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KJX839/Inclisiran

Clinical Trial Protocol CKJX839A11201 / NCT04666298

A placebo-controlled, double-blind, randomized trial to evaluate the effect of different doses of inclisiran given as subcutaneous injections in Japanese participants with high cardiovascular risk and elevated low-density lipoprotein cholesterol (LDL-C) (ORION-15)

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List of abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADA	Anti-drug antibodies
AE	Adverse Event
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	antinuclear antibody
Apo-A1	apolipoprotein A1
Apo-B	apolipoprotein B
APTT	Activated partial thromboplastin time
ASCVD	Atherosclerotic cardiovascular disease
ASMA	anti-smooth muscle antibody
AST	Aspartate Aminotransferase
[redacted]	[redacted]
BP	blood pressure
BUN	Blood Urea Nitrogen
CAD	Coronary artery disease
CD	carbohydrate-deficient
CD-ROM	Compact Disc – Read Only Memory
CHF	chronic heart failure
CK	Creatine Kinase
CKD	Chronic kidney disease
[redacted]	[redacted]
[redacted]	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	Cardiovascular
CVD	Cardiovascular disease
DDE	Direct Data Entry
DILI	Drug-induced liver injury
DMC	Data monitoring committee
EAS	European Atherosclerosis Society
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	Europeans Medicines Agency
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
ESC	European Society of Cardiology
FH	Familial hypercholesterolemia

GalNAc	N-Acetylgalactosamine
GCP	Good Clinical Practice
GCS	Global Clinical Supply
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
h	Hour
HAV	Hepatitis A Virus
HbA1c	Hemoglobin A1c
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HoFH	Homozygous familial hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
HSV	Herpes Simplex Virus
IA	Interim analysis
IAS	International Atherosclerosis Society
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IP-10	Interferon-gamma-inducible protein 10
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine system
JAS	Japan Atherosclerosis Society
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor

LFT	Liver function test
LLN	lower limit of normal
LMT	lipid-modifying therapies
Lp(a)	lipoprotein a
MAR	missing at random
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	myocardial infarction
mL	milliliter(s)
MMRM	Mixed Model with Repeated Measurement
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NLA	National Lipid Association
NYHA	New York Heart Association
PAD	Peripheral artery disease
PCR	Protein-creatinine ratio
PCS	potentially clinically significant
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
siRNA	small interfering ribonucleic acid
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	[redacted]
TBL	total bilirubin
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TNF-α	Tumor necrosis factor-alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UTI	Urinary Tract Infection
VLDL-C	very low-density lipoprotein cholesterol

[redacted]	[redacted]
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Inclisiran	In this protocol, the dose is shown with inclisiran sodium unless otherwise specified. Inclisiran is also referred to as KJX839. 300 mg inclisiran sodium is equivalent to 284 mg inclisiran. 200 mg inclisiran sodium is equivalent to 189 mg inclisiran. 100 mg inclisiran sodium is equivalent to 94.5 mg inclisiran.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1

Amendment rationale

The main purpose of this amendment is based on the Health Authority request below:

- The exclusion criteria #9 (uncontrolled hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) was revised. Health Authority commented that participants with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg, who require immediate treatment of hypertension, cannot be enrolled in this study from the safety standpoint. Therefore, the exclusion criteria was revised to exclude the participants with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg.
- [redacted]
- Several safety assessments were added.

[redacted]

The amendment further corrected two small inconsistencies, between the protocol and the pregnancy follow-up informed consent form regarding the length of the follow-up period in case of a pregnancy, and the Table 6-3 for blinding levels.

Furthermore, some minor changes and corrections of inconsistencies and typographical errors have been done.

Changes to the protocol

The revisions made to the protocol are listed below.

- Section 3, Section 4.1: [redacted]
- Section 5.2: Exclusion criteria #9 was revised. [redacted]
- Section 6.4: The blinding level in case of Safety event (single participant unblinded) in Table 6-3 was corrected to align with the emergency breaking case in Section 6.6.3.
- Table 8-1: Safety assessments were added.
- Section 8.4: Safety assessments were added in Table 8-2 and Table 8-3.
- Section 8.4.5: Appropriateness of safety measurement was added.

- Section 10.1.4: To align with the pregnancy follow-up informed consent form, a small adjustment was made to the length of the follow-up period in case of a pregnancy: "until one year after birth" is replaced by "until one year after the baby was due to be born".
- Section 12.5.2: Minor changes were made in the output method.

Other minor corrections/clarifications were made where applicable. 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 IRBs/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.

Protocol summary

Protocol number	CKJX839A11201
Full Title	A placebo-controlled, double-blind, randomized trial to evaluate the effect of different doses of inclisiran given as subcutaneous injections in Japanese participants with high cardiovascular risk and elevated low-density lipoprotein cholesterol (LDL-C) (ORION-15)
Brief title	Study of efficacy and safety of inclisiran in Japanese participants with high cardiovascular risk and elevated LDL-C
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The aim of the ORION-15 protocol is to evaluate the pharmacodynamic response in Japanese participants [redacted]
Primary Objective(s)	The primary objective of this study is to demonstrate superiority of inclisiran treatment at different dose levels (100 mg, 200 mg, and 300 mg) to placebo on LDL-C levels at Day 180.
Secondary Objectives	The secondary objectives of this study are: To evaluate the effect of inclisiran until Day 180 on the following: ● PCSK9 levels over time ● LDL-C levels over time ● Other lipids, lipoproteins, apolipoproteins (total cholesterol, triglycerides, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a)) ● Proportion of participants achieving lipid control target pre-specified by JAS 2017 guideline ● Individual responsiveness to different doses To evaluate safety and tolerability profile of inclisiran
Study design	This is a placebo-controlled, double-blind, randomized trial in Japanese participants. 308 eligible participants will be randomized to inclisiran sodium 300 mg (n=100), inclisiran sodium 200 mg (n=100), inclisiran sodium 100 mg (n=54), and placebo (n=54). The expected duration of the participants' involvement in the study will be approximately 374 days which includes screening (up to 14 days), Day 1 study drug administration, two additional injections on Day 90 and Day 270, and the follow-up period to Day 360. [redacted]
Study population	This trial includes Japanese participants with history of coronary artery disease (CAD) or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD) or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or participants with heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-C.

Key Inclusion criteria	● Male or female participants ≥ 20 years of age. ● Participants with history of CAD or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, CKD, non-cardiogenic cerebral infarction, PAD or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or participants with HeFH diagnosed by JAS 2017 guideline. ● As per the JAS 2017 guideline, participants should meet serum LDL-C value at screening as follow: ● Serum LDL-C ≥70 mg/dL for participants with history of CAD with additional risk factors such as HeFH, acute coronary syndrome (ACS) or diabetes complicated by other risk factors (non-cardiogenic cerebral infarction, PAD, CKD, metabolic syndrome, overlap of major risk factors, smoking) ● Serum LDL-C ≥100 mg/dL for participants with history of CAD without additional risk factors or HeFH participants without CAD history ● Serum LDL-C ≥ 120 mg/dL for participants categorized in 'high risk' ● Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening. ● Estimated glomerular filtration rate (eGFR) calculated with the revised equations for eGFR in Japan (Matsuo et al 2009) >30 ml/min/1.73 m^2 at screening. ● Participants on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events (AE). Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and an appropriate electronic Case Report Form (eCRF). ● Participants not receiving statins must have documented evidence of intolerance to at least one statin. ● For all participants, the lipid-lowering therapy should have remained stable (stable dose and no medication change) for ≥ 30 days before screening with no planned medication/ dose change until Day 180
Key Exclusion criteria	● Participants diagnosed with homozygous familial hypercholesterolemia (HoFH). ● 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 participant at significant risk (according to investigator's judgment) if he/she participates in the clinical study. ● New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%. ● Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation. ● Major adverse cardiovascular event within 3 months prior to randomization. ● Uncontrolled hypertension: systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg prior to randomization despite antihypertensive therapy. ● Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart. ● Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years. ● Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.
Study treatment	Study treatment will be administered as a single s.c. injection of one of below arms on Day 1, Day 90 and Day 270. ● 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) ● 200 mg inclisiran sodium (equivalent to 189 mg inclisiran) ● 100 mg inclisiran sodium (equivalent to 94.5 mg inclisiran) ● Placebo Inclisiran is also referred to as KJX839.
Treatment of interest	The randomized treatment (inclisiran or placebo) with individualized, optimal standard of Care (SoC) lipid-lowering treatment. The dose of the permitted lipid-lowering medications must have remained stable for ≥30 days before screening with no

	planned medication or dose change until Day 180. Further details are provided in Section 6.
Efficacy assessments	LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)]), and PCSK9
Pharmacodynamic assessments	Mentioned in efficacy assessments
[redacted]	[redacted]
Key safety assessments	AEs, SAEs, vital signs, clinical laboratory values (hematology, coagulation, biochemistry, steroid hormones, and urinalysis), and electrocardiograms (ECGs), ADA
Other assessments	[redacted]
Data analysis	The primary analysis on percentage of change in LDL-C from baseline to Day 180 will be performed using a MMRM (Mixed Model with Repeated Measurement) model at a one-sided significance alpha level of 0.025. Same analysis will also be performed on key secondary endpoints, and summary statistics will be provided for all efficacy and safety analysis.
Key words	inclisiran, PCSK9, Hypercholesterolemia, LDL-C

1 Introduction

1.1 Background

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually (WHO 2017). Cardiovascular (CV) disease is the leading cause of mortality in Japan as well (MHLW 2018). Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for the development of CVD (Grundy et al 2004, Go et al 2014). Lowering LDL-C has been shown to reduce the risk of death, heart attack or stroke and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005, Castilla-Guerra et al 2016).

