NOVARTIS

Novartis Research and Development

KJX839/Inclisiran

Clinical Trial Protocol CKJX839D12304 / NCT05763875

A Double-blind, Randomized, Placebo- and Active-Comparator Controlled Study to Evaluate the Efficacy of Inclisiran as Monotherapy in Patients with Primary Hypercholesterolemia Not Receiving Lipid-Lowering Therapy (VictORION-Mono)

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List of abbreviations

ACC	American College of Cardiology
ADR	Adverse Drug Reaction
AE	Adverse Event
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANCOVA	Analysis of covariance
Apo A-1	Apolipoprotein A-1
Apo B	Apolipoprotein B
APTT	Activated Partial Thromboplastin time
ASCVD	Atherosclerotic Cardiovascular Disease
ASMA	Anti-smooth muscle antibody
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
BUN	Blood Urea Nitrogen
CD-transferrin	Carbohydrate-deficient transferrin
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
cm	centimeter(s)
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
CRO	Contract Research Organization
CSR	Clinical study report
CTIS	Clinical Trials Information System (European Medicines Agency)
CTT	Clinical Trial Team
CV	Cardiovascular
CVD	Cardiovascular Disease
DHA	Docosahexaenoic acid
DILI	Drug-Induced Liver Injury
dL	deciliter(s)
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EPA	Eicosapentaenoic acid

ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GalNAc	N-Acetylgalactosamine
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
HAV	Hepatitis A Virus
HbA1c	Glycated hemoglobin (hemoglobin A1c)
HBc	Hepatitis B core antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HEV	Hepatitis E Virus
HSV	Herpes simplex virus
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
Ig	Immunoglobulin
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
kg	kilogram(s)
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	Low Density Lipoprotein Receptor
LFT	Liver function test
LLT	Lipid-Lowering Therapy
Lp(a)	Lipoprotein (a)
LPLV	Last participant last visit
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCP	Multiple Comparison Procedure
MCV	Mean Corpuscular Volume

MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mmol	millimol(s)
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
non-HDL-C	non-High-Density Lipoprotein Cholesterol
NYHA	New York Heart Association
OHP	Off-site Healthcare Professional
p.o.	oral(ly)
PCE	Pooled cohort equations
PCR	Protein-creatinine ratio
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PD	Pharmacodynamic(s)
PMM	Pattern-Mixture Model
PT	Prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Analysis Set
RDO	Retrieved Drop Out
RISC	Ribonucleic acid-Induced Silencing Complex
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interference
s.c.	subcutaneous(ly)
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 also referred to as COVID-19
SCR	Screened Set
siRNA	small interfering ribonucleic acid
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TBL	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-Emergent Adverse Event
TFQ	Trial Feedback Questionnaire
TSH	Thyroid stimulating hormone
U/L	Units/Liter
ULN	Upper limit of normal
US	United States (of America)
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
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
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 source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the International Council for Harmonization (ICH) E9(R1) addendum, estimand is 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 participants 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.
Hybrid Trial Design	A trial model incorporating both onsite (traditional site based) and offsite (decentralized) elements within the same study design.
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 or the participant allocated to an invalid stratification factor

Off-site	Describes any trial activities that are performed at a location that is not the investigative site (where the investigator will conduct the trial), such as a home or another appropriate location.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, including those used in a study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant at an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
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	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
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 electronic source.
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
Telemedicine	Electronic information and telecommunications technologies (both video-based and audio-only) to facilitate the delivery of health care and health related education where participant and investigator and site personnel are not in the same location.
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 when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form (ICF).

Amendment 1 (08-Feb-2023)

Amendment rationale

In order to minimize missing data after discontinuation of study treatment, the amendment incorporates continued efforts to measure endpoints on all participants until Day 180, even for those who may have prematurely discontinued study treatment.

For regulatory purposes, to provide an estimate of treatment effect under conditions that better resemble clinical practice, the amendment includes a "Treatment-policy Estimand" that assesses efficacy of inclisiran in LDL-C lowering irrespective of addition of other LLTs, in parallel to the original estimand, referred to as "Monotherapy Estimand", which directly evaluates effect of inclisiran as monotherapy.

This amendment also incorporates additional guidance for the investigator on lifestyle instructions to be given to the participants as recommended by the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (Arnett et al 2019).

In addition, the discontinuation from study treatment criteria are updated to provide additional guidance to the investigator on specific reasons for discontinuation of study treatment including liver enzyme elevation and CK criteria, severe and persistent (> 14 days despite appropriate treatment) reactions at the injection site and any anaphylactic reactions, and intolerable adverse events.

To avoid unnecessary study treatment discontinuations, the actions taken in response to addition of other LLTs have been updated so that study treatment will not be automatically discontinued when other LLTs are taken after randomization (except for those targeting PCSK9, and RNAi-based therapies).

Finally, minor typos and inconsistencies have been corrected in the protocol.

As of the date of this amendment, no sites were initiated and no participants were recruited.

Changes to the protocol

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

The protocol summary was updated to reflect a ±5 day study window for the double-blind treatment period based on the Day 1 randomization date and a window of +5 days after the Day 150 visit for the Safety Follow-up / End of Study (EOS) visit. The summary also specifies that the last dose of p.o. ezetimibe/placebo will be taken the day before the Day 150 visit. Finally, inclusion criterion #4 states that triglycerides will be measured from participants in a fasting state, and exclusion criterion #10 was clarified to reflect Secondary hypercholesterolemia e.g., hypothyroidism (thyroid stimulating hormone (TSH) above the upper limit of normal (ULN)) rather than below the lower limit of normal at screening. In the Treatment of Interest Section, the additional clarification that treatment of interest is without other LLT was removed.

Section 2 was updated to add a "Treatment-policy Estimand" that assesses efficacy of inclisiran irrespective of addition of other LLTs, in parallel to the "Monotherapy Estimand" which is

based on the original estimand but uses the hypothetical strategy to handle discontinuation of study treatment instead of the treatment-policy strategy as previously specified.

Section 3 and Figure 3-1 were updated to specify that participants who prematurely discontinue study treatment are expected to continue to with all planned study visits and be retained in the study until Day 180 End of Study (EOS). This section also describes that a window of ± 5 days based on the Day 1 randomization date is allowed for the double-blind treatment period of 150 days. Clarified that safety follow-up/EOS will be conducted 30+5 days after the Day 150 Visit.

Section 3.3 clarifies that the last dose of p.o. ezetimibe/placebo will be taken by the participant on the day before the Day 150 visit.

In Section 3.4, the visit window is specified as 30 + 5 days after the Day 150 Visit. Figure 3-1 inclisiran/placebo at the Day 90 post-baseline visit. Section 9.1.1 is cited to describe the circumstances under which study treatment is discontinued. Section 9.2 is referred to in case a subject withdrawals consent and the follow-up actions that are needed by the Investigator.

Section 5.1 Inclusion criteria

- Inclusion criterion #4 was updated to clarify that triglycerides will be obtained from participant's lipids panel in a fasting state.

Section 5.2 Exclusion criteria

- Exclusion criterion #10 was clarified to reflect Secondary hypercholesterolemia e.g., hypothyroidism (thyroid stimulating hormone (TSH) above the upper limit of normal (ULN)) rather than below the lower limit of normal at screening.
- Exclusion criterion #12 specifies Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening will be determined by the central laboratory using the Modification of Diet in Renal Disease (MDRD) formula

Section 6.1.4, The safety follow-up / End of Study (EOS) visit window is specified as between 30 and 35 days after the Day 150 Visit.

Table 6-3 Prohibited medication, the prohibited medication table clarifies the prohibition periods and actions taken for the different medication classes, prior to randomization and starting from randomization and throughout the study. Any prohibited medication taken during the prohibition period until randomization result in non-randomization of a participant. The action taken for other LLTs (except for PCSK9 monoclonal antibodies) starting after randomization was modified to have the investigator request the participant to stop the LLTs, and to contact Novartis for further guidance. Investigators should also contact Novartis if the participant receives systemic cyclosporine and tacrolimus, systemic steroids, vitamin A derivatives or retinal derivatives for the treatment of dermatologic conditions or antiviral therapies after randomization and until the end of the study.

Section 6.7.1, added that the treatment compliance for p.o. ezetimibe/placebo should also be captured in the appropriate eCRF at each visit from Visit 2 / Day 30 through Visit 4 / Day150 .

Section 8 and Table 8-1 were updated to specify that participants who prematurely discontinue study treatment, are required to complete all planned study visits and be retained until Day 180. This section also describes that a window of ± 5 days based on the Day 1 randomization date is

allowed for the double-blind treatment period of 150 days. Day 180 is clarified as occurring between 30 + 5 days after the Day 150 Visit

Table 8-1 Assessment schedule was updated as follows:

- HbA1c will be collected at screening (and not at randomization).
- Ezetimibe/placebo compliance will be captured in the clinical database from Day 30 until the visit following the last dose of p.o. ezetimibe/placebo.
- End of Treatment Disposition form will be completed prior to Day 150 for participants who discontinue study treatment early.
- Footnote #14 specifies that if the urinalysis dipstick results are abnormal, then the urine sample will be sent to the central laboratory where a macroscopic panel will be performed with a reflexive microscopic panel.

Section 8.3 specifies that the unblinded lipid panel results will be provided to the Investigator and Sponsor at the Screening Visit only.

Table 8-3, an assessment of HbA1c only has been added at Screening, to ensure that the participant does not meet the HbA1c exclusion criterion. The Hematology panel on Day 1 will not include a HbA1c measurement. Urinalysis and renal follow-up section was updated to specify that central lab will perform a macroscopic panel, followed by a reflexive microscopic panel.

Section 8.4.2 describes that the baseline ECG is read and interpreted locally by the Investigator and any clinically significant abnormalities will be reported on the adverse events CRF.

Section 8.5.3 Lifestyle instructions, were added so that investigators can instruct their participants between randomization and Day 180 on the ways to prevent ASCVD by promoting a healthy lifestyle throughout life.

Section 9.1.1, was updated to clarify that if the participant permanently discontinues p.o. ezetimibe/placebo or s.c. inclisiran/placebo, then the participant's entire study treatment must be stopped. Language has been added to state that participants must be retained in the study until Day 180 even if they prematurely discontinue study treatment. To provide the investigator with specific examples and to be consistent with prior inclisiran studies, specific liver enzyme elevation and CK criteria, language regarding severe and persistent (>14 days despite appropriate treatment) reactions at the injection site and any type of anaphylactic reactions, and intolerable adverse events are added to the list of discontinuation criteria from study treatment.

Section 9.3, was updated to clarify that the safety follow-up call or the EOS visit should be conducted at least 30 days after the Day 150 visit.

Section 10.1.1, For action taken regarding investigational study drug or comparator, it was clarified that the action taken for 'Drug Interrupted' is applicable for ezetimibe/placebo only, whereas, 'Dose not Changed' and 'Permanently Discontinued' is applicable to both, study drug and comparator drug.

Section 12.4.2 was updated to reflect the changes in the estimands in Section 2.1. The last paragraph of this section was removed in the amendment because the method described does not apply to all the missing values under the new estimands.

Section 12.4.3 was updated to describe the strategies used by each of the two estimands for handling intercurrent events.

