomitant Medications

The following medications/treatments are permitted during the study:

- Hormone replacement therapy
- Lipid-lowering medications; subjects already on lipid-lowering medications (such as statins and/or ezetimibe) should remain on the dose that they have received at time of study entry.
- 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 (or a study subject's partner) becomes pregnant during the course of the study, the study drug administration must be discontinued and the pregnancy should be followed through to outcome. 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. Reporting of pregnancy and any associated AEs are specified in Section 8.3.4.

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

5.5 Blinding

Not applicable, this is an open-label study.

6 SCHEDULE and Sequence of Procedures

The Schedule of Events/Assessments (Table 6-1 and Table 6-2) summarizes the study assessments by time point.

This study consists of three study periods:

- Observation Period: Consent/Study Entry until first dose on Day 1 (ORION-3)
- Treatment Period: Day 1 (ORION-3) to Day 360
  - Group 1 (inclisiran only arm)
  - Group 2 (evolocumab treatment; switching arm)
- Follow-up Treatment Period: Day 360 to EOS
  - all subjects on inclisiran

The expected duration of the subjects' involvement in the study will be approximately 4 years, which includes consent, study drug administration, and follow-up through the EOS visit (final visit which occurs 90 days following the final administration of study drug, or at least 30 days following the final administration of study drug if the study ends early or if the subject discontinues the study early).

At each visit, LDL-C levels, AEs, SAEs, concomitant medications, vital signs, and safety laboratory assessments will be collected.

6.1 Schedule of Events/Assessments

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 Study Design and Schedule of Assessments (Group 1; Inclisiran Only Arm)

	Study Entry [m]	Observation Visits [a]	First Dose [q]	Treatment & Follow-Up (first 2 years) [f]												FU Visits (dosing) [f]	FU Visits (regular) [f]	EOS [p]
Study Day		every 30 days (± 7)	Day 1	FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 540 (± 7)	FU10 570 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)	FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 870 FU16, 1080 FU18, 1260	
***COVID 19 visit window (months)**															(± 2)	(± 2)	(± 2)	
Informed consent	X																	
Inclusion / Exclusion Criteria	X																	
Physical Examination (including full neurological examination & weight)			X						X						X		X(D1080) [e]	X
[redacted]																		
Vital Signs [b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG[c]			X						X						X		X(D1080) [e]	X
HbA1c [n] and serum glucose	X		X					X				X				X (D810 and 1350)	X (D1080)	X
Hematology [d]	X	X	X						X						X		X (D1080)	X
Coagulation [d]	X	X	X	X (S)	X (S)	X (S)		X (S)	X		X (S)	X (S)	X (S)		X	X (S)	X (S) / X (D1080)	X
Full Chemistry [d]	X	X	X						X						X		X (D1080)	X
Limited Chemistry				X	X	X		X		X	X	X	X	X		X	X (D 870, 1260)	
Urinalysis (local) [g]	X	X	X [g]		X	X		X	X		X	X		X	X	X	X	X
Pregnancy test (local) [i]	X	X	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
Stored samples [k]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X
Efficacy parameters (LDL-C, lipids, PCSK9) [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Study Entry [m]	Observation Visits [a]	First Dose [q]	Treatment & Follow-Up (first 2 years) [f]											FU Visits (dosing) [f]	FU Visits (regular) [f]	EOS [p]
Study Day		every 30 days (± 7)	Day 1	FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 540 (± 7)	FU10 570 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)	FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 870 FU16, 1080 FU18, 1260	
***COVID 19 visit window (months)**															(± 2)	(± 2)	(± 2)	
Lipoproteins [l] [Lp(a), ApoB]	X	X	X				X		X				X		X			X
Study drug administration: inclisiran			X[o,q]			X			X			X			X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Product deficiencies (including AE/SAEs related to the drug or device deficiency	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted] AE = adverse event; ECG = electrocardiogram; FU=follow-up; EOS = end of study; HbA1c= glycated hemoglobin A1C; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; S = Stored sample; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

*: The visit window is extended to +/- 2 months (in addition to existing visit window) during the COVID-19 pandemic, to allow on-site visits (rather than remote visits) to occur as much as possible. [a] Observation visits every 30 days (±7 days) until study drug is available.

[b] Vital signs: blood pressure and heart rate will be measured prior to injection. On Day 1 (vital signs will also be measured at 4 hours after injection).

[c] ECG should be performed prior to the injection.

[d] Hematology, chemistry (including glucose, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing (of which some will be collected and stored for future analyses).. Blood samples for determination of laboratory values will be performed prior to study drug injection. All laboratory testing will be performed with subjects in a fasted state. See Section 7.1.6 for a list of laboratory parameters. Lab tests performed by study's designated Central Lab facility from entry into the study to EOS. On days when inclisiran is injected, if indicated, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).

[e] Physical and neurological examinations, weight, and ECG performed once yearly.

[f] Visit windows are ± 2 days for the Day 30 visit, and ± 7 days from Day 90 onwards.

[g] Urinalysis collection is prior to the injection on Day 1; supplies from the Central Lab must be used to perform the urinalysis.

[h] Urine pregnancy test performed and results available prior to the injection on Day 1; supplies from the Central Lab must be used to perform the test.

[i] Women of childbearing potential will have a pregnancy test at each visit.