The Japan Atherosclerosis Society (JAS) 2017 guidelines (Kinoshita et al 2018) recommend statins as first-line pharmacotherapy for lowering LDL-C, with consideration of non-statin lipid-modifying therapies (LMT) such as ezetimibe and/or bile acid sequestrants either as add-on to statins or as monotherapy where statins may not be appropriate. This guideline is similar to other major guidelines across the world such as the American College of Cardiology/American Heart Association (ACC/AHA), European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), National Lipid Association (NLA), and the International Atherosclerosis Society (IAS).

Approximately 100 million people worldwide are treated with lipid-lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death, nonfatal myocardial infarction (MI) and nonfatal stroke or associated events (Casula et al 2012). Despite the availability of statins alone or in combination with other lipid-lowering medications, many patients remain above the LDL-C control target (Jones et al 2012, Jameson et al 2014, Barkas et al 2015, Fitzgerald et al 2017). This is particularly true in participants with pre-existing CHD and/or diabetes or a history of familial hypercholesterolemia (FH), who are at the highest risk and require the most intensive management (Davidson et al 2005).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in controlling the levels of low density lipoprotein receptors (LDLRs) on the surface of hepatocytes (Khvorova 2017). PCSK9 is expressed and secreted into the bloodstream predominantly by the liver, binds LDLR both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, (Lakoski et al 2009, Mousavi et al 2009) thereby increasing the circulating LDL-C levels.

Recently developed and approved PCSK9-blocking monoclonal antibodies reduce PCSK9 and lower LDL-C levels, and were also shown to significantly reduced the risk of CV events (Sabatine et al 2017, Schwartz et al 2018).

Small interfering ribonucleic acids (siRNAs) selectively and catalytically silence the translation of their complimentary target messenger RNAs (mRNAs) in a sequence specific manner through the formation of effector RNA-induced silencing complexes (RISCs), utilizing a highly specific endogenous mechanism for regulating gene expression (Ray et al 2019). Inclisiran is a chemically modified double-stranded small interfering RNA, conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RISC and directs catalytic breakdown

of mRNA for PCSK9. This inhibits translation of PCSK9 protein. Reduced intrahepatic PCSK9 increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation (Fitzgerald et al 2017).

In the ORION clinical development program, 3660 participants with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalent, and/or heterozygous familial hypercholesterolemia (HeFH) were studied in three confirmatory 18-months phase III studies comparing inclisiran versus placebo adjunctive to maximally tolerated statin therapy and an additional 681 participants were treated in phase I and phase II studies. In the phase III studies, treatment with inclisiran sodium 300 mg given by subcutaneous (s.c.) injection on Day 1, Day 90 and every 6 months thereafter resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 49.5% to 57.6%, with time-adjusted average reductions of 44.3% to 53.8% sustained over 18 months. The efficacy of inclisiran was consistent across phase I, phase II and phase III studies, with no differences across a broad range of subpopulation.

There were no clinically relevant differences in the safety profile of inclisiran compared with placebo, except for a higher incidence of treatment-emergent adverse events (TEAEs) at the injection site with inclisiran. However, all TEAEs at the injection site were localized, predominantly mild, transient, and resolved without sequelae. Inclisiran is not associated with an increased risk for hepatic or renal dysfunction, hypersensitivity, neurologic events and neurocognitive disorders, or ophthalmological events and there was no difference from placebo in new onset or worsening of diabetes. The potential for immunogenicity of inclisiran is low. Additional details on the efficacy and safety of inclisiran are available in the Investigator Brochure (IB).

1.2 Purpose

The aim of the ORION-15 protocol is to evaluate the pharmacodynamic response in Japanese participants [redacted]

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

2 Objectives and endpoints

This study is designed to evaluate the efficacy, safety, tolerability [redacted] of subcutaneous inclisiran injection(s) in Japanese participants.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate superiority of inclisiran treatment at different dose levels (100 mg, 200 mg, and 300 mg) to placebo on LDL-C levels at Day 180	● Percentage change in LDL-C from baseline to Day 180
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To evaluate the effect of inclisiran until Day 180 on the following: ● PCSK9 levels over time	● Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180
● LDL-C levels over time	● Percentage change in LDL-C from baseline to Days 14, 30, 60, 90, 104, 120, and 150 ● Absolute change in LDL-C from baseline to Day 180 ● Proportion of participants in each group with LDL-C greater than 80% of the baseline value at Day 180 ● Proportion of participants in each group with greater or equal to 50% LDL-C reduction from baseline at Days 14, 30, 60, 90, 104, 120, 150, and 180
● Other lipids, lipoproteins, apolipoproteins (total cholesterol, triglycerides, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a))	● Percentage change in other lipids, lipoproteins, apolipoproteins from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180
● Proportion of participants achieving lipid control target pre-specified by JAS 2017 guidelines	● Proportion of participants in each group who attain lipid control target pre-specified by JAS 2017 guideline for their level of cardiovascular risk at Day 180
● Individual responsiveness to different doses	● Individual responsiveness defined as the number of participants reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 14, 30, 60, 90, 104, 120, 150, and 180
● To evaluate the safety and tolerability profile of inclisiran	● Incidence, severity and relationship to study drug of TEAEs and Serious Adverse Events (SAEs); anti-drug antibodies (ADA) measurement

Objective(s)	Endpoint(s)
[redacted]	[redacted]

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of doses of 100 mg, 200 mg, and 300 mg of inclisiran versus placebo on percent change in LDL-C levels at Day 180 in participants with high cardiovascular risk and elevated LDL-C despite maximum tolerated dose of statin, regardless of treatment discontinuations for any reason and regardless of change in the dose of allowed concomitant medication.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of additional medications, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

1. Population: Japanese participants with history of coronary artery disease (CAD) or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD) or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or Japanese participants with HeFH despite maximum tolerated dose of statin. Further details about the population are provided in Section 5.
2. Endpoint: percentage change from baseline to Day 180 in LDL-C levels
3. Treatment of interest: the randomized treatment (the investigational treatment of inclisiran at different dose levels or the control treatment placebo) with the optimal SoC lipid-lowering therapy. The type and dose of the concomitant lipid-lowering therapy must remain stable until Day 180. Further details about the investigational treatment and control treatment are provided in Section 6

4. Intercurrent events :
    1. Treatment discontinuations for any reason: ignore (treatment policy strategy)
    2. Unforeseen change in the dose of allowed concomitant medications: ignore (treatment policy strategy)

The summary measure: difference between different inclisiran dose groups and the placebo group in percentage change in LDL-C levels from baseline to Day 180.

2.2 Secondary estimands

Secondary estimands corresponding to key secondary efficacy endpoints are defined similarly to the primary estimand. These endpoints, and the corresponding summary measures, are listed below. Population, treatment of interest, and intercurrent events are defined similarly as for the primary estimand.

- Endpoint: Percentage change in PCSK9 from baseline to Day 180; the summary measure: difference between different inclisiran dose groups and the placebo group in percentage change in PCSK9 from baseline to Day 180
- Endpoint: Absolute change in LDL-C from baseline to Day 180; the summary measure: difference between different inclisiran dose groups and the placebo group in absolute change in LDL-C levels from baseline to Day 180

3 Study design

This study is a Phase II, placebo-controlled, double-blind, randomized trial in Japanese participants with history of coronary artery disease (CAD) or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, chronic kidney disease (CKD), non-cardiogenic cerebral infarction, peripheral artery disease (PAD) or combination of other risk factors and categorized in 'high risk' assessed by Suita Score), or Japanese participants with HeFH and elevated LDL-C despite maximum tolerated dose of statin(s) to evaluate the efficacy, safety, tolerability, [redacted] of subcutaneous inclisiran injection(s). The study will be a Japanese multi-center study with approximately 50 study sites. Informed consent will be obtained from participants before the initiation of any study-specific procedures.