Section 12.4.4 was updated to summarize the methods for imputing missing values not related to intercurrent events.

Section 12.4.5 was updated to include the tipping point analyses to assess the robustness of the inferences to various assumptions about the missing data.

Section 12.4.6 was updated to remove the originally specified supplementary analyses as they are no longer necessary or applicable.

Section 12.5.1 was updated to reflect the changes in the estimands in Section 2.1. Also, the paragraph about missing value imputation was updated to be in line with the strategy for the primary endpoints.

Table 16-2 is updated to be consistent with Section 9.1.1 for the liver laboratory triggers and action taken.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Protocol summary

Protocol number	CKJX839D12304
Full Title	A Double-blind, Randomized, Placebo- and Active-Comparator Controlled Study to Evaluate the Efficacy of Inclisiran as Monotherapy in Patients with Primary Hypercholesterolemia Not Receiving Lipid-Lowering Therapy (VictORION-Mono)
Brief title	Efficacy and safety of inclisiran as monotherapy in patients with primary hypercholesterolemia not receiving lipid-lowering therapy.
Sponsor and Clinical Phase	Novartis / Phase III
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of the study is to evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as monotherapy to participants with primary hypercholesterolemia who are not on any lipid-lowering therapy (LLT).
Primary Objective(s)	The primary objectives of the study are: ● To demonstrate the superiority of inclisiran as monotherapy, compared with placebo, in reducing low-density lipoprotein cholesterol (LDL-C) as measured by percentage change from baseline to Day 150 ● To demonstrate the superiority of inclisiran as monotherapy, compared with ezetimibe, in reducing LDL-C as measured by percentage change from baseline to Day 150
Secondary Objectives	The secondary objectives of this study are: ● To assess the efficacy of inclisiran as monotherapy, compared to ezetimibe and placebo, on absolute change in LDL-C, percentage change in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC)/high -density lipoprotein cholesterol (HDL-C) ratio, apolipoprotein B (Apo B), Apo B/apolipoprotein A-1 (Apo A-1) ratio and lipoprotein (a) (Lp(a)) from baseline to Day 150 ● To assess the safety and tolerability of inclisiran as monotherapy, compared to placebo and ezetimibe.
Study design	This study is a randomized, double-blind, placebo- and active comparator-controlled, multicenter study in adult participants with primary hypercholesterolemia, not receiving any lipid-lowering therapy (LLT) and who have a 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk of less than 7.5%. The study consists of: ● A screening period up to 14 days ● A double-blind treatment period of 150 ± 5 days based on the Day 1 randomization date; and ● A Safety Follow-up / End of Study (EOS) visit conducted 30 +5 days after the Day 150 visit All participants who fulfill the inclusion/exclusion criteria will be randomized at baseline (Day 1) in a 2:1:1 double-blind fashion to one of three treatment arms: ● subcutaneous (s.c.) inclisiran and oral (p.o.) placebo (inclisiran arm) ● s.c. placebo and p.o. ezetimibe (ezetimibe arm) ● s.c. placebo and p.o. placebo (placebo arm). Participants will receive inclisiran sodium 300 mg or placebo by s.c. injection by a healthcare professional at the study site on Day 1 and Day 90. Participants will also be dispensed oral ezetimibe or placebo on Day 1, Day 30, and Day 90, and will be asked to take 1 capsule once a day from Day 1 through the day before the Day 150 visit. The overall study duration is approximately 190 days but can vary depending on individual screening and the visit windows allowed for the treatment period and EOS visit.
Rationale	Statin use up-regulates PCSK9 levels. Therefore, therapies that target PCSK9 may perform differently as monotherapy than when added to statin treatment. The study is aimed to evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as monotherapy to participants without background lipid-lowering agents, to inform an

	understanding of the new PCSK9 inhibition approach with inclisiran and help establish efficacy expectations for inclisiran in patients who cannot take statins.
Study population	Approximately 300 randomized adult participants (≥ 18 to ≤ 75 years of age) with primary hypercholesterolemia at low risk for their first cardiovascular event (10-year ASCVD risk of less than 7.5%), and who are not on any LLT.
Key Inclusion criteria	● Signed informed consent must be obtained prior to participation in the study ● Adults ≥ 18 to ≤ 75 years of age ● Fasting LDL-C value of ≥ 100 mg/dL (equivalent to 2.59 mmol/L) but < 190 mg/dL (equivalent to 4.92 mmol/L) ● Fasting Triglycerides ≤ 400 mg/dL (equivalent to 4.52 mmol/L) ● With a 10-year ASCVD risk score of less than 7.5%, estimated using the pooled cohort equations (PCE) ● Have not been on any LLT within 90 days
Key Exclusion criteria	● Use of any LLT within 90 days of screening including statins, ezetimibe, bempedoic acid, psyllium preparations, fibrates, bile-acid sequestrants, PCSK9 monoclonal antibodies, red yeast rice, niacin > 200 mg/day, omega-3 fatty acids [docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA), with a total dose > 1000 mg/day], or any drug with unknown ingredients taken for the purpose of lipid-lowering, including over-the-counter or herbal therapies ● Use of systemic cyclosporine or tacrolimus, systemic steroids, vitamin A derivatives or retinal derivatives for the treatment of dermatologic conditions (vitamin A in a multivitamin preparation is permitted), or antiviral therapies (protease inhibitors or direct acting antivirals) within 30 days of screening ● Participants on medications that are known to induce changes in lipids and lipoproteins (including but not limited to anticoagulants, loop diuretics, thiazide diuretics, beta blockers, amiodarone, estrogens, selective estrogen receptor modulators, androgens, anabolic steroids, and anticonvulsants) unless they are on a stable dose of such medications for at least 30 days prior to screening and have no planned dose change or treatment discontinuation during the study duration ● History of ASCVD (including acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, and peripheral artery disease including aortic aneurysm) ● Diabetes mellitus or fasting plasma glucose (FPG) at screening ≥ 7.0 mmol/L (equivalent to 126 mg/dL) or glycated hemoglobin (HbA1c) ≥ 6.5% (equivalent to 7.8 mmol/L or 140 mg/dL) ● Secondary hypercholesterolemia, e.g., hypothyroidism [thyroid stimulating hormone (TSH) above the upper limit of normal (ULN)] or nephrotic syndrome at screening
Study treatment	Study drug: ● KJX839 / Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution for injection ● Matching s.c. placebo in 1.5 mL solution for injection Control drug: ● Ezetimibe 10 mg p.o. ● Matching p.o. placebo
Treatment of interest	The randomized 2:1:1 double-blind treatment of: ● s.c. injections of inclisiran sodium 300 mg and p.o. placebo (inclisiran arm), ● s.c. injections of placebo and p.o. ezetimibe (ezetimibe arm) or ● s.c. injections of placebo and p.o. placebo (placebo arm)
Efficacy assessments	Efficacy assessments (using Central lab) are as follows: ● LDL-C (primary) ● PCSK9 ● non-HDL-C ● TC/HDL-C ratio ● Apo B ● Apo B/Apo A-1 ratio ● Lp(a)
Key safety assessments	Adverse event monitoring (adverse events (AEs) and serious AEs (SAEs), vital signs, laboratory parameters (blood, urine)

Other assessments	[redacted]
Data analysis	The primary efficacy endpoint of percentage change from baseline to Day 150 in LDL-C will be analyzed using an Analysis of Covariance (ANCOVA) model. The model will assume unequal variances between treatment groups, and include treatment, stratification factor, and baseline value as fixed effects. The two primary endpoint hypotheses will be tested using an equally weighted Dunnett test. Secondary endpoints will be analyzed using the same ANCOVA model as for the primary endpoint. The primary endpoint and secondary endpoints in the comparison between inclisiran and each comparator (placebo or ezetimibe) will be included in a multiple comparison procedure, in order to control the overall study type I error rate at 0.025 (one-sided test).
Key words	Inclisiran, ezetimibe, LDL-C, monotherapy, primary hypercholesterolemia

1 Introduction

1.1 Background

The prevalence of atherosclerotic cardiovascular disease (ASCVD) is increasing in many countries due to an aging population combined with atherogenic lifestyles. Mortality from ASCVD has been declining in most developed countries as a result of improvement in risk management and clinical intervention. However, ASCVD remains the leading cause of death among chronic diseases. Cardiovascular disease (CVD) results in over 17 million deaths annually (WHO 2021). ASCVD continues to be the most important health issue in the developed world and has also become one of the most pressing health problems in developing countries in the past decade.

High blood cholesterol is a major risk factor for ASCVD. Reduction in Low-Density Lipoprotein Cholesterol (LDL-C) levels have been shown to reduce subsequent cardiovascular events, for both primary and secondary prevention of ASCVD. Current consensus statements recommend consideration of an aggressive treatment goal of LDL-C less than 70 mg/dL (1.8 mmol/L) for high risk or very high risk patients.

Despite the success of statin therapy, significant gaps remain in the treatment of hypercholesterolemia. Many patients on statin regimens still experience complications of atherosclerosis. Others have persistently high LDL-C levels due to severe forms of hypercholesterolemia, poor tolerability of available medications, or persistent non-compliance to available medications due to complex reasons such as behavioral, psychological, and educational factors. For these populations, new effective lipid-lowering therapies (LLT) that impose less medication administration burden and improve compliance may offer significant clinical benefits (Assmann et al 2006, Banach et al 2016, Fox et al 2018).

The hepatic cell surface low-density lipoprotein receptor (LDLR) plays an essential role in plasma clearance of circulating LDL-C and in whole body cholesterol homeostasis, while proprotein convertase subtilisin/kexin type 9 (PCSK9) is instrumental in recycling and regulation of LDLR (Brown and Goldstein 2006, Horton et al 2007). PCSK9 is expressed and secreted into the bloodstream predominantly by the liver. It binds to the LDLR both intracellularly and extracellularly, promotes the lysosomal degradation of these receptors in hepatocytes (Lakoski et al 2009, Mousavi et al 2009), and consequently increases the circulating LDL-C levels. The inhibition of PCSK9 offers an effective approach to lower LDL-C.

The inhibition of PCSK9 can be achieved by PCSK9-binding monoclonal antibodies that prevent the interaction of PCSK9 with LDLR. PCSK9-binding monoclonal antibodies have shown to reduce LDL-C by 55-65% (Sabatine et al 2017, Schwartz et al 2018). These PCSK9 monoclonal antibodies require an injection frequency of every 2 to 4 weeks, necessitating up to 26 injections per year (Navarese et al 2015, Zhang et al 2015), which leads to a significant medication administration burden on patients.