[redacted]

[k] Plasma glucose and lactate will be collected at intervals throughout the study and stored for future analyses. See Section 7.1.8 for details. Additional blood samples will be collected every 180 days and aliquots of plasma and serum stored for future analyses.

[l] Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), C-reactive protein (CRP), and PCSK9. A standard lipid panel will be done at all visits (Day 1 to EOS) however some PCSK9 samples will be stored for future analyses and ultracentrifugation is to be done only at Day 1, Day 210, Day 360, Day 570, Day 720 and EOS.

[m] Until study drug is available, subjects will attend a basic observation visit at 30 day intervals. These visits will include safety labs (hematology, chemistry, coagulation) and recording of AEs, SAEs, and concomitant medications.

[n] HbA1c assessed every 270 days. Therefore, HbA1C to be assess at follow-up visits on Days 270, 540, 810, 1080, and 1350.

[o] Subjects will be observed in the clinic for at least 4 hours post their first inclisiran injection before being discharged (Day 1 for subjects in Group 1; inclisiran only arm)

[p] EOS will occur 90 days following the final administration of study drug. However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

[q] There should be a minimum of 7 days between Study Entry or last observation visit and Day 1.

Table 6-2 Study Design and Schedule of Assessments (Group 2; Switching Arm)

	Study Entry[o]	Observation Visits [a]	First Dose[t]	Treatment & Follow-Up (first 2 years) [f]											FU Visits (dosing) [f]	FU Visits (regular) [f]	EOS[s]
Study Day		every 30 days (± 7)	Day 1	FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 510 (± 7)	FU10 540 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)	FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 900 FU16, 1080 FU18, 1260	
***COVID 19 visit window (months)**															**(± 2)**	**(± 2)**	**(± 2)**	
Informed consent	X																	
Inclusion / Exclusion Criteria	X																	
Physical Examination (including full neurological examination & weight)			X						X						X		X(D1080) [e]	X
[redacted]				[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]			
[redacted]				[redacted]	[redacted]	[redacted]		[redacted]	[redacted]									
Vital Signs [b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG[c]			X						X						X		X(D1080) [e]	X

	Study Entry[o]	Obser-vation Visits [a]	First Dose[t]	Treatment & Follow-Up (first 2 years) [f]											FU Visits (dosing) [f]	FU Visits (regular) [f]	EOS[s]
Study Day		every 30 days (± 7)	Day 1	FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 510 (± 7)	FU10 540 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)	FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 900 FU16, 1080 FU18, 1260	
***COVID 19 visit window (months)**															**(± 2)**	**(± 2)**	**(± 2)**	
HbA1c [q] and serum glucose	X		X					X					X			X (D810 and 1350)	X (D1080)	X
Hematology [d]	X	X	X						X						X		X (D1080)	X
Coagulation [d]	X	X	X	X (S)	X (S)	X (S)		X (S)	X		X (S)	X (S)		X (S)	X	X (S)	X (S) / X (D1080)	X
Full Chemistry [d]	X	X	X						X						X		X (D1080)	X
Limited Chemistry				X	X	X		X		X	X	X	X	X		X	X (D 900, 1260)	
Urinalysis (local) [g]	X	X	X [g]		X	X		X	X		X	X		X	X	X	X	X
Pregnancy test (local) [i]	X	X	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		

	Study Entry[o]	Obser-vation Visits [a]	First Dose[t]	Treatment & Follow-Up (first 2 years) [f]											FU Visits (dosing) [f]	FU Visits (regular) [f]	EOS[s]
Study Day		every 30 days (± 7)	Day 1	FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 510 (± 7)	FU10 540 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)	FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 900 FU16, 1080 FU18, 1260	
***COVID 19 visit window (months)**															**(± 2)**	**(± 2)**	**(± 2)**	
Stored samples [k]	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X
Efficacy parameters (LDL-C, lipids, PCSK9) [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipoproteins [m] [Lp(a), ApoB]	X	X	X				X		X			X			X			X
Study drug administration: evolocumab [l,n]			X[t]	Every 14 days through Day 336					X [p]									
Inclisiran									X[r]		X			X		X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted] AE = adverse event; ECG = electrocardiogram; FU=follow-up; EOS = end of study; HbA1c= glycated hemoglobin A1C; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; S = Stored sample; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

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

[a] Observation visits every 30 days (±7 days) until study drug is available.

[b] Vital signs: blood pressure and heart rate will be measured prior to injection. On Day 360 (transition visit), vital signs will also be measured at 4 hours after injection.

[c] ECG should be performed prior to the injection.

[d] Hematology, chemistry (including glucose, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing (of which some will be collected and stored for future analyses). Blood samples for determination of laboratory values will be performed prior to study drug injection. All laboratory testing will be performed with subjects in a fasted state. See Section 7.1.6 for a list of laboratory parameters. Lab tests performed by study's designated Central Lab facility from entry into the study to EOS. On days when inclisiran is injected, if indicated, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).

[e] Physical and neurological examinations, weight, and ECG performed once yearly.

[f] Visit windows are ± 2 days for the Day 30 visit, and ± 7 days from Day 90 onward.

[g] Urinalysis collection is prior to the injection on Day 1; supplies from the Central Lab must be used to perform the urinalysis.

[h] Urine pregnancy test performed and results available prior to the injection on Day 1; supplies from the Central Lab must be used to perform the test.

[i] Women of childbearing potential will have a pregnancy test at each visit.