Approximately 400 participants will be screened, and approximately 308 eligible participants will be randomized into 4 treatment groups:

1. 300 mg inclisiran sodium (equivalent to 284 mg inclisiran), n=100
2. 200 mg inclisiran sodium (equivalent to 189 mg inclisiran), n=100
3. 100 mg inclisiran sodium (equivalent to 94.5 mg inclisiran), n=54
4. placebo, n=54

Inclisiran is also referred to as KJX839.

[redacted]

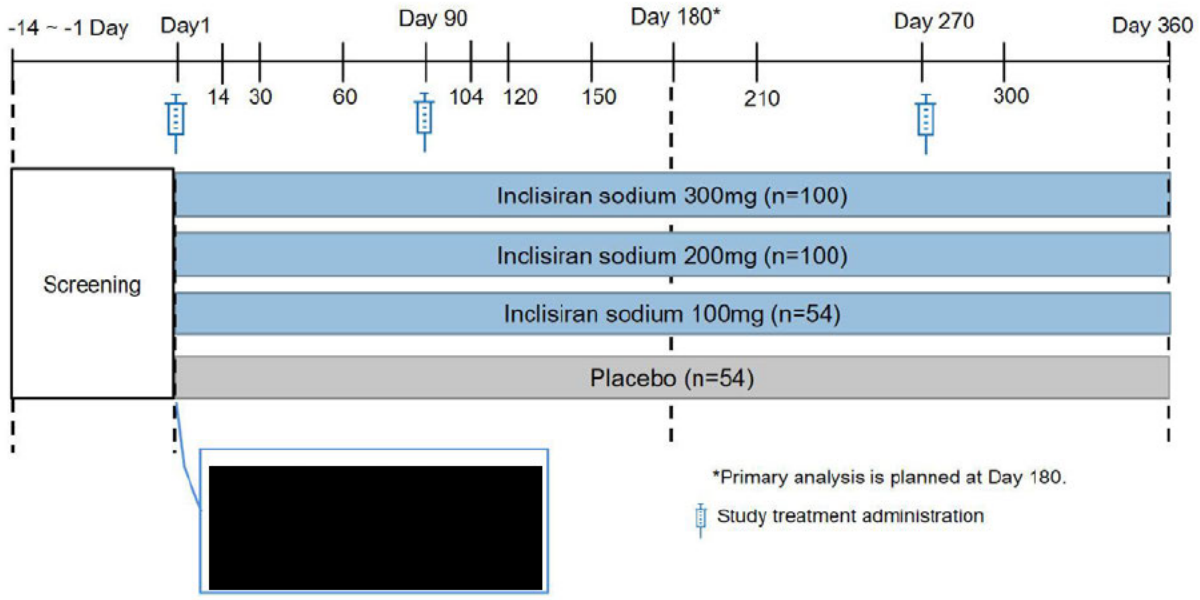
[redacted]

The expected duration of the participants' involvement in the study will be approximately 374 days which includes screening (up to 14 days), Day 1 study drug administration, two additional injections on Day 90 and Day 270, and the follow-up period to Day 360.

The primary analysis will be conducted after all participants have finished Day 180 visit assessments or discontinued before Day 180 visit.

After the primary analysis, double-blind treatment period is maintained to Day 360, although sponsor members (except for blinded monitors) will be unblinded for the planned regulatory submission in Japan. Details are mentioned in Section 6.4.

Figure 3-1 Study design



Placebo volume will be matched to test product volume within each dose and injection. For example, the placebo group for the 200 mg dose will receive 1.0 mL of placebo whereas the placebo group for the 300 mg dose will receive 1.5 mL of placebo. Study treatment will be administered by the unblinded investigator or nurse to blind the arm and dose strengths. Details are described in Section 6.4. Each participant will receive a total of three injections of inclisiran or placebo (Table 3-1).

Table 3-1 Dosing regimens

Study Drug and Dose	Number of randomized participants	Volume (mL)
Placebo for 100 mg	12	0.5
100 mg inclisiran sodium	54	0.5
Placebo for 200 mg	21	1.0
200 mg inclisiran sodium	100	1.0
Placebo for 300 mg	21	1.5

Study Drug and Dose	Number of randomized participants	Volume (mL)
300 mg inclisiran sodium	100	1.5

After the first study drug administration, participants will be observed in the clinic for at least 4 hours to have vital signs completed before being discharged. Participants will receive a second dose of study drug at the Day 90 visit and a third dose at Day 270. Participants will be observed for 30 min after the second dose (Day 90) and the third dose (Day 270) to have vital signs collected. Participants will also undergo the scheduled visit assessments as per the Assessment Schedule (Table 8-1) [redacted]

4 Rationale

4.1 Rationale for study design

[redacted] The optimal dose in the non-Japanese participants has also been confirmed as safe and efficacious in the phase III program. [redacted]

4.1.1 Rationale for choice of background therapy

It is required that investigators ensure that participants receive individualized, optimal standard of Care (SoC) lipid-lowering treatment, which must remain unchanged until Day 180. Based on the inclusion criteria, participants must be receiving statin(s) on maximum tolerated dose, otherwise the statin intolerance must be documented.

Based on JAS 2017 guideline, it is appropriate to consider statins as the first medication of choice for controlling LDL-C levels. In cases where the target cannot be achieved with monotherapy using statins, the combined use of medications such as ezetimibe should be considered. As no specific background medication is required during the study, any statin and other lipid-lowering treatment approved for use may be used.

4.2 Rationale for dose/regimen and duration of treatment

The 300 mg s.c. inclisiran sodium dosing schedule on Day 1, Day 90 and every six months thereafter has been shown to be maximally efficacious and safe in the ORION Phase III clinical program described briefly below. This dose regimen was selected for Phase III on the basis of phase I, II clinical studies, also described briefly below, as well as PD modeling in adult participants to provide maximal efficacy with an acceptable safety profile. The infrequent twice yearly regimen will decrease the overall burden to the participants, usually associated with more frequent dosing.

In the prior Phase I study, maximum reductions in LDL-C and PCSK9 levels with inclisiran were achieved with single s.c. doses of 300 mg inclisiran sodium, with no additional meaningful benefit observed at higher doses. In the multiple dose phase, maximal LDL-C reductions were also observed on inclisiran sodium doses of 300 mg.

Based on the results of the Phase I study, the Phase II Dose Finding Study (ORION-1) tested the efficacy of a single dose (200 mg, 300 mg, or 500 mg) or two doses (100mg, 200mg or 300mg) of inclisiran sodium 90 days apart. All inclisiran sodium single and double-dose groups reduced LDL-C and PCSK9 levels significantly at Day 180 in a dose dependent manner up to 300 mg. The 300 mg dose of inclisiran sodium was the lowest dose that provided maximal efficacy for both LDL-C lowering and PCSK9 inhibition. This was the dose selected for the confirmatory Phase III program. Doses up to 900 mg (3-fold the therapeutic dose) have been studied in Phase I study. No dose limiting safety events were observed up to the highest dose tested.

Three large pivotal phase III studies in adult participants with ASCVD, ASCVD risk equivalent, and/or HeFH demonstrated that 300 mg inclisiran sodium s.c. on Day 1, Day 90 and every 6 months thereafter, the highest dose regimen used in the present study, resulted in statistically significant placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 49.5% to 57.6%, with time-adjusted average reductions (time-adjusted percent change in LDL-C levels from baseline after Day 90 and up to Day 540) of 44.3% to 53.8% sustained over 18 months. This dose and regimen also showed good tolerability of inclisiran sodium, with a safety profile similar to placebo, except for a higher incidence of AEs at the injection site with inclisiran. Injection site reactions (ISRs) were generally mild and self limiting. No participant populations were identified that required an inclisiran dose adjustment. .

This current study is designed to demonstrate the optimal dose in Japanese participants is the same as (or different from) non-Japanese participants. The four treatment arms are therefore the same as those evaluated in the multiple dose assessments in the ORION-1 dose finding study in non-Japanese participants, namely inclisiran sodium 300mg, 200mg, 100mg, and placebo [redacted] and confirmation of an optimal dose for Japanese participants.