The inhibition of PCSK9 can also be achieved by small interfering RNA (siRNA) that can selectively and catalytically silence the translation of messenger ribonucleic acids (mRNAs) to reduce the intracellular synthesis of PCSK9 protein. Inclisiran (KJX839) is a chemically modified double-stranded siRNA, conjugated on the sense strand with triantennary

N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RNA-induced silencing complexes (RISC) and directs catalytic breakdown of mRNA for PCSK9. This then leads to the inhibition of the synthesis of PCSK9 protein. Reduced intrahepatic PCSK9 increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which ultimately improves LDL-C uptake and lowers LDL-C levels in the circulation (Fitzgerald et al 2017). This novel mechanism has been proven to be effective. In the ORION-9, -10, and -11 Phase III studies, treatment with inclisiran sodium 300 mg administered 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 to Day 510 of 48% to 52%, with time-adjusted average reductions of 44% to 54% over 18 months in participants with ASCVD, ASCVD risk equivalent, and/or heterozygous familial hypercholesterolemia (HeFH) (Raal et al 2020, Ray et al 2020). 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 in these Phase III trials. AEs at the injection site were localized, mild and transient in nature. Inclisiran is not associated with an increased risk for hepatic or renal dysfunction, hypersensitivity, neurologic events and neurocognitive disorders, or ophthalmological events and there is no difference from placebo in new onset or worsening of diabetes. The potential for immunogenicity of inclisiran is low.

The long-term safety of inclisiran has been observed in two safety extension studies ORION-8 (the extension study of ORION-9, -10 and -11) and ORION-3 (the extension study of the Phase II trial ORION-1). The overall safety profile observed in ORION-8 and ORION-3 was similar to that reported in inclisiran-treated participants of its feeder studies (ORION-9, -10, and -11; ORION-1). The favorable safety profile for inclisiran remains unaltered in light of the additional longer-term safety data from ORION-8 and -3. Additional details on the efficacy and safety of inclisiran are available in the Investigator's Brochure (IB).

1.2 Purpose

The purpose of the study is to evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as monotherapy to participants with primary hypercholesterolemia who are not on any LLT. This selected, not-on-treatment population allows for an assessment of the treatment effects and safety of inclisiran in the absence of confounding factors, such as statin intolerance or concomitant treatment with other LLT such as statins or ezetimibe. For ethical reasons related to conducting a placebo-controlled study in which some participants would receive no active anti-hyperlipidemia treatment, this trial will enroll patients with low cardiovascular risk who do not require cholesterol lowering therapy per treatment guidelines.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate the superiority of inclisiran as monotherapy, compared with placebo, in reducing LDL-C as measured by percentage change from baseline to Day 150	● Percentage change in LDL-C from baseline to Day 150
● To demonstrate the superiority of inclisiran as monotherapy, compared with ezetimibe, in reducing LDL-C as measured by percentage change from baseline to Day 150	● Percentage change in LDL-C from baseline to Day 150
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To assess the efficacy of inclisiran as monotherapy, compared to ezetimibe and placebo, on absolute change in LDL-C, percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp (a) from baseline to Day 150	● Absolute change in LDL-C, percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp (a) from baseline to Day 150
● To assess the safety and tolerability of inclisiran as monotherapy, compared to placebo and ezetimibe	● Incidence of TEAEs and SAEs, safety laboratory values at each visit

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

There will be two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a “Monotherapy Estimand” and a “Treatment-policy Estimand”.

For the “Monotherapy Estimand,” the clinical question of primary interest is: what is the reduction in LDL-C, quantified by difference of mean percentage changes from baseline to Day 150, in trial participants with primary hypercholesterolemia and a 10-year ASCVD risk of less than 7.5% who are not on any LLT, and receive inclisiran as monotherapy, compared to the reduction in those who are on placebo or ezetimibe, if participants had not died or discontinued study treatments, and if other lipid-lowering therapy were not available.

The justification for the Monotherapy Estimand is that it will capture the effect of inclisiran as monotherapy in reducing LDL-C, in line with the study purpose of assessing the treatment effects of inclisiran in the absence of confounding factors such as concomitant treatment with other LLTs.

The Monotherapy Estimand is described by the following attributes:

Population: Participants with primary hypercholesterolemia and a 10-year ASCVD risk of less than 7.5%, who are not on any LLT. ASCVD risk will be estimated using the Pooled Cohort Equations (PCE) (Grundy et al 2019).

Endpoint: Percentage change from baseline to Day 150 in LDL-C.

Treatments of interest: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe).

Handling of intercurrent events:

- Information following permanent discontinuation of study treatment will be handled with a hypothetical scenario of what would happen if the participants had not prematurely discontinued any study treatment (hypothetical strategy).
- Participants who died will be handled in a hypothetical scenario of what would have happened had they not died (hypothetical strategy).
- Use of other LLT will be treated in a hypothetical scenario of what would happen if other LLT were not available (hypothetical strategy).

Summary measure: The summary measure to be used is the difference of mean percentage changes.

In addition, for regulatory purposes, the "Treatment-policy Estimand" was added in parallel as a primary estimand. This estimand shares the same population, endpoint, and summary measure as the Monotherapy Estimand but considers different treatments of interest and adopts alternative strategies for handling intercurrent events:

Treatments of interest: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other LLTs added during the study.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be ignored (treatment-policy strategy).
- Death will be handled as an unfavorable outcome using a composite variable strategy.
- Use of other LLTs will be ignored (treatment-policy strategy).

The Treatment-policy Estimand answers the clinical question regarding inclisiran efficacy in LDL-C lowering as compared to placebo or ezetimibe irrespective of adherence to study drug or addition of other LLTs, with death being an unfavorable outcome.

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 12.4.

2.2 Secondary estimands

The secondary estimands address the same clinical question as the primary estimands, albeit for different endpoints. For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy Estimand will be defined in a similar way as for the primary endpoint. They share the same population, strategies for handling intercurrent events, summary measure, as well as the same treatments of interest as the primary estimands. They differ by the definition of the endpoints, these being:

- Absolute change in LDL-C from baseline to Day 150
- Percentage change in PCSK9, non-HDL-C, TC/HDL-C ratio, Apo B, Apo B/Apo A-1 ratio and Lp(a) from baseline to Day 150

The statistical methods and inference approaches are described in Section 12.5.

3 Study design

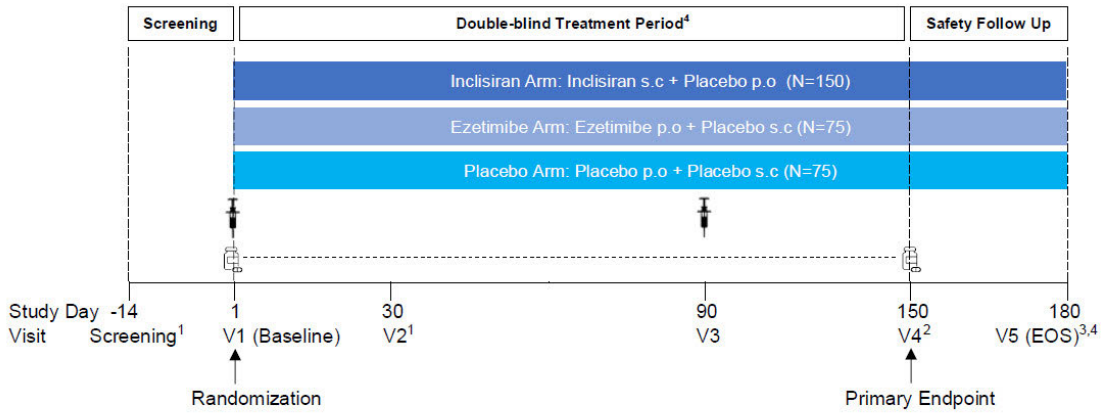
This study is a randomized, double-blind, placebo- and active comparator-controlled, multicenter study in adult participants with primary hypercholesterolemia not receiving any LLT and who have a 10-year ASCVD risk of less than 7.5%, estimated using the PCEs (Grundy et al 2019). This study will evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as a monotherapy in comparison to ezetimibe and placebo.

The study design is depicted in Figure 3-1. The study consists of:

- a screening period of up to 14 days;
- a double-blind treatment period of 150 ± 5 days based on the Day 1 randomization date; and
- a safety follow-up / End of Study (EOS) visit conducted 30 +5 days after the Day 150 Visit

The overall study duration is approximately 190 days but can vary depending on individual screening and the visit windows allowed for the treatment period and EOS visit.

Figure 3-1 Study Design



[1] Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations.

[2] Visit 4 is also the EOT visit if the participant completes the study treatment as per protocol.

[3] Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations or over the telephone if an on-site visit is not possible. During a telephone call, only AEs/SAEs and concomitant medications will be followed.

[4] When study treatment is discontinued early, participants should continue with all of their planned study visits and be retained until Day 180.

s.c inclisiran/placebo injection

p.o ezetimibe/placebo (one capsule daily from Day 1 until the day before the Day 150 visit)

3.1 Off-site procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed at an off-site location, as defined in Table 8-1. A hybrid model is planned for this study incorporating both onsite and off-site visits. The off-site procedures will be

utilized in certain countries and sites as determined by protocol needs and based on national and local/site regulations.

One or more of the following elements may be implemented to support off-site visits where allowed by national and local regulations:

- Telemedicine
- Off-site healthcare professional (OHP)
- Direct-to-participant shipment of study supplies
- Direct-to-participant shipment of study treatment (i.e., oral ezetimibe/placebo, refer to Section 6.3)

3.1.1 Responsibility of Investigators

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety and wellbeing of participants. This includes the following (including, but not limited to):

- the identification, management and reporting of AEs and SAEs are performed in accordance with the protocol and applicable regulations
- OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit
- where relevant, the investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination

3.1.2 Responsibility of OHPs

OHPs must have the required qualifications, training, and experience to conduct off-site assessments. OHPs are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

The OHPs will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHPs that are not provided by Novartis this must be agreed with Novartis before use.

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

3.1.3 Telemedicine

The sponsor has qualified and contracted a third-party vendor to provide telemedicine platform technology for this study. The selected platform is a validated system complying with relevant ICH E6 GCP guidelines (ICH E6 Guideline 2017). Trial participants can interact with site

personnel using online communication tools built into the platform, enabling the following capabilities:

- Secure videoconferencing which allows the participant, OHP and site personnel to be connected
- Reminders to be automatically sent to participants (e.g. visit or dosing reminders)

3.2 Screening

At screening, participants will sign the Informed Consent Form (ICF) and their eligibility will be assessed through the review of study inclusion/exclusion criteria. The ICF must be signed before initiation of any study-specific procedures and assessments (see Section 5.1 and Section 7 for details). If at the time of ICF signature the participant is not fasting, he/she will have to return for the blood draw in a fasting state.

During the screening visit, the participant's individual 10-year ASCVD risk will be estimated using the PCEs, an algorithm derived from five prospective community-based studies representing a broad spectrum of the US-population as described in the multi-society guideline on the management of blood cholesterol (Grundy et al 2019).

The investigator must ensure that each participant has not been treated with LLT or other prohibited medications (see Table 6-3) for at least 90 days prior to the screening visit. If the participant is on any of the permitted concomitant medications (see Table 6-2) known to induce lipid and lipoprotein changes, the dose of such medications must have been stable for ≥ 30 days prior to the screening visit with no plan to change the dose or to discontinue during the study duration.

The screening period can be up to 14 days to allow adequate time for the completion of all qualifying screening and eligibility evaluations and potentially repeating some of the screening evaluations (e.g., laboratory results), as applicable (see Section 8.1). A participant who enters screening and is determined not eligible during the screening period or at the time of randomization will be considered a screen failure.