[redacted]

[k] Plasma glucose and lactate will be collected at intervals throughout the study and stored for future analyses. See Section 7.1.8 for details. Additional blood samples will be collected every 180 days and aliquots of plasma and serum stored for future analyses.

[l] Diary cards should be turned in to study site coordinator at follow-up visits on Day 30, 90, 180, 270 and 360.

[m] Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), C-reactive protein (CRP), and PCSK9. A standard lipid panel will be done at all visits (Day 1 to EOS) however some PCSK9 samples will be stored for future analyses and ultracentrifugation is to be done only at Day 1, Day 210, Day 360, Day 510, Day 720 and EOS.

[n] Day 1 in clinic; Days 14 through 336 to be self-injected according to label; for subjects in Transition 2; at Visit Day 360 in the clinic.

[o] Until study drug is available, subjects will attend a basic observation visit at 30 day intervals. These visits will include safety labs (hematology, chemistry, coagulation) and recording of AEs, SAEs, and concomitant medications.

[p] Only subjects in Transition 2 will receive a final dose of evolocumab at Visit Day 360 with the first dose of inclisiran.

[q] HbA1c assessed every 270 days. Therefore, HbA1C to be assess at follow-up visits on Days 270, 540, 810, 1080, and 1350.

[r] Subjects will be observed in the clinic for at least 4 hours post their first inclisiran injection before being discharged

[s] EOS will occur 90 days following the final administration of study drug. However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

[t] There should be a minimum of 7 days between Study Entry or last observation visit and Day 1.

6.2 General Conduct of the Study

On completion of study MDCO-PCS-15-01 (ORION-1), eligible subjects will be consented for this study. Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all subjects before the performance of any protocol-specific procedure. In countries where applicable, on signing consent and being entered into this study, the investigator will be informed by the IXRS regarding the treatment allocation, and therefore, whether placebo or inclisiran was administered in study MDCO-PCS-15-01 and the subject will be informed accordingly.

Until study drug is available subjects will attend a basic visit for safety and concomitant medications at 30 day intervals. Once study drug is available, eligible subjects will receive a single injection of study drug on Day 1 (ORION-3).

Note: Data on medical history and concomitant medications will be reported from Baseline of ORION-1. Details will be described in the Statistical Analysis Plan (SAP).

6.3 Study Entry

- Sign Informed Consent
- Assessment of inclusion/exclusion criteria
- Vital signs: blood pressure and heart rate will be measured prior to injection
- Central laboratory assessments (hematology, chemistry [including HbA1c], and coagulation)
- Urinalysis (local, using supplies provided)
- Pregnancy test (local, using supplies provided)
- Collection of additional blood samples
- Assessment of lipids/lipoproteins
- Concomitant medications recording
- AE/SAE collection

Entry into the study should only occur once subject eligibility is confirmed.

6.4 Observation Visit(s)

Until study drug is available subjects will attend a basic visit at 30 day intervals (±7 days), where the following procedures will be performed:

- Central laboratory assessments (hematology, chemistry, coagulation and lipids)
- Urinalysis (local, using supplies provided)
- Pregnancy test (local, using supplies provided)
- Assessment of lipids/lipoproteins
- Concomitant medications recording
- AE/SAE collection

Once study drug is available, eligible subjects will receive study drug on Day 1 (ORION-3).

6.5 Day 1 of ORION-3

The following procedures will be performed prior to the injection:

- Vital signs: blood pressure and heart rate will be measured prior to injection
- 12-lead ECG
- Central laboratory assessments (hematology, chemistry [including HbA1c], and coagulation)
- Physical examination including full neurological examination (see APPENDICX A)
- Urinalysis (local, using supplies provided)
- Pregnancy test (local, using supplies provided); results must be available prior to dosing
- [redacted]
- Assessment of lipids/lipoproteins
- Concomitant medications
- AE/SAE collection

Study drug administration will occur at this visit for all subjects. Inclisiran will be given by the investigator. Subjects receiving evolocumab will receive training in self-injection technique and the first injection will be supervised by the investigator or designee.

After first study drug administration of inclisiran only, subjects will be observed in the clinic for at least 4 hours post injection before being discharged. The following procedures will be performed 4 hours after the injection, only for those subjects receiving inclisiran:

- Vital signs: blood pressure and heart rate
- [redacted]
- Concomitant medications
- AE/SAE collection

6.6 Treatment and Follow-Up Visits

All subjects will return to the study center 30 days (± 2 days) after first study drug administration for Follow-Up Visit 1 and after 90 days (± 7 days) for Follow-Up Visit 2.

Group 1 (inclisiran only arm) subjects will return at Day 180 (± 7 days) for their second study drug administration of inclisiran, and then at 30 and 90 days after each subsequent study drug administration of inclisiran.

- Dosing visits will take place on Days 180, 360, 540, 720, 810, 990, 1170 and 1350.
- Safety follow-up visits will occur on Days 30, 90, 210, 270, 390, 450, 570, 630, 870, 1080, 1260, and EOS (Day 1440).

Group 2 (switching arm) subjects will return to the study center at Days 180, 210, 270 for study related procedures. At Day 360 visit, subjects in Group 2 (switching arm) are assigned to either Transition 1 (staged) or Transition 2 (concurrent) (see Section 3.1).

Study drug administration of inclisiran and safety follow-up visits for both Transition 1 (staged) and Transition 2 (concurrent) will occur as follows:

- Dosing visits will take place on Day 360 (first dose of inclisiran), Day 450, Day 630, 810, 990, 1170, and 1350.