The primary endpoint will be evaluated at Day 180, however treatment will continue to Day 270 with a final assessment at Day 360. The rationale for the 1 year duration is to provide an assessment of long term safety in Japanese participants. It fulfills the Japanese regulatory requirement that the clinical safety data for 1 year should be included in clinical data package.

4.3 Rationale for choice of control drugs (comparator/placebo)

This study is a placebo controlled study. Placebo is used to control for potential bias in the evaluation of efficacy and safety of the drug. The design, including the placebo comparator, is similar to the Phase II Dose Finding Study in non-Japanese participants (ORION-1) t[redacted]

4.4 Purpose and timing of interim analyses

There is no interim analysis (IA) planned.

4.5 Risks and benefits

Reduction of LDL-C has been associated with reduced cardiovascular 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.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, close clinical monitoring of safety parameters, as well as periodic review of the safety data by an independent data monitoring committee (DMC). Participants will also be observed in the clinic for at least 4 hours post injection on Day 1 (first dosing of inclisiran) and for at least 30 minutes post injection on Day 90 and Day 270 before being discharged.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy was to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

5 Study Population

This will be a multi-center study conducted in Japan. A total of approximately 308 randomized Japanese participants are planned for inclusion in the study: 100 participants per each of two inclisiran sodium dose groups (200 mg and 300 mg); plus 54 participants in the 100mg inclisiran sodium dose and the placebo groups. Since 23% screening failure rate is expected, approximately 400 participants will be screened.

It is intended to enroll approximately 30 participants with HeFH in total.

[redacted]

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female participants ≥20 years of age.
3. Participants with history of CAD or participants categorized in 'high risk' by JAS 2017 guideline (diabetes, CKD, non-cardiogenic cerebral infarction, PAD or combination of other risk factors and categorized in 'high risk' assessed by Suita Score in Section 16.3) or participants with HeFH diagnosed by JAS 2017 criteria (Section 16.4).
4. As per the JAS 2017 guidance, participants should meet serum LDL-C value at screening as follow:
   - Serum LDL-C ≥70 mg/dL for participants with history of CAD with additional risk factors such as HeFH, ACS or diabetes complicated by other risk factors (non-

cardiogenic cerebral infarction, PAD, CKD, metabolic syndrome, overlap of major risk factors, smoking)

- Serum LDL-C ≥100 mg/dL for participants with history of CAD without additional risk factors or HeFH participants without CAD history
- Serum LDL-C ≥ 120 mg/dL for participants categorized in 'high risk'

5. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
6. Estimated glomerular filtration rate (eGFR) calculated with the revised equations for eGFR in Japan (Matsuo et al 2009) >30 ml/min/1.73 m^2 at screening.
7. Participants on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events (AE). Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and appropriate electronic Case Report Form (eCRF).
8. Participants not receiving statins must have documented evidence of intolerance to at least one statin.
9. For all participants, the lipid-lowering therapy should have remained stable (stable dose and no medication change) for ≥ 30 days before screening with no planned medication/ dose change until Day 180.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives of enrollment within 30 days (e.g. small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g. biologics), whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
3. Participants diagnosed with homozygous familial hypercholesterolemia (HoFH).
4. 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 participant at significant risk (according to investigator's judgment) if he/she participates in the clinical study.
5. 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.
6. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%.
7. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
8. Major adverse cardiovascular event within 3 months prior to randomization.
9. Uncontrolled hypertension: systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg prior to randomization despite antihypertensive therapy.
10. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT),

aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart. The repeat test should be done and confirmed before the randomization.

11. Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years.
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, or if diagnosed between screening visit and randomization visit regardless of whether there is evidence of local recurrence or metastases
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) pregnancy test
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of study treatment. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Barrier methods of contraception: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps).
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
- If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

15. Known history of alcohol and/or drug abuse within the last 5 years.

16. Planned use of other investigational products or devices during the course of the study.
17. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    - Participants who are unable to communicate or to cooperate with the investigator.
    - Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency).
    - Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
    - Have any medical or surgical condition, which in the opinion of the investigator would put the participant at increased risk from participating in the study.
    - Persons directly involved in the conduct of the study.
18. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.
19. Participants who need LDL-C apheresis treatment.

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The sponsor will provide the following investigational and control drugs as single-use vials for s.c. injection (Table 6-1).

Placebo will be supplied by sponsor to clinical study site as sterile normal saline (0.9% sodium chloride in water for injection) for s.c. injection. Placebo will be administered as s.c. injection in an amount matched to the doses within the active inclisiran sodium described in Table 3-1.

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
inclisiran sodium 300 mg (equivalent to inclisiran 284 mg) in 1.5 mL solution	Solution for Injection	Subcutaneous injection	Open label supply in vials; blinding at site by unblinded site personnel	Sponsor (global)

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Placebo	Solution for Injection	Subcutaneous injection	Open label supply in vials; blinding at site by unblinded site personnel	Sponsor (global)

Inclisiran is also referred to as KJX839

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants will be assigned at Day 1 (Baseline) to one of the following 4 treatment arms/groups.

1. 300 mg inclisiran sodium (equivalent to 284 mg inclisiran), n=100
2. 200 mg inclisiran sodium (equivalent to 189 mg inclisiran), n=100
3. 100 mg inclisiran sodium (equivalent to 94.5 mg inclisiran), n=54
4. Placebo, n=54

Inclisiran is also referred to as KJX839.

6.1.4 Treatment duration

The expected duration of the participants' involvement in the study will be approximately 374 days which includes screening (up to 14 days), Day 1 study drug administration, two additional injections on Day 90 and Day 270, and the follow-up period to Day 360.

Participants may be discontinued from treatment earlier due to safety reasons and/or at the discretion of the investigator or the participant. They will continue to be followed up in the study unless informed consent is withdrawn (Section 9.1.1 and Section 9.1.2).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications/treatments are permitted during the study:

- Hormone replacement therapy

- Lipid-lowering medications; participants on lipid-lowering medications (such as statins and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change until Day 180
- Prescription medications prescribed to treat pre-existing medical conditions such as diabetes and hypertension
- Prescription or non-prescription medications, when necessary to treat an AE, and at the discretion of the investigator

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
*Newly added therapies including dietary supplements used to lower LDL-C (e.g., statins, ezetimibe, lomitapide, probucol, niacin, bile acid absorption inhibitors)	After the screening until Day 180	● Participant in screening phase: Participant should be screening failure. ● Participant in treatment phase: Study treatment should be discontinued.
Monoclonal antibodies for PCSK9 and LDL-C apheresis treatment	Throughout the study period	● Participant in screening phase: Participant should be screening failure. ● Participant in treatment phase: Study treatment should be discontinued.

* The lipid-lowering therapy should have remained stable (stable dose and no medication change) for ≥ 30 days before screening and until Day 180.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigational site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

At Day 1 (baseline), all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system

that automates the assignment of participant numbers to a randomization numbers. These randomization numbers are linked to the different treatment code, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by LDL-C at screening visit (≥130 mg/dL or < 130 mg/dL), current use of statins or other lipid-modifying therapies (Yes or No), [redacted] otherwise the randomization ratio will be 2:2:1:1.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Participants, investigator staff, persons performing the assessments and sponsor blinded monitors will remain blind to the identity of the treatment from the time of randomization until the final database lock at Day 360. On the other hand, the sponsor members except for blinded monitors will remain blind until the primary analysis database lock at Day 180. Blinding is kept by using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding defined respectively for each role and will not be accessible by anyone else involved in the study with the following exceptions:

- Unblinded site personnel
- Unblinded monitors
- Bioanalysts (to avoid unnecessary analysis of placebo samples)
- Independent DMC and independent statistician/programmer supporting DMC activities

(2) Each site must have both blinded and unblinded investigators or nurses available. The study treatment will be handled by unblinded pharmacist or designated unblinded person. The study treatment will be administered by unblinded investigator or nurse. Unblinded site personnel including investigators, nurse, and pharmacist will be responsible for study drug management and administration only and must not be involved in any efficacy and safety assessment. Once the designated roles are determined, the role should not be switched at any time after the first randomization at each site.

The sponsor members (except for blinded monitors) and other parties (as needed) will be unblinded after the primary analysis database lock at Day 180 for the planned regulatory submission in Japan, while participants, investigator staff, persons performing the assessments, and sponsor blinded monitors will remain blinded until the final database lock at Day 360. The primary analysis data at Day 180 including the randomization data will strictly be kept available only for the specific sponsor members until the final database lock at Day 360.