3.3 Double-blind treatment

Baseline visit

All participants who fulfill the inclusion/exclusion criteria (Section 5.1 and Section 5.2) will be randomized at baseline (Day 1) in a 2:1:1 double-blind fashion to one of three treatment arms: s.c. inclisiran and p.o. placebo (inclisiran arm); s.c. placebo and p.o. ezetimibe (ezetimibe arm); or s.c. placebo and p.o. placebo (placebo arm). Participants will be stratified by their screening LDL-C result (LDL-C ≤ 130 mg/dL vs. LDL-C > 130 mg/dL). Following randomization at the Baseline visit (Day 1), the participant will receive inclisiran sodium 300 mg or placebo by subcutaneous injection by a healthcare professional at the study site. The participant will also be dispensed one bottle of oral ezetimibe or placebo, and will be asked to take 1 capsule once a day, starting with the day of the Baseline visit (Day 1).

At the Baseline visit, all participants will be instructed to comply with lifestyle changes according to clinical guidelines (Grundy et al 2019), and these instructions will be reinforced at every visit.

Post-Baseline visits

Following the Baseline visit, participants will have study visits on Day 30, Day 90, and Day 150. The participant will receive a second subcutaneous injection of 300 mg inclisiran sodium or placebo on Day 90 (Figure 3-1), administered by a healthcare professional at the study site. The participant will also be dispensed oral ezetimibe or placebo on Day 1, Day 30, Day 90 and will be asked to continue to take 1 capsule once a day from Day 1 through the day before the Day 150 visit. Please refer to Section 9.1.1 for reasons for early discontinuation of study treatment and the study procedures to follow. Section 9.2 provides instructions in case a participant withdraws informed consent.

3.4 Safety Follow-up/EOS

The End of Study (EOS) visit (Day 180) will be the safety follow-up conducted 30 +5 days after the Day 150 visit. No data beyond EOS will be collected in the electronic Case Report Form (eCRF). If a participant discontinues from the study early, the investigator must do their best to ensure that the participant returns for an EOS visit.

4 Rationale

4.1 Rationale for study design

Statin use up-regulates PCSK9 levels. Therefore, therapies that target PCSK9 may perform differently as monotherapy than when added to statin treatment. The study is aimed to evaluate the efficacy and safety of inclisiran sodium 300 mg, administered as monotherapy to participants without background LLT, to inform an understanding of the new PCSK9 inhibition approach with inclisiran and help establish efficacy expectations for inclisiran in patients who cannot take statins.

LLT is not required per American Heart Association (AHA)/American College of Cardiology (ACC) primary prevention guidelines in patients with primary hypercholesterolemia who have a low 10-year ASCVD risk (< 5%) or a borderline risk (5% to < 7.5%) without risk enhancers if the participants have LDL-C measured less than 190 mg/dL (Arnett et al 2019, Grundy et al 2019). This trial is designed to be conducted in this population, in order to remove confounding by statin use or a history of statin intolerance, and to meet ethical requirements.

4.1.1 Rationale for choice of background therapy

The participants must fulfill the requirement of not being on any lipid-lowering background therapy within 90 days prior to the screening and throughout the study. The purpose is to remove any potential confounding effect caused by statin intolerance or concomitant LLT such as statins or ezetimibe, in the monotherapy setting.

4.2 Rationale for dose/regimen and duration of treatment

A Phase II study (ORION-1) has shown that 300 mg dose of inclisiran sodium administered as one or two doses is the lowest dose to achieve near-maximal reductions in PCSK9 (70.9% and 74.5%, respectively) and LDL-C (50.9% and 59.7%, respectively) levels. Three Phase III studies (ORION-9, -10, and -11) in adults with ASCVD, ASCVD risk equivalents and/or HeFH demonstrated that 300 mg inclisiran sodium s.c. 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 50% to 58%, with time-adjusted average reductions of 44% to 54% sustained over 18 months. In these studies, this dose also showed good tolerability of inclisiran, with a safety profile similar to placebo, except for a higher incidence of AEs at the injection site. Based on nonclinical and clinical data, including Phase I, II and III clinical studies as well as pharmacodynamic (PD) modeling in adult participants, the same dose will be used in the present study. The inclisiran dose and regimen in the study is 300 mg s.c. administered at Baseline and Day 90. This is the approved dose by the United States Food and Drug Administration (FDA) and in the European Union (EU).

ORION-1 also demonstrated that two injections on Day 1 and on Day 90 produced a significant percentage LDL-C reduction of 52.6% at Day 180. In ORION-9, -10, and -11, two initial injections (Day 1 and Day 90) led to a similar percentage reduction in LDL-C at Day 150. The magnitude of this reduction was then maintained with subsequent injections every 6 months. Based on these data, a 6-month study duration with two injections of blinded study medication is deemed as sufficient for observing the effect of inclisiran as a monotherapy, compared to placebo and ezetimibe. In addition, this duration will leave placebo-treated participants with the shortest unprotected period of no LLT as participants' lipid-lowering need may change following the study enrollment.

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

A placebo-controlled arm is a standard design in drug development to assess efficacy and safety and ensures that differences in outcome will be a reliable and realistic measure of the treatment effect of inclisiran. The use of placebo as a comparator is justified as the trial population has a 10-year ASCVD risk of less than 7.5% and does not need to be on any LLT per AHA/ACC primary prevention guidelines (Arnett et al 2019).

The monotherapy use of inclisiran is anticipated mostly in participants who do not tolerate statins well or are unwilling to take a statin due to their concerns on the side effects of statins. The current non-statin treatment options include ezetimibe, fibrates and nicotinic acid, used alone or in combination. Ezetimibe, an intestinal cholesterol absorption inhibitor, is the most commonly used non-statin therapy that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Therefore, it is reasonable to use ezetimibe as an active comparator, in addition to a placebo arm.

4.4 Purpose and timing of interim analyses/design adaptations

There are no planned interim analyses or design adaptations.

4.5 Risks and benefits

In general, the risk of participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring of safety parameters. The risk is further reduced by a minimal study duration of approximately 6 months. Participants are not anticipated to be exposed to greater risks when participating in off-site assessments. OHPs will perform assessments for sites participating in the hybrid trial model according to the protocol and study manuals for onsite visits wherever possible, thus data integrity is also expected to be comparable to onsite assessments. Safety management in an off-site setting will adhere to the same quality standards as for the traditional onsite model and remains under the responsibility of the investigator (refer to Section 3.1.1).

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 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.

In non-clinical toxicity studies, inclisiran was not carcinogenic or genotoxic. There was no effect on paternal performance, spermatogenesis, estrous cycle, and uterine or ovarian parameters. Inclisiran did not show evidence of embryolethality, fetotoxicity, or teratogenicity. In addition, there were no effects of inclisiran on the development of the F1 generation, including survival, growth, physical and reflexological development, behavior, and reproductive performance.

The overall clinical experience with inclisiran includes the following completed studies:

- Three completed Phase I studies; ALN-PCSSC-001 in participants with elevated LDL-C, ORION-6 in participants with mild to moderate hepatic impairment, and ORION-7 in participants with renal impairment (mild, moderate, severe)
- Two completed Phase II studies; ORION-1 in participants with ASCVD or ASCVD risk equivalent, and ORION-2 in participants with homozygous familial hypercholesterolemia
- Three completed Phase III studies; ORION-9, -10, and -11 in participants with HeFH, ASCVD or ASCVD risk equivalents

The safety profile of inclisiran in clinical studies is well characterized and based on data obtained from 3 large pivotal trials (ORION-9, -10, -11) that included 1,833 participants treated with inclisiran for up to 18 months (Wright et al 2021) and was generally comparable to placebo. The only inclisiran-related adverse drug reaction (ADR) identified in clinical studies was a higher incidence of TEAEs at the injection site, including injection site erythema, injection site hypersensitivity, injection site pruritus, injection site rash, and injection site reaction. All TEAEs at the injection site were localized, mild or occasionally moderate, transient and resolved without sequelae. The impact of this side effect is further mitigated by the infrequent dosing regimen of inclisiran.

In Phase III studies (ORION-9, -10, -11) in participants with HeFH, ASCVD or ASCVD risk equivalents, inclisiran administered on Day 1, Day 90 and every 6 months thereafter lowered LDL-C by approximately 50% or more versus placebo in participants on maximally tolerated statin therapy with or without other LLT (Raal et al 2020, Ray et al 2020).

It is widely recognized that LDL-C plays a major role in the initiation and progression of ASCVD, and accumulated exposure of elevated LDL-C is causally related to the development of ASCVD. As the degree and duration of exposure to elevated LDL-C levels increases the atherosclerotic burden, early treatment of hypercholesterolemia in primary prevention is essential to the prevention of ASCVD events. The participants in this trial have a 75% chance of being randomized to a LLT (inclisiran or ezetimibe). In addition to the potential reduction in LDL-C, the benefit a participant may have by participating in this study is the opportunity to learn more about primary hypercholesterolemia and how to reduce future progression to clinical ASCVD and prevention of ASCVD events.

4.6 Rationale for planned off-site procedures

Off-site procedures are planned in this study to minimize burden on participants, and offer them increased flexibility to participate in the study from an off-site location (as described in Section 3.1 and defined in Table 8-1). This has the potential to broaden access to clinical trials for both participants and investigators. The hybrid approach will allow participants to maintain contact with investigator, both in person during clinic visits at site and through the telemedicine platform during off-site participation.

4.7 Rationale for Public Health Emergency mitigation procedures

In addition to the planned off-site procedures, in the event of a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, additional mitigation procedures to ensure participant safety and trial integrity may be implemented. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or additional visits by OHPs to the participant's home, can replace onsite study visits (in addition to the already planned off-site visits), for the duration of the disruption until it is safe for the participant to visit the site again.

Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study population consists of approximately 300 randomized adult participants (≥ 18 to ≤ 75 years of age) with primary hypercholesterolemia (fasting LDL-C ≥ 100 mg/dL but < 190 mg/dL) at low risk for their first cardiovascular event (10-year ASCVD risk score of < 7.5%), and who are not receiving any LLT.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Adults ≥ 18 to ≤ 75 years of age
3. Fasting LDL-C value of ≥ 100 mg/dL (equivalent to 2.59 mmol/L) but < 190 mg/dL (equivalent to 4.92 mmol/L)

4. Fasting triglycerides ≤ 400 mg/dL (equivalent to 4.52 mmol/L)
5. With a 10-year ASCVD risk score of less than 7.5%, estimated using the pooled cohort equations (PCE)
6. Have not been on any lipid-lowering therapy within 90 days

5.2 Exclusion criteria

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

1. Use of any lipid-lowering therapy within 90 days of screening including statins, ezetimibe, bempedoic acid, psyllium preparations, fibrates, bile-acid sequestrants, PCSK9 monoclonal antibodies, red yeast rice, niacin > 200 mg/day, omega-3 fatty acids (DHA and/or EPA, with a total dose > 1000 mg/day), or any drug with unknown ingredients taken for the purpose of lipid-lowering, including over-the-counter or herbal therapies
2. Use of systemic cyclosporine or tacrolimus, systemic steroids, vitamin A derivatives or retinal derivatives for the treatment of dermatologic conditions (vitamin A in a multivitamin preparation is permitted), or antiviral therapies (protease inhibitors or direct acting antivirals) within 30 days of screening
3. Participants on medications that are known to induce changes in lipids and lipoproteins (including but not limited to anticoagulants, loop diuretics, thiazide diuretics, beta blockers, amiodarone, estrogens, selective estrogen receptor modulators, androgens, anabolic steroids, and anticonvulsants) unless they are on a stable dose of such medications for at least 30 days prior to screening and have no planned dose change or treatment discontinuation during the study duration
4. History of ASCVD (including acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, and peripheral artery disease including aortic aneurysm)
5. Diabetes mellitus or fasting plasma glucose at screening ≥ 7.0 mmol/L (equivalent to 126 mg/dL) or HbA1c ≥ 6.5% (equivalent to 7.8 mmol/L or 140 mg/dL)
6. New York Heart Association (NYHA) class III or IV heart failure or last known left ventricular ejection fraction < 30% at screening.
7. Uncontrolled severe hypertension: systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg at screening despite antihypertensive therapy, confirmed with a repeat measurement
8. Uncontrolled serious cardiac arrhythmia (recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation, or supraventricular tachycardia) within 90 days prior to randomization that is not controlled by medications
9. 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) > 3 x the upper limit of normal (ULN), or total bilirubin (TBL) > 2 x ULN at screening
10. Secondary hypercholesterolemia, e.g., hypothyroidism (thyroid stimulating hormone (TSH) above the upper limit of normal (ULN)) or nephrotic syndrome at screening
11. Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within 5 years prior to randomization

12. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening as determined by the central laboratory using the Modification of Diet in Renal Disease (MDRD) formula
13. Pregnant or nursing (lactating) women
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using effective methods of contraception during dosing of study treatment. Effective 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 bilateral 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 the 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 if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal 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 are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).
15. Use of any RNAi-based therapeutics, including but not limited to siRNA or Antisense Oligonucleotide (ASO) Therapies within 5 half-lives or 30 days whichever is longer, prior to screening
16. Participation in another investigational device or drug study currently, or within 5 half-lives (if drug) or 30 days whichever is longer, prior to screening
17. Known history of alcohol and/or drug abuse within the past 5 years prior to randomization

18. Severe concomitant disease that carries the risk of reducing life expectancy to less than 2 years
19. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to
    - Unlikely to understand or comply with the protocol requirements, instructions, and study-related restrictions
    - 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

6 Treatment

6.1 Study treatment

Participants will be randomized 2:1:1 to double-blind s.c. injections of inclisiran sodium 300 mg and p.o. placebo (inclisiran arm); s.c. injections of placebo and p.o. ezetimibe (ezetimibe arm); or s.c. injections of placebo and p.o. placebo (placebo arm).

6.1.1 Investigational and control drugs

The sponsor will provide the following investigational and control drugs, refer to Table 6-1.

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 284 mg inclisiran*) in 1.5 mL	Solution for injection	s.c.	Solution for injection in prefilled syringe**	Global
Matching s.c. placebo in 1.5 mL	Solution for injection	s.c.	Solution for injection in prefilled syringe**	Global
Ezetimibe 10 mg	Capsule	p.o.	Bottle	Global
Matching p.o. placebo	Capsule	p.o.	Bottle	Global

*Inclisiran is also referred to as KJX839
**The prefilled syringe (PFS) is a device component of the combination product, and it is regulated as part of the combination product in the context of this clinical trial. The PFS is not investigational, and no separate approval is required.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Participants will be randomized at the baseline visit (Day 1) to one of the following three double-blind treatment groups in a 2:1:1 ratio:

A) Inclisiran sodium 300 mg s.c. and placebo p.o. (inclisiran arm)

B) Placebo s.c. and ezetimibe 10 mg p.o. (ezetimibe arm)

C) Placebo s.c. and placebo p.o. (placebo arm)

Each participant will receive one injection of blinded inclisiran or placebo on Day 1, and a second injection of blinded inclisiran or placebo on Day 90, unless there is a need for discontinuing inclisiran/placebo in the course of the study (refer to Section 3.3 and Section 9.1.1). Each participant will take blinded oral ezetimibe or placebo once daily on Day 1 until the day before the Day 150 visit, unless there is a need for discontinuing oral ezetimibe/placebo in the course of the study.

Subcutaneous injections of inclisiran sodium 300 mg and placebo will not be dispensed to the participants but rather administered by qualified, healthcare personnel at the study site on Day 1 and Day 90 of the study. Oral ezetimibe and placebo will be dispensed to the participants on Day 1, Day 30 and Day 90; and taken by the participant daily from Day 1 until the day before the Day 150 visit. Randomization will be stratified by screening LDL-C level (≤ 130 mg/dL versus > 130 mg/dL).

6.1.4 Treatment duration

The planned study treatment duration is 150 ±5 days . The EOS visit will be conducted 30 +5 days after the Day 150 visit.

Participants may be discontinued from the study treatment earlier due to safety reasons, at the discretion of the investigator or the participant. They will continue to be followed up in the study until EOS as per Assessment Schedule (Table 8-1).

Depending on the availability of inclisiran in the investigator's country, the decision to switch a participant to a commercially available inclisiran product or to one of the locally available standard of care treatments after EOS will be left to the investigator's clinical judgment.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical 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.

The investigator should instruct the participant to notify the study site about any new medications he/she takes after the participant is enrolled into the study. All medications, procedures, and significant non-drug therapies used by/performed on the participant within 30 days prior to the first visit (Screening visit) must be documented in the appropriate page of the eCRF.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” as listed in Table 6-3. Specifically, participants should receive full supportive care during the study,

including treatment with antibiotics, antiemetics, antidiarrheals, analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Several medications and medication classes have been reported to affect the lipid profile. In order to accurately assess the effect of inclisiran as a monotherapy, it is desired to avoid any changes in lipids and lipoproteins induced by other medications. The medications listed in Table 6-2 are permitted if the doses of such medications are stable at least for 30 days prior to screening. The use of these medications by participants must remain unchanged from screening and throughout the trial. If the investigator suspects any drug to be lipid-change inducing but not listed in Table 6-2, the investigator should contact the Novartis medical monitor before randomizing a participant.

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, also referred to as COVID-19) vaccines are permitted among participants in this trial. There is no evidence to suggest that participants receiving either inclisiran/placebo or ezetimibe are at increased risk for AEs following a COVID-19 vaccination. However, since both inclisiran/placebo and COVID-19 vaccines are administered s.c., it is recommended that the COVID-19 vaccine is administered +/- 7 days from s.c. inclisiran/placebo administration. Further, it is recommended that a different anatomical location is used for COVID-19 vaccine and s.c. inclisiran/placebo to help differentiate potential local adverse reactions. COVID-19 vaccination administrations that occur either within 30 days prior to the first visit (Screening visit) and during the course of this study should be documented on the appropriate eCRF.

Influenza vaccination, pneumococcal vaccination, or any other vaccines are also permitted among participants in this trial. Similar to the recommendations on COVID-19 vaccines, a 7-day window between these vaccines and s.c. inclisiran/placebo administration and a different anatomical location are suggested.

Table 6-2 Medication allowed under certain conditions

Class of medication	Condition
Anticoagulants	Stable dose for at least 30 days prior to screening and throughout the study
Loop diuretics and thiazide diuretics	Stable dose for at least 30 days prior to screening and throughout the study
Beta blockers	Stable dose for at least 30 days prior to screening and throughout the study
Amiodarone	Stable dose for at least 30 days prior to screening and throughout the study
Estrogens*	Stable dose for at least 30 days prior to screening and throughout the study
Selective estrogen receptor modulators	Stable dose for at least 30 days prior to screening and throughout the study
Androgens	Stable dose for at least 30 days prior to screening and throughout the study
Anabolic steroids	Stable dose for at least 30 days prior to screening and throughout the study
Anticonvulsants	Stable dose for at least 30 days prior to screening and throughout the study

*Please note that as per Exclusion Criterion #14, female participants of child-bearing potential who are on oral contraception only (i.e. estrogens and progesterone) should be on stable dose for a minimum of 3 months prior to Day 1 and throughout the study.

6.2.2 Prohibited medication

Use of the treatments in Table 6-3 is not allowed. This table is not considered all-inclusive. If in doubt, the investigator should contact the Novartis medical 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 his/her participation in the study.

Table 6-3 Prohibited medication

Class of medication	Prohibition period	Action taken
LLT [statins, ezetimibe (other than control drug), bempedoic acid, psyllium preparations, fibrates, bile-acid sequestrants, red yeast rice, niacin > 200 mg/day, omega-3 fatty acids (DHA and/or EPA with a total dose > 1000 mg/day)], or any drug with unknown ingredients taken for the purpose of lipid-lowering, including over-the-counter or herbal therapies	At least 90 days prior to screening and until randomization	Do not randomize the participant Ask participants to stop taking LLTs.
	Randomization and throughout the study	Contact Novartis for further guidance.
Systemic cyclosporine and tacrolimus Systemic steroids Vitamin A derivatives or retinal derivatives for the treatment of dermatologic conditions (vitamin A in a multivitamin preparation is permitted) Antiviral therapies (protease inhibitors or direct acting antivirals)	At least 30 days prior to screening and until randomization	Do not randomize the participant
	Randomization and throughout the study	Contact Novartis for further guidance.
Investigational drugs Any RNAi-based therapeutics, including but not limited to siRNA or ASO Therapies	At least 30 days or 5 half-lives, whichever is longer, prior to screening and until randomization	Do not randomize the participant
	Randomization and throughout the study	Discontinue study treatment
Monoclonal antibodies directed towards PCSK9 such as evolocumab and alirocumab	At least 90 days prior to screening and until randomization	Do not randomize the participant
	Randomization and throughout the study	Discontinue study treatment

6.3 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.

Site staff will identify the study medication kits to administer/dispense to the participant by contacting the Interactive Response Technology (IRT) and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before administration/dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

For sites participating in the hybrid trial model with off-site visits by OHPs, where delivery of oral ezetimibe/placebo directly to a participant's secure off-site location (e.g. home) is permitted by national and local governing regulations, then dispatch of oral ezetimibe/placebo directly to the participant may be performed under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 2 months' supply. In this case, regular phone calls or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

In addition, as per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of study medication(s) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment(s) even without performing an on-site visit. The dispatch of study medication(s) from the site to the participant's home remains under the accountability of the investigator.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated 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 Country Organization (CO) Quality Assurance.

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 investigator 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 field monitors during site or remote monitoring visits, and at the completion of the trial.

If study treatment is administered at home (i.e., p.o. ezetimibe/placebo), participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

If a participant enters the study on medication that is known to be lipid change inducing (see Table 6-2), those medications should be specifically monitored. Changes (dose change or discontinuation) are not allowed during the study participation.

6.3.2 Instruction for prescribing and taking study treatment

Blinded s.c. injections of inclisiran/placebo, will not be dispensed to the participants, but will be administered by qualified healthcare personnel at the study site.

The preferred site of injection is the abdomen. Alternative injection sites include the upper arm or thigh. Injections should not be made into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos, or skin infections.

Participants will be administered an injection of blinded s.c. inclisiran/placebo on Day 1 and Day 90, as specified in the Assessment Schedule (Table 8-1) after all other study assessments have been completed for the visit.