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

Pre-injection procedures will be as follows:

- [redacted]
- Vital signs: blood pressure and heart rate will be measured at each visit and prior to injection where applicable
- Physical examination, including full neurological examination (APPENDICX A) and 12-lead ECG will be performed once yearly (Day 360, 720, 1080)
- Central laboratory assessments as per Schedule of Assessments (Table 6-1 and Table 6-2) and Section 7.1.6.
- HbA1c assessment at Days 270, 540, and then every 270 days until the end of the study
- [redacted]
- Assessment of lipids/lipoproteins at all visits
- Urinalysis every 90 days (local, using supplies provided)
- Pregnancy test at all visits (local, using supplies provided)
- Study drug administration (as per the Schedule of Assessment)
- Concomitant medications at all visits
- AE/SAE collection at all visits

Note: At Day 360, subjects in Group 2 (switching arm) will attend the Transition Visit instead.

6.6.1 Inclisiran Transition Visit - Day 360 (Group 2; Switching Arm)

When subjects in Group 2 (switching arm) return to the study center at Day 360 (± 7 days), the first administration of inclisiran will be provided. Procedures will be as follows:

- [redacted]
- Vital signs: blood pressure and heart rate will be measured prior to injection
- Physical examination, including full neurological examination (APPENDICX A) and 12-lead ECG
- Central laboratory assessments (hematology, chemistry and coagulation testing)
- [redacted]
- Assessment of lipids/lipoproteins
- Urinalysis (local, using supplies provided)
- Pregnancy test (local, using supplies provided)
- Concomitant medications

- AE/SAE collection
- Study drug administration
  - First dose of inclisiran
  - For subjects in Transition 2, their first inclisiran administration should occur prior to the final administration of evolocumab (to be given up to 30 minutes after inclisiran administration using a separate injection site)

The following procedures will be performed 4 hours after the first inclisiran injection:

- Vital signs: blood pressure and heart rate
- [redacted]
- Concomitant medications
- AE/SAE collection

6.6.2 Treatment & Follow Up Visits After Day 360

Refer to Section 6.6 for the schedule of follow-up visits and the assessments to be completed following the Day 360 transition visit to inclisiran.

6.7 Unscheduled Visit

If deemed necessary by the Investigator, subjects may attend an unscheduled visit at the clinic. These visits are not part of the protocol per se and will not be recorded in the eCRF but should be noted in the subject's medical notes.

6.8 End of Study Visit

Subjects will receive study drug for approximately 4 years (or until the investigator's recommendation of discontinuation, sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or until an administrative decision is made to end the study). Regardless of treatment arm (inclisiran or evolocumab), the EOS visit will be the final safety follow-up visit which occurs 90 days (at Day 1440) following the final administration of study drug. However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

If subjects, who have completed the EOS (90 days after last dosing), wish to continue treatment with inclisiran (and no decision or recommendation was made to discontinue the trial) they will be given the opportunity to enroll into ORION-8 (open-label extension trial)

A subject's participation in the study is complete when:

- All ongoing SAEs have been followed to resolution or stabilization (Section 5.3.1) and
- The following procedures/assessments have been completed:
  - Vital signs: blood pressure and heart rate
  - Physical examination (including weight and full neurological examination as described in (APPENDICX A)
  - 12-lead ECG
  - Central laboratory assessments (hematology, chemistry and coagulation testing)
  - Urinalysis (local, using supplies provided)

- Pregnancy test (local, using supplies provided) is negative
- [redacted]
- Assessment of lipids/lipoproteins
- Concomitant medications
- AE/SAEs have been collected

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 Vital Signs

Vital signs include heart rate and blood pressure.

7.1.3 Physical Examination

The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, abdominal, extremities and full neurologic evaluations (APPENDIX A), and recording of weight. Significant changes from Baseline (Day 1 of ORION-3) at an assessment will be collected as AE data.

7.1.4 Electrocardiograms

Twelve lead ECGs will be collected at Days 1, 360, 720, 1080 and at the EOS visit only, unless clinically indicated. Significant changes from Baseline (Day 1 of ORION-3) at an assessment will be collected as AE data.

[redacted]

7.1.6 Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1 and Table 6-2). Additional aliquots of plasma or serum will be collected at each time point and stored for any clinically indicated efficacy or safety analyses to be conducted at the end of the study.

Subjects will be in a fasted state for all clinical laboratory assessments. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual. Note: Efficacy laboratory assessments (eg, LDL-C and PCSK9) are described in Section 7.2.

Laboratory assessments will include:

Hematology – Day 1, Day 360, Day 720, Day 1080 and EOS: hemoglobin, hematocrit, erythrocytes, reticulocytes, platelet counts, mean cell hemoglobin (MCH), mean corpuscular

volume (MCV), mean corpuscular hemoglobin concentration (MCHC), white blood cell count, differential blood count.

Coagulation - Day 1, Day 360, Day 720, Day 1080 and EOS: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT). Coagulation samples will also be collected at all other visit, however, these samples will be stored for any clinically indicated safety analyses to be conducted at the end of the study.

Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments (Table 6-1 and Table 6-2). Analysis will vary based on visit day as follows:

- **Full serum chemistry - Day 1, Day 360, Day 720, Day 1080 and EOS**
  AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), uric acid, creatine phosphokinase, albumin, total protein, urea (BUN), creatinine, sodium, potassium, chloride, inorganic phosphate, , direct and indirect bilirubin, , estimated glomerular filtration rate (eGFR), calcium, and bicarbonate.
  - Fasting serum glucose and glycated hemoglobin A1C (HbA1C): Days 1, 1080 and EOS only
  - High sensitivity C-reactive protein (hsCRP) (fasting): Days 1, 360, 720 and EOS only.
- **Limited serum chemistry all subjects – Days 30, 90, 180, 270, 390, 450, (510 Group 2 only), 540, (570 Group 1 only), 630, 810, (870 Group 1 only), (900 Group 2 only), 990, 1170, 1260, and 1350**

ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, and tryptase (as required).

- Fasting serum glucose and HbA1C: Days 270, 540, 810 and 1350 only
- Tryptase and inflammatory markers such as interleukin 6 (IL6), interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) may be performed from stored samples centrally at a later date, as required. Should a subject develop anaphylaxis on days when inclisiran is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).

Urinalysis: Urinalysis will be performed at the time points defined in the Schedule of Assessments 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 lab. The following parameters will be assessed: Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells/leukocytes, pH, and urine sediment (microscopic examination will be only performed in the event of abnormalities).

Urine Pregnancy: Urine pregnancy testing will be conducted locally at the visits specified in the Schedule of Assessments, using the supplies provided by the Central Laboratory.

[redacted]

7.1.8 Stored samples

[redacted]

Plasma glucose will be collected at all study visits except Days 210, 390 and 570 and stored for any clinically indicated safety analyses to be conducted at the end of the study.

Lactate will be collected at Study Entry, Observation Visits, on Days 1, 30, 90, 180, 360, 720 and 1080 and stored for any clinically indicated safety analyses to be conducted at the end of the study.

7.2 Assessment of Efficacy

Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1 and Table 6-2). Subjects will be in a fasted state for all efficacy laboratory assessments of Lipids/lipoproteins. Parameters to be assessed will include: TC, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-B, Lp(a), CRP, and PCSK9.

[redacted]

[redacted]

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including 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

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 risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death of it were more severe
- Requires hospitalization or prolongs hospitalization
- 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,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject 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, an MI that may be considered minor could also be an SAE if it prolonged hospitalization.

8.1.3 Special Situations Events

Information that is not necessarily considered an adverse event but which can possibly contribute to the overall knowledge concerning the safety of the compound will be considered a special situation event (Section 8.2.4).

8.2 EVALUATING ADVERSE EVENTS

8.2.1 Pre-existing conditions

Planned hospital admissions and/or surgical operations for an illness or disease that existed at baseline and did not aggravate during the study are not to be reported as AEs.

8.2.2 AE Severity

The severity of every AE must be assessed by the investigator using a three-point grading system.

1 = Mild: Discomfort noticed, but no disruption to daily activity. Requires minimal or no treatment.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity. Requires therapeutic measures.

3 = Severe: Inability to work or perform normal daily activity. May require systemic drug therapy or other treatment.

8.2.3 Relationship to Study Drug

The relationship of an AE to study treatment will be assessed by using a binary assessment. The investigator should determine whether there is a 'Reasonable possibility' or 'No reasonable possibility' that the study product caused the event based on the definitions below.

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

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

8.2.4 Requirements for Additional Safety Data Collection

8.2.4.1 Special Situations

Special Situations designated for this study are the following:

- Medication errors that fall into the following categories:

- wrong subject (ie, not administered to the intended patient)/wrong study product (inclisiran vs evolocumab)
- wrong dose (including overdose, underdose, change in dosing regimen, strength, form, concentration, amount);
- wrong route of administration
- 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

8.2.4.2 Other Safety Related Information

Injection site reactions (ISR) including individual signs or symptoms at the injection site following investigational product administration should be recorded on specifically designed eCRF pages. Photographs of ISR, if they were obtained during the study visits, should be forwarded to study inbox.

Other safety related information that requires collection, evaluation and reporting safety information in this study are:

- Abnormal neurological examination, eg, peripheral sensory and motor evaluation, an assessment of gait, pain, position, strength and reflexes (APPENDICX A).
- Potential anaphylactic reactions assessed by Sampson criteria (APPENDIX B). If Sampson criteria are positive, confirm by elevation of tryptase in blood plasma measured within 30 minutes of symptoms.

Hyperglycemia-related AEs and medications initiated to control hyperglycemia will be collected at each follow-up visit. New onset of diabetes in subjects with no medical history of diabetes will be reported when:

- HbA1C becomes ≥6.5% and/or
- Two consecutive values of fasting plasma glucose that are ≥126 mg/dL

In the case that a new concomitant medication is added for control of plasma glucose, further information regarding the subject will be collected to assess for a diagnosis of new onset diabetes.

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 (Day 1 of ORION-3) >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.

8.3 PROCEDURE FOR ADVERSE EVENT REPORTING

8.3.1 Serious Adverse Event Reporting

All SAEs that occur in subjects between Study Entry and Day 1, as well as in subjects assigned to inclisiran or evolocumab treatment from study Day 1 through the EOS visit must be reported to

the Sponsor's Global Pharmacovigilance Department (GPV) within 24 hours of awareness of the event using the SAE/AESI Report Form designated to the ORION-3 study.