Unblinded monitors will be available to perform study medication accountability and to deal with study issues involving the unblinded site personnel.

The randomization codes associated with participants from whom [redacted] ADA samples are taken will be disclosed to bioanalysts who will keep [redacted] ADA results confidential until the primary analysis database lock at Day 180.

Any [redacted] ADA and results from lipid/lipoprotein/PCSK9 measurements after the first administration of study drug until the final database lock will be blinded for participants, investigator staff, persons performing the assessments and blinded monitors, while they will be unblinded to the sponsor members (except for blinded monitors) after the primary analysis database lock at Day 180.

After Day 180, investigators will be notified by the central laboratory in case a LDL-C value has increased by more than 50% or 30 mg/dL compared with the value at Baseline.

Unblinding will occur in the case of participant emergencies and at the conclusion of the study.

Table 6-3 Blinding levels

	Time of Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Primary Analysis at Day 180**
Participant	B	B	UI	B
Blinded site staff (blinded investigators/ blinded nurses)	B	B	UI	B
Unblinded site staff (unblinded investigators/ unblinded nurses/ unblinded pharmacist)	B	UI	UI	UI
Blinded monitors	B	B	UI	B
Drug Supply and Randomization office	UI	UI	UI	UI
Unblinded sponsor staff (e.g. bioanalysts, unblinded monitors)	B	UI	UI	UI
Trial Statistician/ Trial programmer/ data analyst	B	B	UI	UI
Independent DMC and independent statistician and programmer	B	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded
UI Allowed to be unblinded on individual participant level

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments are not permitted.

6.5.1 Dose modifications

Study drug administration should be temporarily interrupted or permanently discontinued in participants with:

1. Intolerable AEs, or if the investigator believes that continuing dosing will be detrimental to the participant's mental or physical health. This includes severe or serious reactions at the injection site and any anaphylactic type reactions.
2. Liver laboratory values meeting the study drug interruption criteria listed in Table 16-4 and Table 16-5.
3. Unexplained creatine kinase (CK) values >5 x ULN confirmed by repeat test when the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction.

Study treatment may be restarted at the discretion of the investigator, if the reason for discontinuation has resolved.

The dose interruptions must be recorded on an appropriate eCRF.

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT >300 U/L] whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase (ALP), albumin, and CK.

Perform relevant examinations (Ultrasound or Magnetic resonance imaging (MRI), Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (https://livertox.nih.gov/rucam.html).

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver function test (LFT) abnormalities.

Table 6-4 Guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities

Disease	Assesment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by informing the participant that compliance is necessary for the participant's safety and the validity of the study. The investigator should also instruct the participant to adhere closely to the scheduled study visits. Study treatment will not be dispensed to the participant but will be administered at designated study visits at the study site by unblinded qualified personnel. Study drug administration information should be captured within each designated visit on an appropriate eCRF. The unblinded site personnel or designee must also maintain an inventory record of study drug (inclisiran/placebo) received and administered.

6.6.2 Recommended treatment of adverse events

AE should be treated according to local practice and guidelines, and is at the discretion of the investigator and treating physician.

Medication used to treat AEs must be recorded on appropriate eCRF page(s).

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

After an emergency unblinding, study drug should be permanently discontinued. The participant will continue to be followed up in the study unless informed consent is withdrawn (Section 9.1.1 and Section 9.1.2).

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Unblinded site personnel will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), which immediately before dispensing the medication kit to the unblinded investigator/nurse, the unblinded pharmacist will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

Study treatment must be received by a unblinded site personnel (unblinded pharmacist or a designated unblinded person) at the study site, handled and stored safely and properly and kept in a secured location to which only the unblinded site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

The unblinded pharmacist or qualified designee will prepare the investigational product to be administered to the participant on that day. The procedure for preparing investigational product is provided in the Pharmacy Manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The unblinded site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the unblinded site personnel will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis unblinded monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

Participants will be administered a single s.c. injection of 100 mg, 200 mg or 300 mg inclisiran sodium or placebo at predefined time points as described in the Assessment Schedule (Section 8.1.1). Study drug injection will be administered by unblinded investigators or nurse. The site of injection is the abdomen, alternating sides for each injection. The arm and thigh are other locations for injections. Injections should not be done into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections. Detailed instructions for study drug administration are found in the Pharmacy Manual.

AE at the injection site must be reported as described in Section 8.4.4.2.

Participants must be observed in the clinic for at least 4 hours post injection on Day 1 (first dosing of inclisiran) and for at least 30 minutes post injection on Day 90 and Day 270 before being discharged.

Should a participant develop signs or symptoms of anaphylaxis when study drug 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 possible). (Details in Section 8.4.4.2)

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

All injections to the participant as well as study drug interruptions/discontinuations (i.e. no injection at a designated dosing visit) during the study must be recorded on an appropriate eCRF.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - [redacted]

- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. (Every effort should be done to keep the visit window within ± 7 days after Day 1/Baseline as much as possible.) Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, adverse events and concomitant medications should be recorded on the eCRF.

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

- Fasted for at least 10 hours for all visits for fasting lipids and glucose blood samples
- Blood samples for steroid hormones should be collected at the same morning time throughout the study due to diurnal variation.
- 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

During the Coronavirus disease 2019 (COVID-19) pandemic that limits or prevents on-site study visits, the collection of samples may be modified by Novartis and will be communicated to the Investigator.

Table 8-1 Assessment Schedule

Period	Screening	Treatment												
Visit Name	Screening	V1 (Baseline)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	TD/ EOS[2]
Days	-14 to -1	1	14	30	60	90	104	120	150	180	210	270	300	360
Informed consent	X													
Inclusion / Exclusion criteria	X	X												
Demography	X													
Medical history/current medical conditions	X	X												
Medical History: Statin intolerance (if applicable)	X	X												
Smoking history	X													
Physical Examination (complete)	S													S
Physical Examination (short)		S	S	S	S	S	S	S	S	S	S	S	S	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight[4]		X												X
Electrocardiogram (ECG)	X	X								X				X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting plasma glucose	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Cytokines[18]		X[20]	X	X	X	X	X	X	X	X	X	X	X	X
hsCRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening	Treatment												
Visit Name	Screening	V1 (Baseline)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	TD/ EOS[2]
Days	-14 to -1	1	14	30	60	90	104	120	150	180	210	270	300	360
Coagulation Panel	X	X		X						X				X
Fasting Lipids[5,6]	X[7]	X	X	X	X	X	X	X	X	X				
Steroid Hormones[8,9,10]		X								X				X
Urinalysis	X	X								X				X
Pregnancy Test (serum)[11]	X													
Pregnancy Test (urine)[12]	S	S				S						S		S
ADA Sample collection[14]		X		X		X				X		X		X
Randomization		X												
Study drug administration[16]		X				X						X		
Prior/Concomitant medication/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant lipid-lowering therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reaction assessment		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening	Treatment												
Visit Name	Screening	V1 (Baseline)	[redacted]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	TD/ EOS[2]
Days	-14 to -1	1		14	30	60	90	104	120	150	180	210	270	300	360

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[redacted]
[2] TD: Study treatment discontinuation. For the participant who discontinues the study treatment but continues to participate in the study, the participant should come to the TD visit as soon after the treatment discontinuation as possible. Thereafter, the participant will be back to the regular visits as per the Assessment Schedule (Table 8-1) except for ADA sample collection. EOS: End of Study
[3] Vital signs will be measured prior to injection and 4 hr after the first (Day 1), and 30 min after the second (Day 90) dose and the third dose (Day 270)
[4] Height will be collected only at baseline and used to calculate body mass index.
[5] Fasted for at least 10 hours for all visits for fasting lipids and glucose blood samples
[6] Fasting lipids include LDL-C, total cholesterol, 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)), and PCSK9.
[7] At screening, only LDL-C and triglycerides are tested. Other fasting lipids will not be done at screening visit.
[8] Blood samples for steroid hormones should be collected at the same morning time throughout the study due to diurnal variation.
[9] Estradiol and progesterone: only for female before menopause. Blood samples for estradiol and progesterone will not be collected from the participants who are taking hormone replacement therapy and/or using oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception.
[10] Testosterone: only for male.
[11] Only in females of child-bearing potential
[12] Only in females of child-bearing potential (prior to study treatment administration, if applicable). Done locally.
[redacted]
[14] ADA serum samples will be collected prior to injection, if an injection is scheduled for that visit.
[redacted]
[16] For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as possible).
[redacted]
[18] Cytokines: IL-6, IFN-γ, TNF-α
[redacted]
[20] [redacted]

8.1 Screening

Screening

Screening procedures (Table 8-1) will be performed within 2 weeks prior to randomization to assess the eligibility only after the ICF has been signed.