Blinded bottles containing 35 capsules of p.o. ezetimibe/placebo will be dispensed to the participants on Day 1 (1 bottle), Day 30 (2 bottles), and Day 90 (2 bottles) as assigned by the IRT. Participants should be instructed to take the p.o. ezetimibe/placebo (1 capsule) at approximately the same time each day as follows:

- Each dose may be taken with a glass of water with or without food.
- Participants should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, participants should not take the p.o. ezetimibe/placebo again before the next scheduled dose.
- Participants should be instructed not to make up missed doses. A missed dose is defined as when the full dose is not taken within 8 hours of the approximate time of the usual daily dosing. That day's dose should be skipped and the participant should continue treatment with the next scheduled dose.
- On Day 1, Day 30, and Day 90, the dose should be taken after all assessments have been completed for the visit. The last dose of p.o. ezetimibe/placebo should be taken the day before the Day 150 visit.

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*)	300 mg	Day 1 and Day 90
matching s.c. placebo	0 mg	Day 1 and Day 90
Ezetimibe 10 mg	10 mg	once daily, Day 1 until day before Day 150 visit
matching p.o. placebo	0 mg	once daily, Day 1 until day before Day 150 visit

*also known as KJX839

All kits of study treatment assigned by the IRT will be recorded in the IRT system. All injections of inclisiran/placebo given 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 and within IRT. All interruptions/discontinuations of p.o. ezetimibe/placebo

(i.e., doses not taken by the participant) during the study must be recorded on an appropriate eCRF; whereas bottles not dispensed to a participant must be recorded within IRT.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 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. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative 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.

6.4.2 Treatment assignment, randomization

At Visit 1 (Day 1), all eligible participants will be randomized via 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 random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, 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 screening LDL-C results (≤ 130 mg/dL vs. > 130 mg/dL).

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

6.5 Treatment blinding

Participants, investigator staff, persons performing the assessments, and the Novartis trial team will remain blind to the identity of the treatment from the time of randomization until database lock.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

The following methods will be used to maintain the blind:

(1) Randomization data will be kept strictly confidential until the time of final database lock.

(2) The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor. A double-dummy design is used because the identity of the study treatment (inclisiran versus ezetimibe and matching placebos) cannot be disguised, as the drug products are visibly different.

(3) Data with unblinding potential, such as lipid results and PCSK9 results collected after the randomization visit, will be kept blind until the time of final database lock.

6.6 Dose escalation and dose modification

6.6.1 Definitions of dose limiting toxicities (DLTs)

DLTs are not applicable for the study.

6.6.2 Dose modifications

There are no dose adjustments or modifications of study treatment [i.e., study drug (s.c. inclisiran/placebo) or control drug (p.o. ezetimibe/placebo)]. For study treatment interruptions, discontinuations, and other follow-up requirements, please refer to Section 10.1.1, Section 10.2.1, Table 16-2, and Table 16-3.

6.6.3 Follow-up for toxicities

All participants must be followed up for adverse events and serious adverse events for 30 days following the last doses of s.c. inclisiran/placebo or p.o. ezetimibe/placebo, whichever comes last.

6.6.3.1 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 drug-induced liver injury (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 TBL > 1.5 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 [TBL > 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, TBL, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase (ALP), albumin, and creatine kinase (CK). If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

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. 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.

Table 6-5 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 6-5 Guidance on clinical and diagnostic assessments to rule out alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A (HAV), B (HBV), C (HCV), E (HEV)	● Immunoglobulin (Ig) M anti-HAV; hepatitis B virus surface antigen (HBsAg), IgM & IgG anti-hepatitis B core antigen (HBc), HBV deoxyribonucleic acid (DNA); anti-HCV, HCV ribonucleic acid (RNA), IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV) infection	● IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	● Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	● Ethanol history, GGT, mean corpuscular volume (MCV), carbohydrate-deficient (CD)-transferrin
Nonalcoholic steatohepatitis	● Ultrasound or MRI
Hypoxic/ischemic hepatopathy	● Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	● Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 years 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 – triiodothyronine (T3), thyroxine (T4), TSH;

cardiovascular disease (CV) / ischemic hepatitis – electrocardiogram (ECG), prior hypotensive episodes; Type 1 diabetes / 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.

Please also refer to Section 16.2 for liver event and laboratory trigger definitions & follow-up requirements.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance of the p.o. study treatment (ezetimibe/placebo) by instructing the participant to take it exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document and the appropriate eCRF at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Blinded investigational s.c. injections (inclisiran/placebo) will be administered at the study site. This information must be captured in the source document, the appropriate eCRF and in the Drug Accountability Log.

6.7.2 Recommended treatment of adverse events

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

For participants with injection site reaction, antihistamines, local or systemic steroids can be used at the investigator's discretion depending on the severity of the reaction.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.7.3 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.

Most often, discontinuation from study treatment 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/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name
- 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 treatment 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) or until participant completed the EOS visit as per Assessment Schedule (Table 8-1).

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 level of 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 (ICH E6 Guideline 2017) 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 treatment (inclisiran) can be found in the IB and information about common side effects known about the other study treatment (ezetimibe) can be found in the local package insert. 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 (IN) 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
- Optional Consent for Additional Research to allow future research on data/samples collected during this study
- As applicable, Informed Consent for Off-site Visits/Procedures to allow for off-site visits/procedures as described in Section 3.1
- 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.

Participants will be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists when all study assessments are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1) During the double-blind treatment period, a window of +/- 5 days based on the Day 1 randomization date is acceptable for Visit 2 (Day 30), Visit 3 (Day 90), and Visit 4 (Day 150). Visit 5 (Day 180 or EOS) will be 30 days after Day 150 visit, with an acceptable window of up to + 5 days. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who prematurely discontinue from study treatment are to continue with planned study visits and be retained until Day 180 as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must 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 to obtain fasting lipids and/or glucose blood samples. If the participant is not fasting at the time of Informed Consent signature, he/she will have to return for a blood draw in a fasting state.
- Must refrain from unaccustomed strenuous physical activity for 48 hours prior to any study visit.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Screening**	**Baseline**	**Double-Blind Treatment Period[4]**			**Safety Follow-up**
Visit Name	**Screening[1]**	**V1**	**V2[1]**	**V3**	**V4 [2]**	**V5 (EOS)[3,4]**
Days	**-14 to -1**	**1**	**30**	**90**	**150**	**180 +5**
Informed consent	X					
Inclusion / Exclusion criteria	X	X				
Demography	X					
Smoking and alcohol history	X					
Medical history/current medical conditions	X					
Prior or concomitant medication[5]	X	X	X	X	X	X
Surgical/medical procedures[5]	X	X	X	X	X	X
Physical Examination	S	S		S		S
Body Height/Weight	X					
Vital Signs[6]	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X
Lifestyle instructions		S	S	S	S	S
Electrocardiogram (ECG)		X				
Follicle stimulating hormone (FSH)	X[7]					

Period	**Screening**	**Baseline**	**Double-Blind Treatment Period[4]**			**Safety Follow-up**
Visit Name	**Screening[1]**	**V1**	**V2[1]**	**V3**	**V4 [2]**	**V5 (EOS)[3,4]**
Days	**-14 to -1**	**1**	**30**	**90**	**150**	**180 +5**
Pregnancy Test (serum)[8]	X					
Pregnancy Test (urine)[9]		X	X	X	X	X
Thyroid stimulating hormone[10]	X					
Fasting Lipid Profile[11]	X	X	X	X	X	
Fasting Lp(a)[12]		X			X	
PCSK9[13]		X	X	X	X	
Clinical Chemistry[10]	X					
Limited Chemistry[10]		X	X		X	X
Hematology[10]		X				X
HbA1c[10]	X					X
Urinalysis[14]	X					X
Coagulation Panel[10]		X				
Enter participant visit in IRT	X	X	X	X	X	X
Randomization		X				
Study drug administration - s.c. inclisiran/placebo		X[15]		X[15]		
Dispense ezetimibe/placebo		S	S	S		

Period	**Screening**	**Baseline**	**Double-Blind Treatment Period[4]**			**Safety Follow-up**
Visit Name	**Screening[1]**	**V1**	**V2[1]**	**V3**	**V4 [2]**	**V5 (EOS)[3,4]**
Days	**-14 to -1**	**1**	**30**	**90**	**150**	**180 +5**
Control drug administration - p.o. ezetimibe/placebo		X[16]	X[16]	X[16]	X[16]	
Ezetimibe/placebo compliance			X[16]	X[16]	X[16]	
Disposition form	X				X[17]	X

X Assessment to be recorded in the clinical database or received electronically from a vendor
1 Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations.
2 Visit 4 is also the EOT visit if the participant completes the study treatment as per protocol.
3 Visit may be performed off-site in certain countries and sites as determined by protocol needs and based on national and local/site regulations or over the telephone if an on-site visit is not possible. During a telephone call, only AEs/SAEs and concomitant medications will be followed.
4 When study treatment is discontinued early, participants should continue with all of their planned study visits and be retained until Day 180. A window of +/- 5 days based on the Day 1 visit date is acceptable for Visit 2 (Day 30), Visit 3 (Day 90), and Visit 4 (Day 150).
5 All medications, procedures, and significant non-drug therapies used by/performed on the participant within 30 days prior to the first visit (Screening visit) and throughout the study must be documented in the appropriate page of the eCRF.
6 Blood pressure and pulse will be taken 3 times in sitting position.
7 Required for any female participant who is considered as surgically sterile or post-menopausal in the absence of medical documentation confirming this reproductive/menopausal status at screening (see Section 8.4.3).
8 Only in women of childbearing potential (see Section 5.2 - Exclusion Criterion #14 and Section 8.4.3). Serum samples will be sent to the central lab for analysis.
9 Only in women of childbearing potential (see Section 5.2- Exclusion Criterion #14 and Section 8.4.3). Performed locally, using central laboratory kit supplies. If urine test is positive, a serum sample will be sent to the central lab for analysis.
10 Performed by the central lab. See Table 8-3.
11 Performed by the central lab. Includes LDL-C, Apo A-1, Apo B, Apo B/Apo A-1 ratio, non-HDL-C, TC, HDL-C, TC/HDL-C ratio, triglycerides.
12 Performed by the central lab.
13 Performed by the central lab. An additional aliquot will be made from the PCSK9 sample in order to allow analysis of proteins related to dyslipidemia or study drug mechanism.
14 Performed locally, using central laboratory kit supplies. If Macroscopic Panel (Dipstick) results are positive (abnormal) for Leukocyte Esterase, Nitrite, Blood, and/or Protein, then a urine sample will be sent to central lab to perform a Macroscopic Panel and a Microscopic Reflexive Panel if positive for Leukocyte Esterase, Nitrite, Blood, Protein. Refer to Table 8-3.
15 Subcutaneous inclisiran/placebo will be administered by qualified healthcare personnel after all other study assessments have been completed for this visit.

Period	Screening	Baseline	Double-Blind Treatment Period[4]			Safety Follow-up
Visit Name	Screening[1]	V1	V2[1]	V3	V4 [2]	V5 (EOS)[3,4]
Days	-14 to -1	1	30	90	150	180 +5

16 Participant to take one capsule ezetimibe/placebo a day starting from Day 1 until the day before the Day 150 visit (see Section 6.3.2).
Compliance will be checked until the visit following the last dose of ezetimibe/placebo.