The completion and processing of the SAE/AESI Report Form should be per the instructions in the provided SAE/AESI Report Form completion guidelines. Each SAE/AESI must be recorded on the sources documents and entered 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/AESI 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.

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.

8.3.2 Nonserious Adverse Event Recording

All nonserious AEs that occur in subjects between Study Entry and Day 1, as well as in subjects assigned to inclisiran or evolocumab treatment from study Day 1 up to EOS must be assessed and recorded on the source documents and eCRFs, regardless of causal relationship to the study drug.

8.3.3 Medication Error Reporting

Medication errors (with or without an associated AE) need to be recorded as medication errors in the eCRF.

Medication errors and an associated SAE need to be recorded in the eCRF and reported to the Novartis Safety department using SAE/SS Report Form as described in Section 8.3.1.

Medication errors and an associated nonserious AE need to be recorded in the eCRF as described in Section 8.3.2.

A mis-dosing protocol deviation (refer to Section 12.3) would need to be reported as a medication error if it was an "unintended error" as defined in Section 8.3.1.

8.3.4 Pregnancy Reporting

Occurrences of pregnancy in a study subject or study subject's partner from study Day 1 through the EOS visit must be reported within 24 hours using the Pregnancy/Lactation Exposure Report Form.

In cases where a pregnancy occurs with a SAE, the SAE Report Form must be used to report the SAE and the Pregnancy Report Form must be used to report the pregnancy. When a pregnancy occurs without any concurrent SAE, the Pregnancy Report Form should 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.

8.3.5 Reporting the Special Situations Events

The occurrence of the special situation events that are listed in Section 8.2.4 must be reported to the **Novartis safety** department using SAE/SS Report Form for the ORION-3 study. The SAE/SS Report Form should indicate that the reported event is the event of Special Situation.

The Special Situation events do not need to be serious to be reported.

8.4 Study Stopping Criteria

8.4.1 Data Monitoring Committee Stopping Rules

The DMC will use all available evidence and its collective judgment in making a recommendation to stop or modify the ORION-3 study for safety. Any statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise.

8.4.2 Sponsor Discontinuation Stopping Criteria

The Sponsor will review data on an ongoing basis and may, on discussion with the DMC, 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 Sponsor . In addition, Sponsor retains the right to discontinue development of inclisiran at any time.

If a study is prematurely terminated or discontinued, 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 Sponsor , all study materials must be collected and all care report forms (CRFs) completed to the greatest extent possible.

The Sponsor 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 will be used 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 ID 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 MDCO and documented in the site files.

This study will utilize the same EDC system used in the ORION-1 study to collect the data defined by this protocol, [redacted]. Data already collected for medical history, ongoing concomitant medications, and ongoing adverse events will be retained and utilized in analysis as defined by the SAP.

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 Study will be defined as the last visit of the last subject.

10 Statistical Plan

This study will be an open label, long term extension study with an active comparator (evolocumab), in approximately 490 subjects who have completed study MDCO-PCS-15-01 (CKJX839A12201) (ORION-1), to evaluate the efficacy, safety, and tolerability of long-term Inclisiran injections. The primary objective of this study is to evaluate the effect of inclisiran treatment on LDL-C levels at Day 210 compared to Baseline of ORION-1 in Group 1 (inclisiran only arm). A separate SAP document will provide more detailed specifications in data analysis and presentation.

10.1 Sample Size

This is an extension of the MDCO-PCS-15-01 (CKJX839A12201) (ORION-1) study. All eligible and willing subjects who have completed the ORION-1 study to at least Day 210 and whose LDL-C has returned to within 20% of the Baseline of ORION-1 value or who have reached Day 360 can be enrolled into the ORION-3 study. Subjects withdrawn from the ORION-1 study at any time are not eligible for the ORION-3 study.

10.2 General Statistical Considerations and Definitions

10.2.1 General Statistical Methods

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

A SAP will be written after finalizing of the eCRF and before database lock. The specifications in this document will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

Note: Data on medical history and concomitant medications will be reported from Baseline of ORION-1. Details will be described in the Statistical Analysis Plan (SAP).

Statistical analyses will be carried out using SAS® statistical analysis software version 9.2 or higher (SAS® Institute, Inc., Cary, North Carolina, USA).

10.2.2 Analysis Population

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

10.2.2.1 Intent-to-Treat (ITT) Population

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

10.2.2.2 Modified Intent-to-Treat (mITT) Population

The mITT Population will include all subjects who receive at least one dose of study drug and have both the Baseline (Day 1 of ORION-3) and the Day 210 follow-up LDL-C assessment. Treatment classification will be based on the allocated treatment. This will be the primary population for analysis of the primary and secondary endpoints.

10.2.2.3 Safety Population

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

10.2.3 Analysis Windows and Day 1

Data analysis windows and definitions of Baseline will be provided in the SAP.

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 will be summarized by treatment group using the ITT, mITT, and Safety Populations.

10.3.2 Study Drug and Concomitant Medications

Study drug administration will be summarized by treatment group (including actual dose received by visits, and missed doses). Summaries of each prior medication, Baseline (Day 1 of ORION-3) concomitant, and new or changed medications will be provided by treatment. Separate summaries will be provided for prior medication use. Medications will be coded using the 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 Endpoint (Inclisiran Only Arm)

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

Descriptive summaries and confidence intervals will be provided.

10.3.3.2 Secondary Efficacy Endpoints (Inclisiran Only Arm)

The secondary endpoints of this study are described in Section 3.4.