In the case where liver function value(s) at screening is outside of the range specified in the exclusion criteria 10, the assessment may be repeated once at least 1 week apart and prior to randomization. If the repeat value remains outside of the specified ranges, the participant is not eligible for the study.

Participants may be re-screened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the participant.

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening phase (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity, relevant medical history/current medical condition present before informed consent was signed (where possible, diagnoses and not symptoms will be recorded), HeFH (yes/no), statin intolerance (if applicable), prior/concomitant lipid-lowering therapy, as well as relevant laboratory tests.

Investigators will have the discretion to record abnormal test findings as medical history in an appropriate eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Participant race and ethnicity are collected and analyzed to confirm the inclusion of Japanese participants as required by Health Authorities.

8.3 Efficacy

Specimens will be obtained at the time points in the Assessment Schedule (Table 8-1). Parameters to be assessed will include: total cholesterol, triglycerides, LDL-C, 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)), and PCSK9.

All efficacy assessments are biomarkers analyzed at a central laboratory.

Participants will be in a fasted state at least 10 hours for all efficacy laboratory assessments. Details regarding the collection, processing, shipping and storage of the samples will be provided in a Laboratory Manual.

After randomization (Day 1) until the primary analysis database lock at Day 180, the results of efficacy laboratory assessments mentioned above will be blinded to participants, investigator staff, persons performing the assessments and the sponsor members.

Unblinding of the sponsor members and other parties (as needed) will occur after the primary analysis database lock at Day 180. However, participants, investigator staff and persons performing the assessment will remain blinded to the results of efficacy laboratory assessments until final database lock.

After Day 180, investigators will be notified by the central laboratory in case a LDL-C value has increased by more than 50% or 30 mg/dL compared with the value at baseline.

8.3.1 LDL-C

The primary efficacy assessment will be LDL-C. Blood samples for LDL-C will be collected at the time points in the Assessment Schedule (Table 8-1), including screening to confirm the eligibility

8.3.2 Other efficacy biomarkers

Other efficacy assessments will include:

- Total cholesterol, triglycerides, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, Lp(a), and PCSK9

Samples for these additional efficacy biomarkers will be collected based on the Assessment Schedule (Table 8-1). At screening, the sample only for triglycerides will be collected to confirm the eligibility.

Plasma samples will be analyzed using a validated enzyme linked immunosorbent assay to determine PCSK9 protein concentration. Full details of the analytical methods used will be described in a separate bioanalytical report.

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments of this study are aligned with Phase II Dose Finding Study in non-Japanese participants (ORION-1)[redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

During the COVID-19 pandemic that limits or prevents on-site study visits regular phone or virtual calls will occur for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

Table 8-2 Safety assessment

Assessment	Specification
Physical exam	**A complete physical examination** will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an adverse event. **A short physical examination** will include the examination of general appearance and vital signs as well as other examinations based on Investigator discretion.In case more detailed neurological examination is required as per the investigator's discretion, the full neurological examination in Section 16.6 can be referred.
Vital signs	Vital signs include blood pressure and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure (BP) will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Table 16-1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Height will be used to calculate body mass index.

8.4.1 Laboratory evaluations

Specimens will be obtained at the time points in the Assessment Schedule (Table 8-1).

Central laboratory will be used for analysis of all specimens collected, with the exception of urine pregnancy tests and urine dipstick tests, which will be done locally (using testing materials supplied by the central laboratory). Serum pregnancy tests at screening will be done by the central laboratory. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in a Laboratory Manual.

Note: Efficacy laboratory assessments (e.g., LDL-C and PCSK9) are described in Section 8.3.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Clinically notable laboratory findings are defined in Section 16.1.

Table 8-3 Clinical Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean cell hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), MCV, Platelets, Red blood cells (RBC), White blood cells (WBC), Differential (% of Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

Test Category	Test Name
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , GGT, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, CK, Direct Bilirubin, total Bilirubin (TBL), Blood Urea Nitrogen (BUN), Uric Acid, Lactate Dehydrogenase (LDH), Hemoglobin A1c (HbA1c) [c], eGFR[c, d]
Inflammatory marker	High sensitivity C-reactive protein (hsCRP) (fasting)
[redacted]	[redacted]
Cytokines	IL-6, IFN-γ, TNF-α
Urinalysis[a]	Macroscopic Panel (Dipstick): Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Urobilinogen, Specific Gravity, urine sediment (microscopic examination will be only performed in the event of abnormalities)
Coagulation[b]	PT, INR, Activated partial thromboplastin time (APTT)
Steroid hormones[e]	Aldosterone, Cortisol, Estradiol[f], Progesterone[f], Testosterone[g]
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)
Other	Fasting Plasma Glucose Tryptase (only in case of anaphylaxis)

[a] Urinalysis will be evaluated by dipstick analyses at the investigational site locally (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 central lab.
[b] Blood samples for determination of coagulation parameters will be performed prior to start of study drug injection on Day 1.
[c] HbA1c and eGFR are tested at screening, Day 90, 180 and 360 only.
[d] eGFR will be calculated with the revised equations in Japan below (Matsuo et al 2009).
eGFR (mL/min/1.73m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female)
[e] Blood samples for steroid hormones should be collected at the same morning time throughout the study due to diurnal variation.
[f] Only for female before menopause. Blood samples for estradiol and progesterone will not be collected from the participants who are taking hormone replacement therapy and/or using oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception.
[g] Only for male

8.4.2 Electrocardiogram (ECG)

ECGs will be done with local ECG machines. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

The ECG tracing must be labeled with study number, participant number, date and time, and filed in the study site source documents.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process by the investigator should be in

place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

A positive urine pregnancy test requires immediate interruption of study drug until serum pregnancy test is performed and found to be negative.

A positive urine pregnancy test should be confirmed with a serum pregnancy test. Local pregnancy test and associated results will not be collected on eCRF.

8.4.4 Other safety evaluations

8.4.4.1 Anti-drug antibody in blood

Additional sample for analysis of the induction of antibodies will be collected at the time points in the Assessment Schedule (Table 8-1) and Table 8-4.

Instructions to be followed regarding sample collection, numbering, processing and shipment are outlined in a Laboratory Manual.

Table 8-4 Assessment Table for ADA

Visit Name	Day	Time (hour)*	ADA Sample number	Dose reference ID
V1	Day 1	Predose (-1h)	201	1
V3	Day 30	0h	202	1
V5	Day 90	Predose (-1h)	203	2
V9	Day 180	0h	204	2
V11	Day 270	Predose (-1h)	205	3
TD/ EOS	Day 360	0h	206	3

* Time (hour): This is used for internal system. For Day 1, Day 90 and Day 270, the sample will be collected anytime prior to injection (predose).

8.4.4.2 Other safety evaluations

Assessment of Cardiovascular Events

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

Injection site reactions

Injection site reactions (ISR) should be monitored at each visit from the Randomization (Day 1) visit onwards (Table 8-1) and through additional contacts with the participant between visits as needed. ISR including individual signs or symptoms at the injection site following study treatment administration should be recorded on an appropriate eCRF page. Every effort should be made to follow up with the participant until resolution of the ISR.

Anaphylactic reactions

Potential anaphylactic reactions should be assessed by Sampson criteria in Section 16.5. If Sampson criteria are positive, confirmation by elevation of tryptase in blood plasma should be obtained within 30 minutes of the onset of anaphylaxis (or as soon as possible).

Hyperglycemia-related events

Laboratory results and newly added concomitant medications should be checked for potential hyperglycemia-related AEs.

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

- HbA1C becomes ≥6.5% and/or
- Two consecutive values of fasting plasma glucose that are ≥126 mg/dL
- If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected.

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

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

8.4.5 Appropriateness of safety measurements

[redacted]

The safety assessments [redacted] are standard for this indication/participant population.