17 End of Treatment disposition form should be completed prior to Day 150 if the participant discontinues study treatment prior to Day 150.

8.1 Screening

Screening

Screening activities must be initiated only after the ICF has been signed.

If a safety laboratory assessment during the screening period is outside of the range specified in the exclusion criteria, the assessment may be repeated one time prior to randomization. If the repeat value remains outside of the specified ranges, the participant will be considered a screen fail and must be excluded from the study.

It is generally not permissible to re-screen a participant if he/she fails the initial screening. Re-screening is allowed once, if a participant has an initiation, a dose change or a discontinuation of medications that are known to induce lipid and lipoprotein changes (see Section 5.2 - Exclusion Criterion #3) within 30 days prior to screening or post screening but before randomization. Participants may be re-screened after being on a stable dose for 30 days or after treatment discontinuation of such medications for 30 days.

Re-screened participants must provide new written informed consent. A new participant number will be assigned to the re-screened participants and the site must record the re-screening information in the corresponding eCRF and in IRT. All screening procedures will need to be re-performed.

8.1.1 Information to be collected on screening failures

Participants who sign the ICF and are subsequently found to be ineligible at time of randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, and inclusion/exclusion eCRF pages must be completed for screen failure participants. No other data are required to be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening period (see Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail.

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 in the appropriate eCRF page.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the eCRF.

Participant demographic and baseline characteristics collected on all participants include: age, sex, race, ethnicity, vital signs, height, weight, smoking/alcohol history, medical history/current medical conditions present before signing the ICF(where possible, diagnoses and not symptoms should be recorded), and relevant laboratory tests.

Participant race/ethnicity data are collected and analyzed to identify any differences in safety and/or efficacy due to these factors, as well as to assess the diversity of the study population as required by Health Authorities.

All prescription and over-the-counter medications, procedures, and significant non-drug therapies, used by/performed on the participant within 30 days prior to the first visit (Screening visit) and throughout the study must be documented in the appropriate page of the eCRF (see Section 6.2.1).

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

8.3 Efficacy

All efficacy assessments are biomarkers which will be analyzed at a central laboratory. Specimens for efficacy assessments will be collected at time points specified in the Assessment Schedule (Table 8-1). Participants must be in a fasted state for all of these laboratory assessments. Details regarding the collection, processing, shipping and storage of the samples for central laboratory will be provided in a Laboratory Manual.

Starting from the time of the randomization visit (Day 1), the results from all lipid parameter measurements must be blinded to participants, investigator staff, persons performing the assessments, the monitors, and the Novartis Clinical Trial Team (CTT) until database lock.

8.3.1 LDL-C

The primary efficacy assessment will be LDL-C, as tested and reported by the central laboratory as part of the Lipid Panel at the frequency shown in Table 8-1. Participants must be fasting for all LDL-C assessments.

8.3.2 Additional efficacy assessments

Additional efficacy assessments will include non-HDL-C, HDL-C, TC, TC/HDL-C ratio, Apo A-1, Apo B, Apo B/Apo A-1 ratio, Lipoprotein A (Lp(a), and PCSK9. Lipid parameters, Lp(a) and PCSK9 will be tested and reported by the central laboratory at the frequency shown in Table 8-1. Participants must be fasting for all lipid and lipoprotein testing.

8.3.3 Appropriateness of efficacy assessments

Inclisiran is a siRNA which acts to inhibit the synthesis of PCSK9 protein, which consequently reduces LDL-C in circulation. LDL-C is a well-defined and validated laboratory parameter and is routinely assessed in clinical trials. LDL-C reduction is an accepted surrogate for CV risk reduction, e.g., for statins and PCSK9- blocking monoclonal antibodies. While multiple factors contributing to the development of ASCVD have been described, strong and consistent evidence from genetics, epidemiology, Mendelian randomization studies, and randomized trials have established that LDL-C is not only a laboratory parameter of increased risk, but also a causal and modifiable factor in ASCVD (Mach et al 2020). Laboratory tests related to the primary and secondary endpoints are in line with the expected efficacy of inclisiran.

8.4 Safety

Safety assessments are specified below, with the Assessment Schedule (Table 8-1) detailing when each assessment is performed.

For details on AE collection and reporting, refer to AE section (Section 10.1).

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Safety assessments

Assessment	Specification
Physical examination	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 AE.
Vital signs	Vital signs include blood pressure (BP) 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 and pulse will be measured three times using an automated validated device 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.
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.

8.4.1 Laboratory evaluations

Specimens will be obtained at the time points detailed in the Assessment Schedule (Table 8-1). Details on what is included in chemistry (full and limited panels), hematology, coagulation, thyroid stimulating hormone, and urinalysis laboratory evaluations as well as pregnancy testing and FSH are provided in Table 8-3.

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF. Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

In addition to Table 8-3, see Section 6.6.3.1 for follow-up on potential DILI cases, Section 10.2.1 for liver safety monitoring, and Section 16.2 for specific liver event and

laboratory test trigger definitions and follow-up requirements and Section 10.2.2 for renal safety monitoring.

Central laboratory will be used for analysis of all specimens collected, with the exception of urine pregnancy tests and manual dipstick urinalysis, 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.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-3 Safety Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), MCV, Platelets, Erythrocytes, Leukocytes, Differential (% of Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
HbA1c	HbA1c
Chemistry (full panel)	AST, ALT, ALP, GGT, TBL, Direct Bilirubin, Indirect Bilirubin, Albumin, Creatinine, eGFR, Blood Urea Nitrogen (BUN), Uric Acid, Fasting Plasma Glucose (FPG), CK, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium
Chemistry (limited panel)	AST, ALT, ALP, GGT, TBL, Creatinine, eGFR, FPG, CK
Urinalysis	Macroscopic Panel (Dipstick): Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen. If dipstick results are positive (abnormal) for Leukocyte Esterase, Nitrite, Blood, and/or Protein, then a urine sample will be sent to the central lab to perform a Macroscopic Panel and a Microscopic Reflexive Panel if there are positive results for Leukocyte Esterase, Nitrite, Blood, and/or Protein. Microscopic Panel: Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells.
Coagulation	PT, INR, Activated partial thromboplastin time (APTT)
Thyroid Function	Thyroid Stimulating Hormone
Pregnancy Test	Serum and Urine Pregnancy (see Section 8.4.3) A confirmatory serum pregnancy test is required in case of a positive urine pregnancy test.
Follicle Stimulating Hormone	FSH (see Section 8.4.3) Required for any female participant considered surgically sterile or post-menopausal in the absence of medical documentation confirming this reproductive/menopausal status at screening.
Liver Event Testing and Liver Follow-up Testing	Albumin, ALP, ALT, AST, CK, GGT, GLDH, INR, PT, and Total Bilirubin (TBL). Test for hemolysis (haptoglobin, reticulocytes, unconjugated [indirect] bilirubin). These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 6.6.3.1, Section 10.2.1 and Section 16.2.
Renal Follow-up	Urine protein for Protein:Creatinine ratio (PCR), Serum Creatinine. Repeat standard urinalysis. Macroscopic Panel (Dipstick) Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen. If dipstick results are positive (abnormal), for Leukecyte Esterase, Nitrite, Blood and/or Protein, then a urine sample will be sent to the central lab to perform a Macroscopic Macroscopic Panel and a Microscopic Reflexive Panel if there are positive results for

Test Category	Test Name
	Leukocyte Esterase, Nitrite, Blood, and/or Protein. Microscopic Panel: Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells. These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.2.2.

8.4.2 Electrocardiogram (ECG)

Single 12 lead ECGs will be conducted using 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.

ECGs will be locally collected and evaluated. Interpretation of the baseline tracing must be made by a qualified physician and documented on the ECG CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site.

The QT interval corrected by Fridericia's formula (QTcF) should be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine. Clinically significant abnormalities at baseline should be reported on the adverse events eCRF.

Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events. 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.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test performed at the screening visit, and urine pregnancy tests at all other study visits. If a urine pregnancy test is positive, then a serum pregnancy test will be performed.

Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following case:

- Surgical bilateral oophorectomy without a hysterectomy.

In the absence of the above medical documentation (confirming that participant is either surgically sterile or post-menopausal, see Section 5.2 - Exclusion Criterion #14 for additional information), FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Trial Feedback Questionnaire

By participating in the clinical trial, participants may be contacted for feedback about their trial experience, as appropriate and in adherence to local regulations and guidelines. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process. The feedback asks questions about trial experience. It does not ask questions about the trial participant's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data.

[redacted]

8.5.3 Lifestyle instructions

Investigators will instruct their participants from the randomization visit through the Day 180 visit that the most important way to prevent ASCVD is to promote a healthy lifestyle throughout life. Prevention strategies must include a strong focus on lifestyle optimization (improvements in diet, physical activity, and avoidance of tobacco use and exposure to secondhand smoke) to minimize the risk of future ASCVD events (Arnett et al 2019).

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug or control drug administration, if any) and can be initiated by either the participant or the investigator. If the participant permanently discontinues p.o. ezetimibe/placebo or s.c. inclisiran/placebo, then the participant's entire study treatment must be stopped. The treatment disposition CRF will be completed to reflect that the participant has permanently discontinued study treatment (both p.o. study drug and s.c. study drug).

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited medication Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant
- Severe and persistent (> 14 days despite appropriate treatment) reactions at the injection site and any type of anaphylactic reactions
- Intolerable adverse events
- Unexplained increases in transaminases (ALT or AST) or total bilirubin confirmed by repeat test as follows:
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for more than 2 weeks
  - ALT or AST > 3 x ULN with simultaneous or subsequent elevation of total bilirubin > 2 x ULN
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

  The investigator should evaluate to see if other causes for the laboratory abnormalities are immediately apparent, such as obstructive gall bladder or bile duct disease, viral or alcoholic hepatitis, malignancy involving the liver, congestive hepatopathy, other hepatotoxins or heritable disorders. Please also refer to Section 16.2 Appendix 2.
- Unexplained CK > 10 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 with no other alternative explanation
- Following emergency unblinding

- Any other laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study

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

Participants who discontinue from study treatment should continue with planned study visits and be retained until Day 180 as indicated in the Assessment Schedule. Refer to Table 8-1 Assessment 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 discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- AEs / SAEs

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 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participant's data privacy rights), 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.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data , and

- No longer wishes to receive study treatment, and
- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definition of these terms.

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 their consent exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participant's data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure or follow-up shown in Table 8-1 Visit Evaluation Schedule for the last participant in the study globally.

Study completion is defined as when the last participant finishes their last study 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 (e.g., each participant will be required to complete the study in its entirety and, thereafter, no further study treatment will be made available to them).

All randomized and/or treated participants should have a safety follow-up call or the EOS visit conducted at least 30 days after the Day 150 visit. The information collected is entered on the EOS eCRFs and/or kept as source documentation, as applicable. 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.

Depending on the availability of inclisiran in the investigator's country, the decision to switch a participant to a commercially available inclisiran product or to one of the locally available standard of care treatments after EOS will be left to the investigator's clinical judgment.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include (but are not limited to) the following:

- 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 participant who discontinued from study treatment: at that time additional instructions will be provided for contacting the participant including information as to when the participant should stop taking drug, when the participant should come in for a final visit(s) that the Safety Follow-up period must be completed if applicable and which visits to be performed. 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.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An 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. Adverse events specified above 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.