The analysis of the secondary endpoints will be descriptive.

[redacted]

10.3.3.4 Interim Analysis

An interim analysis (which will be descriptive) will be conducted upon completion of Day 210 for subjects in Group 1 (inclisiran only arm). A further interim analysis will be conducted when all subjects in Group 1 complete 24 month of treatment with inclisiran. [redacted] The interim analyses are not intended for hypothesis testing, hence no sequential testing boundaries will be applied. Further details will be provided in the SAP.

10.3.4 Safety Analysis

The safety objectives of this study are to:

Evaluate the safety and tolerability profile of inclisiran.

[redacted]

10.3.4.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified as preferred term) occurring during the treatment periods will be counted as a treatment emergent AE (TEAE) either if it is not present at Day 1 (Day 1 of ORION-3) or if it is present at Day 1 (Day 1 of ORION-3) but increased in severity during the treatment periods. Any AEs/SAEs that occur prior to dosing under this extension study will be assessed as part of the evaluation of the ORION-1 safety database.

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 by treatment group, including changes and percent changes from Baseline (Day 1 of ORION-3) at each time point. Analyses will also be performed for each lab parameter by treatment group for incidence rates of potentially clinical significant values for subjects without potentially clinical significant value at Baseline (Day 1 of ORION-3).

Numerical values of laboratory parameters from different local laboratories with different units and normal ranges will be converted to the conventional units and normalized to a standard set of reference/normal ranges. The normalization process will be performed and separated by each of the laboratory parameters.

10.3.4.3 Vital Signs

Change and percent change from Baseline (Day 1 of ORION-3) in vital signs will be summarized descriptively at each scheduled time point by treatment group.

10.3.4.4 Neurological Examinations

The percentage of subjects with a treatment-emergent abnormal neurological examination and the specific abnormality reported will be summarized by treatment group. Any neurological AEs/SAEs that occur prior to dosing under this extension study will be evaluated as part of the ORION-1 safety assessment.

11 Records Retention

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

- At least 2 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 European Union (EU) Directives/Regulations and International Conference on Harmonisation (ICH) guidelines collectively require that essential clinical trial documents (including CRFs) 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* 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region
- *Or* at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product

Investigators shall retain the documents for a longer period, where so required by applicable local requirements.

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 any data clarification forms (DCFs) 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 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, 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 will be recorded in the e-CRF and will be reviewed periodically:

- Missing lipid and/or PCSK9 assessments at Day 1 and/or Day 210
- Inclusion criteria violation
- Exclusion criteria violation.
- Subject taking any prohibited concomitant medication
- Missing an inclisiran dose or a dose delayed by more than 30 days

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 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 before any study-related procedures (including any pretreatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject 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 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/Ethics Committee

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. 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.

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 investigational new 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 entered 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 5
Institution Name	

16 References

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APPENDIX A RECOMMENDED Neurological Examination

MOTOR FUNCTION

When assessing motor function, from a neurological perspective, the assessment should focus on arm and leg movement. You should consider the following:

1. Muscle size
2. Muscle tone
3. Muscle strength
4. Involuntary movements
5. Posture, gait

Symmetry is the most important consideration when identifying focal findings. Compare one side of the body to the other when performing your assessment.

Assessment of a Conscious Patient

Limb assessment of a conscious patient usually involves a grading of strength.

Grade Strength

Grade strength	Description
5	Full range of motion against gravity and resistance; normal muscle strength
4	Full range of motion against gravity and a moderate amount of resistance; slight weakness
3	Full range of motion against gravity only, moderate muscle weakness
2	Full range of motion when gravity is eliminated, severe weakness
1	A weak muscle contraction is palpated, but no movement is noted, very severe weakness
0	Complete paralysis

NB: In a conscious patient, the single best test to quickly identify motor weakness is the "drift test". Have the patient hold their arms outward at 90 degrees from the body. With palms up, have the patient close their eyes and hold the arms for a couple of minutes. "Drifting" will occur if one side is weak.

Lower Extremities

Assess the patient in a supine position. Ask him/her to separate both legs to test for hip abduction. Then ask the patient to bring the legs back together to test for hip adduction. Sit the patient on the side of the bed to assess knee flexion and extension. Ask the patient to flex and extend the knee. If able to do this, apply resistance as these movements are repeated. Test plantar and dorsiflexion by having the patient push down against your hand with their foot and then pull up against your hand with their foot. Remember to compare the left side to the right side.

Upper Extremities

Assess ability to flex elbow (biceps) and straighten (triceps). Assess ability to raise shoulders and return to a resting position. Assess wrist flexion and extension. Test each function with resistance. For focused upper extremity assessment, assess each digit for flexion, extension and lateral movement.

Assessment of an Unconscious Patient

Upper Extremities

1. Observe the patient for spontaneous/involuntary movement.
2. Apply painful stimuli to elicit a motor response (start with central pain; move to peripheral pain if no response occurs).
3. Assess for paralysis of the limb by lifting both arms and releasing them together. If one limb is paralysed it will fall more rapidly than the non paralysed arm.