8.5 Additional assessments

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Any laboratory abnormalities that in the judgment of the investigator, prevents the participant from continuing participation in the study

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- AE/ SAE

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All treated participants should have a safety follow-up call conducted 30 days after the last study visit or 90 days after the last administration of study drug, whichever is longer. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical

investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade.
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome (i.e. not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal or unknown)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment 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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred. (Table 10-1)

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 90 days after the last study visit (or 180 days after the last administration of study drug, whichever is longer) must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAE reporting time frames are as follows:

1. Screen Failures: SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized Participants: SAEs collected between time participant signs ICF until 90 days after the last study visit (or 180 days after the last administration of study drug, whichever is longer) must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 90 days after the last study visit (or 180 days after the last administration of study drug, whichever is longer) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up until one year after the baby was due to be born 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.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-3 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-4. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
    - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
    - New onset dipstick proteinuria ≥ 3+, OR
    - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, urinary tract infection (UTI), extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

10.2.3 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

It is anticipated that the first review occurs after the first 40 randomized participants have reached the Visit 3 (Day 30). Thereafter, the DMC will review safety data regularly based on the DMC charter until the end of the trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical

Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

A Statistical Analysis Plan (SAP) will be finalized before database lock. The specifications in SAP will detail the implementation of all the planned statistical analyses in accordance with the principle features stated in the protocol. [redacted]

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

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Additional analysis may be also conducted to evaluate the impact of COVID-19 pandemic.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participant to whom study treatment has been assigned by randomization, with the exception of those mis-randomized participants who did not receive study drug. Mis-randomized participants are defined as not qualified for randomization and did not take any study treatment, but have been inadvertently randomized into the study. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received.

[redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS set.

Categorical data will be presented as frequencies and percentages. For continuous data, n (non-missing observations), mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below.

The number of participants dosed at each dosing visit, number of study doses administered, and dose administered will be summarized using the safety set. The number of study doses administered will be summarized.

Lipid-modifying therapy use at screening and the baseline/Randomization visit (Day 1) will be summarized by treatment group. New or changed lipid-modifying therapy after baseline will be summarized by treatment group.

Other concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The analysis set used for the primary efficacy analysis will be the FAS.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand is defined in Section 2.1. The corresponding endpoint, i.e. primary analysis variable, is the percentage change in LDL-C from baseline to Day 180. The treatment assessment (summary measure) of the primary estimand is the difference in mean percentage change from baseline to Day 180 between different inclisiran sodium dose groups and the placebo group.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of this study is to evaluate the effect of inclisiran compared to placebo in reducing the percentage change from baseline in LDL-C to Day 180 in Japanese participants with CAD, categorized as 'high risk' by JAS 2017 guidelines, or with HeFH. The global statistical hypotheses that will be tested are as follows:

- H0: $\mu i-\mu 0 = 0$ for i=1,2,3 versus Ha: $\mu i-\mu 0 < 0$ for at least i=1,2,3

Where $\mu 0$ is the mean percentage change in LDL-C from baseline to Day 180 in placebo group, and $\mu 1$, $\mu 2$, $\mu 3$ are the mean percentage changes in LDL-C from baseline to Day 180 in inclisiran sodium 100mg, 200mg and 300mg group respectively.

An MMRM (Mixed-effect Model with Repeated Measurement) will be used as the primary analysis model, with treatment group, visits, interaction between visits and treatment groups, baseline LDL-C and current use of statins or other lipid-modifying therapies as fixed effects.

The significance level of the hypothesis test is 0.025 using one-sided test. To control the overall type-one error rate, Dunnett's test (one step) will be used on the above statistical model to provide adjusted p-values. In addition, point estimate and 95% confidence interval a will be presented for the difference between inclisiran and placebo groups. Also the p-value (before and after multiplicity adjustment) will also be provided.

The primary objective will be achieved if the null hypothesis is rejected.

Full details on the model will be provided in the SAP.

12.4.3 Handling of remaining intercurrent events of primary estimand

The other potential intercurrent events could be death, which considering its expected small number of occurrences with the short follow-up period planned and being consistent with the approach in the other phase III studies, will be treated the same way as for the other missing data.

12.4.4 Handling of missing values not related to intercurrent event

The primary MMRM model implicitly imputes missing data under a missing at random (MAR) assumption.

12.4.5 Sensitivity analyses for primary endpoint/estimand

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

- MMRM analysis with multiple imputation using a control-based pattern mixture model

The control-based pattern mixture model will be used to explore the possibility of missing data being missing not at random. This approach will utilize placebo data for monotone missing inclisiran treatment data.

Full details for sensitivity analyses will be provided in the SAP.

12.4.6 Supplementary analysis

No supplementary analyses are planned.

12.4.7 Supportive analyses

No supportive analyses are planned.

12.5 Analysis of secondary endpoints/estimands

The key secondary efficacy endpoints of this study are the following:

- Percentage change in PCSK9 from baseline to Day 180
- Absolute change in LDL-C from baseline to Day 180

The key secondary efficacy endpoints will be analyzed using the same methods as for the primary efficacy endpoint.

Descriptive statistics on percentage change from baseline in LDL-C, PCSK9, and in other lipids, lipoproteins, apolipoproteins will include number of participants (n), mean, standard deviation, median and interquartile range [first and third quartiles], minimum and maximum. Frequencies and percentages will be calculated for the categorical variables. Percentages are based on the number of participants in the analysis set for whom there are non-missing data.

The two-sided 95% confidence interval for difference will be provided for continuous variables. Odds ratio and 95% confidence interval will be provided for binary variables. Nominal p-values will be provided when applicable.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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

- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, and 150

- Percentage change in LDL-C from baseline to Days 14, 30, 60, 90, 104, 120, and 150
- Proportion of participants in each group with LDL-C greater than 80% of the baseline value at Day 180
- Percentage change in other lipids, lipoproteins, apolipoproteins from baseline to Days 14, 30, 60, 90, 104, 120, 150, and 180
- Proportion of participants in each group with greater or equal to 50% LDL-C reduction from baseline at Days 14, 30, 60, 90, 104, 120, 150, and 180
- Individual responsiveness defined as the number of participants reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 14, 30, 60, 90, 104, 120, 150, and 180
- Proportion of participants in each group who attain Japanese lipid modification targets for their level of cardiovascular risk at Day 180

For other secondary endpoints, only the descriptive statistics by treatment group will be presented.

12.5.2 Safety endpoints

The safety objectives of this study are to evaluate the safety and tolerability profile of inclisiran. For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only treatment-emergent events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only treatment emergent AEs.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The MedDRA dictionary will be used for coding AEs. An AE (classified as preferred term) occurring during the double-blind treatment period will be counted as a TEAE either if it is not present at baseline or if it is present at baseline but increased in severity during the treatment period.

The number (and percentage) of participants with TEAEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity
- by treatment, primary system organ class and preferred term for treatment emergent AEs leading to study drug discontinuation
- by treatment, primary system organ class and preferred term for treatment emergent AEs related to study drug.

- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for death and serious adverse events. The number (and proportion) of participants with adverse events of special interest will be summarized by treatment. Categories of AEs used in this analysis will be specified in the SAP.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

Change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group. Abnormalities will be flagged. Clinical notable vital signs as defined in Table 16-1 will also be summarized.

12-lead ECG

All ECG data will be listed by treatment group, participant and visit.

Clinical laboratory evaluations

Laboratory values will be summarized by treatment group, including changes from baseline at each time point.

A shift analysis by normal range will be done which counts the number of participants with a low, normal or high value at baseline and a low, normal or high value post baseline.

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value

Immunogenicity

ADA evaluations, including treatment-emergent ADA findings, will be summarized by treatment group, participant, and visit. Additional analyses may be performed to describe the relationship between ADA and other study findings and will be detailed in the SAP.

[redacted]

12.5.4 Biomarkers

Not applicable. All are included in the efficacy sections.

[redacted]

12.7 Interim analyses

There is no interim analysis planned.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Approximately 308 participants will be randomized by the IRT system: 100 participants for inclisiran sodium dose groups 200 mg and 300 mg; plus 54 participants in the placebo group and inclisiran sodium dose group 100 mg. Randomization will be stratified by current use of statins or other lipid-modifying therapies, LDL-C category at screening, [redacted].

The sample size assumption was based on the observed results from a previously completed Phase II Dose Finding Study (ORION-1). The difference in mean percentage change from

baseline between the active dose groups and the placebo group for LDL-C at Day 180 is expected to be >30% with a standard deviation of approximately 20%.

The sample size of 308 will provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one inclisiran sodium dose group compared to the placebo. Dunnett's test is used in order to control the family-wise type I error rate at a significance level of alpha=0.025 (one-sided test). The calculation is done using PASS 11 software.