Lower Extremities

1. Observe for spontaneous/involuntary movement.
2. Apply painful stimuli to elicit a motor response. Begin with central pain. Nailbed or peripheral pain can be attempted if the patient doesn't respond to central pain (caution needs to be used when interpreting peripheral pain as it may stimulate spinal reflex responses vs withdrawal or other more deliberate responses).
3. To assess for paralysis of the one limb you can position the patient on their back and flex the knees so that both feet are flat on the bed. Release the knees simultaneously. If the leg falls to an extended position with the hip externally rotated, paralysis is present. The normal leg should stay in the flexed position for a few seconds and then gradually assume its previous position

SENSORY FUNCTION

When assessing sensory function remember that there are three main pathways for sensation and they should be compared bilaterally:

1. Pain and temperature sensation.
2. Position sense (proprioception).
3. Light touch.

Pain can be assessed using a sterile pin. Light touch can be assessed with a cotton wisp. To test proprioception, grasp the patient's index finger from the middle joint and move it side to side and up and down. Have the patient identify the direction of movement. Repeat this using the great toe.

Sensory Tests:

A number of tests for lesions of the sensory cortex can be done. Examples include the following:

- **Stereognosis**: The ability to recognize an object by feel. Place a common object in the persons hand and ask them to identify the object.
- **Graphesthesis:** "Draw" a number in the palm of the person's hand and ask them to identify the number.
- **Two-Point Discrimination:** Simultaneously apply two pin pricks to the skin surface. Continually repeat the test while bringing the two pins closer together, until the individual can no longer identify two separate stimuli. The finger tips are the most sensitive location for recognizing two point differences while the upper arms, thighs and back are the least sensitive.

- **Extinction:** Touch the same spot on both sides of the body at the same time (eg, the left and right forearms. Ask the individual to describe how many spots are being touched. Normally, both sides are felt; with sensory lesions the individual will sense only one.
- **Point Locations:** Touch the surface of the skin and remove the stimulus quickly. Ask the individual to touch the spot where the sensation was felt. Sensory lesions can impair accurate identification, even if they retain their sensation of light touch.

TONE and REFLEXES

Upper motor neuron problems (brain and spinal cord) are associated with increased tone. Lower motor neuron problems are associated with decreased tone.

Look at the muscles on each side of the body in pairs. Assess for symmetry of bulk.

Evaluation of the stretch reflexes assesses the intactness of the spinal reflex arc at various spinal cord levels. The limb should be relaxed while applying a short and snappy blow with a reflex hammer. Hold the hammer loosely in a relaxed manner, making a wrist action. Allow the hammer to bounce.

Reflex responses:

0	No response
1+	Diminished, low normal
2+	Average, normal
3+	Brisker than normal
4+	Very brisk, hyperactive

Lower motor neuron disease is associated with 0 or 1+, upper motor neuron disease is associated with 3+ or 4+.

Biceps Reflex (C5 – C6)

Support the forearm on the examiners forearm. Place your thumb on the bicep tendon (located in the front of the bend of the elbow; midline to the anticubital fossa). Tap on your thumb to stimulate a response.

Triceps Reflex (C7-C8)

Have the individual bend their elbow while pointing their arm downward at 90 degrees. Support the upper arm so that the arm hangs loosely and “goes dead”. Tap on the triceps tendon located just above the elbow bend (funny bone).

Brachioradialis Reflex (C5-C6):

Hold the person’s thumb so that the forearm relaxes. Strike the forearm about 2-3 cm above the radial styloid process (located along the thumb side of the wrist, about 2-3 cm above the round bone at the bend of the wrist). Normally, the forearm with flex and supinate.

Quadriceps Reflex (Knee jerk) L2 – L4

Allow the lower legs to dangle freely. Place one hand on the quadriceps. Strike just below the knee cap. The lower leg normally will extend and the quadriceps will contract.

If the patient is supine: Stand on one side of the bed. Place the examiners forearm under the thigh closest to the examiner, lifting the leg up. Reach under the thigh and place the hand on the thigh of the opposite leg, just above the knee cap. Tap the knee closest to the examiner, (the one that has been lifted up with the examiners forearm).

Achilles Reflex (ankle jerks) L5 – S2:

Flex the knee and externally rotate the hip. Dorsiflex the foot and strike the Achilles tendon of the heel. In conscious patients, kneeling on a chair can help to relax the foot.

Heel Lift

While the patient is supine, bend the knee and support the leg under the thigh. Have the leg "go dead". Briskly jerk the leg to lift the heel of the bed. Normally, the leg will remain relaxed and the heel will slide upward; increased tone will cause the heel and leg to stiffen and lift off the bed.

Babinski Response:

Dorsiflexion of the great toe with fanning of remaining toes is a positive Babinski response. This indicates upper motor neuron disease. It is normal in infants.

CEREBELLAR FUNCTION

The cerebellum is responsible for muscle coordination and balance on the same side. To test cerebellar function use the following tests:

1. Finger to finger test: have the patient touch their index finger to your index finger (repeat several times).
2. Finger to nose test: perform with eyes open and then eyes closed.
3. Tandem walking: heel to toe on a straight line.
4. Romberg test: stand with feet together and arms at their sides. Have patient close his/her eyes and maintain this position for 10 seconds. If the patient begins to sway, have them open their eyes. If swaying continues, the test is "positive" or suggestive of cerebellum problems.

Dizziness that occurs in response to position changes is usually blood pressure initiated. If the patient sways during a Romberg test, but stops when the eyes are opened, the problem is probably visual or CN VIII (vestibular).

APPENDIX B Sampson Criteria for Diagnosing Anaphylaxis

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

1. 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.

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