[redacted]

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should

be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Vital signs range deviations are defined in Table 16-1:

Table 16-1 Clinically notable vital signs

Vital sign		Notable abnormalities
Pulse (beats/min)		either ≥120 + increase ≥25* or > 130 either ≤50 + decrease ≥30* or < 40
BP (mmHg)	systolic	either ≥180 + increase≥30* or > 200
		either ≤90 + decrease≥30* or < 75
	diastolic	either ≥105 + increase≥20* or > 115
		either ≤50 + decrease≥20* or < 40

* Refers to post-BL value as compared to BL value

Notable laboratory values are defined in Table 16-2:

Table 16-2 Clinically notable laboratory abnormalities for selected tests

Parameters	Criteria
Hematology	
Hemoglobin	≤ 10 g/dL
Hematocrit	≤ 0.8 × LLN
WBC (total)	≤ 2.8 $\times 10^3$ / µL, ≥ 16 $\times 10^3$ / µL
Platelet count	≤ 75 $\times 10^3$ / µL, ≥ 700 $\times 10^3$ / µL
HbA1c	≥ 6.5% and ≥0.5% change from baseline
Clinically chemistry	
Creatinine	> 2 mg/dL
CK	> 1 and ≤ 3 × ULN
CK	> 3 and ≤ 5 × ULN
CK	> 5 and ≤ 10 × ULN
CK	> 10 × ULN
ALT	> 1 and ≤ 3 × ULN
ALT	> 3 and ≤ 5 × ULN
ALT	> 5 × ULN
AST	> 1 and ≤ 3 × ULN
AST	> 3 and ≤ 5 × ULN
AST	> 5 × ULN
Total bilirubin	> 2 × ULN
ALP	> 2 × ULN

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-3 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) ● ALT or AST > 3 × ULN and INR > 1.5 ● Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) ● Any clinical event of jaundice (or equivalent term) ● ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ● Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	● ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 16-4 Follow up requirements for liver laboratory triggers with liver symptoms

ALT or AST	**TBL**	**Liver Symptoms**	**Action**
ALT or AST increase without bilirubin increase:			
If normal at baseline: ALT or AST > 3 x ULN **If elevated at baseline:** ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● **No change to study treatment** ● Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms.
If normal at baseline: ALT or AST > 5 x ULN for more than two weeks **If elevated at baseline:** ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● **Interrupt study drug** ● Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies. ● Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT or AST > 8 x ULN	Normal	None	
ALT or AST increase with bilirubin increase:			
If normal at baseline: ALT or AST > 3 x ULN **If elevated at baseline:** ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT or AST > 3 x ULN	Normal or elevated		

ALT or AST	TBL	Liver Symptoms	Action
If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)		Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-5 Follow up requirements for liver laboratory triggers

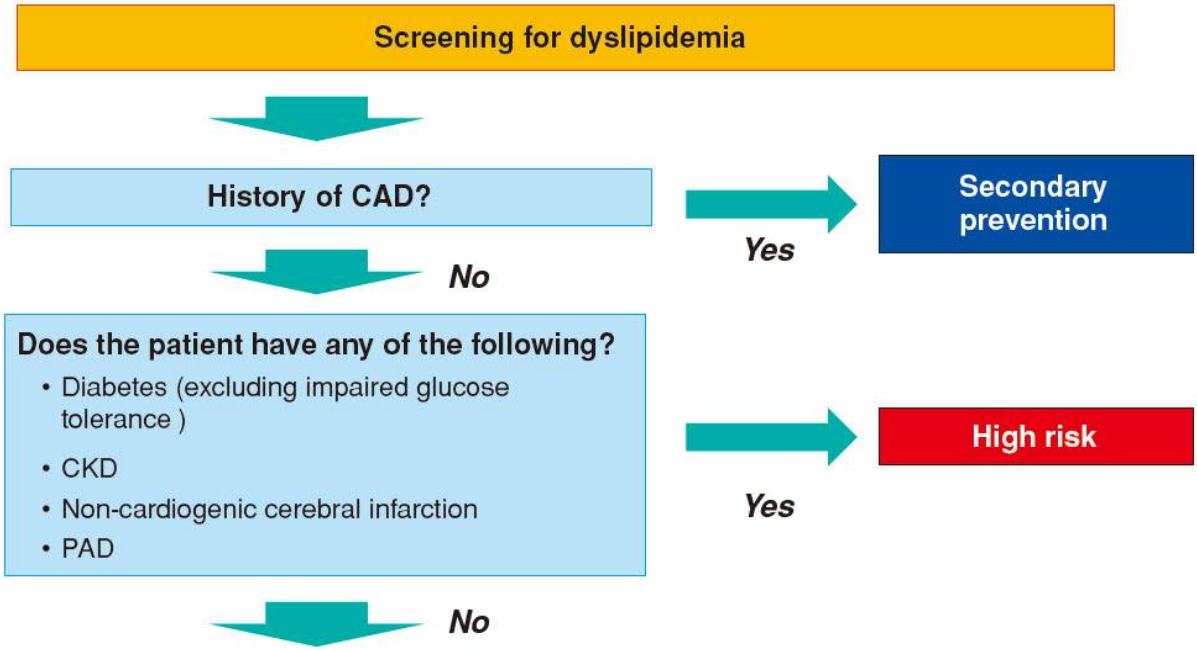
Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Discontinue the study treatment immediately ● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

[a]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Flowchart Using the Suita Score to Establish LDL-C Management Targets, from the Perspective of CAD Prevention (JAS 2017 guideline)

Figure 16-1 Flowchart Using the Suita Score to Establish LDL-C Management Targets, from the Perspective of CAD Prevention



Suita score	Predicted 10-year risk of CAD	Category
≤ 40	< 2%	Low risk
41–55	2% to < 9%	Moderate risk
≥ 56	≥ 9%	High risk

- The Suita score is calculated based on Figure 16-2.
- Note: For patients diagnosed with FH and those diagnosed with familial type III hyperlipidemia, do not use this chart.

Figure 16-2 Model for Predicting CAD Onset Using the Suita Score

	Range	Score
1. Age	35-44	30
	45-54	38
	55-64	45
	65-69	51
	70-	53
2. Gender	Men	0
	Women	-7
3. Smoking*	Yes	5
4. Blood pressure**	SBP <120 and DBP <80	-7
	SBP =120-139 and/or DBP=80-89	0
	SBP =140-159 and/or DBP=90-99	4
	SBP ≥ 160 and/or DBP ≥ 100	6
5. HDL-C	<40	0
	40-59	-5
	≥ 60	-6
6. LDL-C	<100	0
	100-139	5
	140-159	7
	160-179	10
	≥ 180	11
7. Impaired glucose tolerance	Yes	5
8. Family history of premature CAD	Yes	5

Total score of 1-8	Probability of CAD within the next 10 years (%)	Probability range (%)		Median of probability (%)	Category
		Minimum	Maximum		
≤ 35	<1		1.0	0.5	Low risk
36-40	1	1.3	1.9	1.6	
41-45	2	2.1	3.1	2.6	Moderate risk
46-50	3	3.4	5.0	4.2	
51-55	5	5.0	8.1	6.6	
56-60	9	8.9	13.0	11.0	High risk
61-65	14	14.0	20.6	17.3	
66-70	22	22.4	26.7	24.6	
≥ 71	>28	28.1		≥ 28.1	

*Ex-smokers should be regarded as nonsmokers. Note that the risk of CAD decreases by almost half 1 year after smoking cessation and drops to the same level as in nonsmokers after 15 years of smoking cessation.
**The current values are used even if the patient is currently undergoing treatment or not. However, counsel the patient while keeping in mind that patients undergoing treatment for hypertension have a higher risk of CAD than whose who have the same blood pressure value without undergoing treatment.
Note: The advantages and dis-advantages of lipid management in patients aged < 40 years of age are at the discretion of the attending physician; however, if lipid management is to be carried out, then the Suita score absolute risk for 35-44 years of age group is used.

*Source: JAS 2017 guideline (*Kinoshita et al 2018)

16.4 Appendix 4: Diagnostic Criteria for Heterozygous FH in adults (15 years of age or older)

Table 16-6 Diagnostic criteria for heterozygous FH in adults (15 years of age or older)

● Hyper-LDL-cholesterolemia (an untreated LDL-C level ≥ 180 mg/dL)
● Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum
● Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary dyslipidemia.
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.
- Xanthelasma is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on X-ray imaging.

- An LDL-C level of ≥ 250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age, respectively.
- If FH is diagnosed, it is preferable to also examine the patient's family members.
- These diagnostic criteria also apply to HoFH.

*Source: JAS 2017 guideline (*Kinoshita et al 2018)

16.5 Appendix 5: 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 mmHg or >30% decrease from that person's baseline

*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 *and* Sampson et al 2006

16.6 Appendix 6: 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.

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

Table 16-7 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.

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.

Table 16-8 Reflex responses

Reflex responses	Description
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).