The 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 investigational study drug (inclisiran/placebo) or comparator (ezetimibe/placebo). 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 ongoing) and the outcome 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 investigational study drug (inclisiran/placebo) or comparator (ezetimibe/placebo). All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Drug interrupted (applicable for p.o. ezetimibe/placebo only)
   - Permanently discontinued

- Its outcome, which can be:
  - Not recovered / not resolved
  - Recovered / resolved
  - Recovering / resolving
  - Recovered / resolved with sequelae
  - Fatal
  - 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.

AE monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (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 ADRs for the investigational study drug (inclisiran) can be found in the IB. Information about ADRs for the comparator (ezetimibe) can be found in the Package Insert.

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.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

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 Guideline 2004).

- 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 (primary hypercholesterolemia)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study 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 Guideline 2004).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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 a SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form (electronic SAE (eSAE) form with paper backup); all applicable sections of the form must be completed in order to provide a clinically thorough report.

The following categories of SAEs must be reported:

1. 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. SAEs collected between time participant signs ICF until the participant has completed the End of Study Visit

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 immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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 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, EU Clinical Trial Regulation 536/2014 (if applicable) or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the 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 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.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

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 eCRF (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 16-1 in Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 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 16-2 and Table 16-3 (Section 16.2). Repeat liver chemistry tests (i.e., ALT, AST, TBL, albumin, CK, GLDH, 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 (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, either of the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline and value above ULN 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, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed with repeat test done at central lab after ≥ 24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff.

10.3 Committees

There are no committees for this trial.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (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 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 contract research organization (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 (ACT) classification system. Medical history/current medical conditions and AEs 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 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/moved to restricted area to be accessed by independent programmer and statistician. 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., 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 GCP, 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 and identify risks and 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 eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original ICF 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 eCRFs 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

12.1 Analysis sets

The following analysis sets will be used for statistical analyses:

The screened set (SCR) consists of all participants who signed the informed consent. The SCR includes only unique screened participants, i.e., in the case of re-screened participants only the chronologically last screening data is counted.

The Randomized Analysis Set (RAS) consists of all participants who received a randomization number, regardless of receiving trial medication.

The Full Analysis Set (FAS) comprises all randomized participants with the exception of those participants who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat (ITT) principle, participants will be analyzed according to the treatment they have been assigned to at randomization. Efficacy variables will be analyzed based on the FAS.

The Safety Analysis Set (SAF) includes all participants who received at least one dose of study drug. Participants will be analyzed according to the study treatment actually received. The SAF will be used for the analyses of safety variables.

Note: The last part of the definition of the FAS is what is often referred to as misrandomized participants; i.e. participants for whom IRT calls were made by the site either prematurely or inappropriately prior to confirmation of the participant's final randomization eligibility and double-blind medication was not administered to the participant. These participants would subsequently not continue to take part in the study or be followed-up. Misrandomized participants will not be included in the FAS, but they will be included in the RAS. Further exclusions from the FAS may only be justified in exceptional circumstances (e.g., serious GCP violations).

12.2 Participant demographics and other baseline characteristics

The number of participants screened, randomized and included in the FAS will be presented by treatment group and overall, for the SCR. In addition, the reasons for discontinuation prior to randomization will be provided for the SCR as well. The number and percentage of participants in the RAS who completed the study, who discontinued the study and the reason for discontinuation from study will be presented for each treatment group and all participants. The frequency (%) of participants with protocol deviations as well as the criteria leading to data exclusion from analysis will be presented in separate tables for the RAS. Finally, the number of enrolled and randomized participants by region will be presented descriptively for the RAS.

Baseline value is defined as the last non-missing assessment prior to the first dose of study drug unless specified otherwise.

Demographic and other baseline data will be summarized descriptively by treatment group for the FAS. Categorical data will be presented as frequencies and percentages. Continuous variables will be summarized using n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum, and maximum.

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

Other study specific medical history will also be summarized appropriately.

12.3 Treatments

The SAF will be used for the analyses in this section. Categorical data will be summarized as frequencies and percentages. For continuous data, number of non-missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Study drug

The duration of the double-blind treatment will be computed as the time from the first administration of study drug to the first of the following events to occur:

- the last administration plus 180 days for inclisiran or plus 1 day for ezetimibe and placebo,
- the participant's death, or
- the participant's study completion visit or last contact.

This algorithm reflects the planned treatment schedule and the exposure attributable period of the study drug. The duration of the double-blind treatment period will be summarized for the SAF by treatment group descriptively. The overall participant years of treatment will be computed as the sum of participant years of double-blind treatment for all participants.

The number of study doses administered will also be summarized by treatment group.

Prior and concomitant therapies

Prior or concomitant medications will be summarized for the SAF in separate tabulations based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms and grouped by anatomical main group, according to the ATC classification system. Tables will show the overall number and percent of participants receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used during the double-blind period. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

12.4 Analysis supporting primary objectives

The primary aim of the study is to demonstrate the superiority of inclisiran to either placebo or ezetimibe in reducing LDL-C.

The FAS will be used for the primary efficacy analysis.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the percentage change from baseline to Day 150 in LDL-C.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary objectives are to demonstrate the superiority of inclisiran as monotherapy compared to the use of placebo or ezetimibe separately, in reducing LDL-C as measured by percentage change from baseline to Day 150. To this end, the Monotherapy Estimand assesses the treatment effect of inclisiran alone in the absence of confounding factors such as additional LLT.

As described in Section 2.1, in addition to the primary Monotherapy Estimand, the Treatment-policy Estimand was added for regulatory purposes. Both estimands will be considered in parallel as primary analysis.

The primary statistical hypotheses to be tested are:

- H_{IP0}: $\mu_i - \mu_p \geq 0$ vs. H_{IPa}: $\mu_i - \mu_p < 0$
- H_{IE0}: $\mu_i - \mu_e \geq 0$ vs. H_{IEa}: $\mu_i - \mu_e < 0$

where μ_i, μ_p and μ_e are the mean percentage changes in LDL-C from baseline to Day 150 in the inclisiran group, placebo group, and ezetimibe group respectively. The study can be claimed a success if at least one of the above two individual hypotheses is rejected.

The primary efficacy endpoint will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment, stratification factor, and baseline value as fixed effects. Due to probable heterogeneity of variances between treatment groups, an ANCOVA model that assumes unequal variances between treatment groups will be used. The two primary endpoint hypotheses will be tested using an equally weighted Dunnett test (Dunnett 1955).

The multiple comparison procedure (MCP) will be used in statistical hypothesis testing for primary and secondary endpoints to control the overall type I error rate at 0.025 (one-sided test). For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy Estimand will be defined in a similar way as for the primary endpoint, and the MCP will be applied to Monotherapy Estimands and Treatment-policy Estimands separately, to control the overall type I error rate within each set of estimands. Since the Treatment-policy Estimands are intended for regulatory purposes, while the Monotherapy Estimands are intended for all other purposes, no multiplicity adjustment will be made across those two sets of estimands. The testing procedure to be followed is graphically presented in Figure 12-1, and outlined in the following steps:

- First, a weighted Dunnett test with equal weights assigned to each of the two individual primary hypotheses (H_{IP0} and H_{IE0}) is performed. This test will exploit the correlation of the primary endpoint between the two comparisons, with the test statistics derived from the ANCOVA model described as above.
- If one primary hypothesis is rejected, a fraction of its significance level will be passed to the other primary hypothesis while the remaining alpha will be propagated to the family of secondary hypotheses under the same treatment comparison, according to the pre-specified weights as indicated in the graph. The choice of weights for passing alpha to the other primary hypothesis (0.4 and 0.6 respectively) reflects the importance of demonstrating efficacy in the comparison between inclisiran and placebo.
- Within a family of secondary hypotheses (H_{IPk} or H_{IEk}), the hierarchical testing procedure will be used. Refer to Section 12.5.1 for details.

- If one secondary hypothesis in the comparison between inclisiran and placebo H_{IPk} is rejected, a fraction of its significance level will be passed to the next hierarchy of secondary hypotheses under the same treatment comparison, while the remaining alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. If there is no next hierarchy of secondary hypotheses, then the whole alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. Vice versa for the alpha passing from H_{IEk}.

The nodes H_{IP} and H_{IPk} represent the null hypotheses related to the primary and secondary endpoints compared between inclisiran and placebo, while the nodes H_{IE} and H_{IEk} represent the null hypotheses related to the primary and secondary endpoints compared between inclisiran and ezetimibe. The correlations between endpoints and between the two comparisons for each endpoint will also be considered.

The least squares means for the difference between inclisiran and two comparators and corresponding unadjusted two-sided confidence intervals (CI) will be provided separately. The raw p-value for testing the individual hypothesis will also be provided. The superiority of inclisiran to a comparator can be claimed when the corresponding individual null hypothesis is rejected or the raw p-value is statistically significant at corresponding alpha level of current stage.

12.4.3 Handling of intercurrent events of primary estimands

The Monotherapy Estimand will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment:** Discontinuation of study treatments will be treated in a hypothetical scenario of what would happen if the participants had not discontinued study treatments (hypothetical strategy).
- **Death:** Participants who die will be treated in a hypothetical scenario of what would happen if participants had not died (hypothetical strategy).
- **Use of lipid-lowering therapy:** Use of LLT will be treated in a hypothetical scenario of what would happen if other LLT were not available (hypothetical strategy).

The efficacy endpoints after the intercurrent events will be multiply imputed under the missing-at-random assumption.

The Treatment-policy Estimand will account for intercurrent events as follows:

- **Discontinuation of study treatment:** Retrieved dropout (RDO) data collected after discontinuation from study treatments will be used for the analysis (treatment-policy strategy). Missing data after discontinuation from study treatments will be multiply imputed based on RDO data, and when there are no sufficient RDO data, a placebo-based Pattern-Mixture Model (PMM) will be used for multiple imputation.
- **Death:** A composite variable strategy will be utilized to handle the intercurrent event of death, and efficacy parameter measurements after death will be imputed using the subject's baseline values.

- **Use of lipid-lowering therapy:** The data collected after use of other LLTs will be used for analyses (treatment-policy strategy). Missing data will be multiply imputed using a placebo-based PMM.

The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's method (Rubin 1987).

The details will be in the statistical analysis plan (SAP).

12.4.4 Handling of missing values not related to intercurrent event

In the Monotherapy Estimand, missing values not related to intercurrent events will be multiply imputed under the missing-at-random assumption. In the Treatment-policy Estimand, missing values not related to intercurrent events will be multiply imputed using a placebo-based PMM. The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's method (Rubin 1987). Details will be given in the SAP.

12.4.5 Sensitivity analyses

Sensitivity analyses such as tipping point analyses will be conducted to assess the robustness of the inferences to various assumptions about the missing data, and details will be provided in the SAP.

12.4.6 Supplementary analysis

If necessary, supplementary analyses will be conducted and described in the SAP.

Subgroup analyses

Subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline characteristics may be performed. All subgroup analyses will be defined in the SAP prior to database lock.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

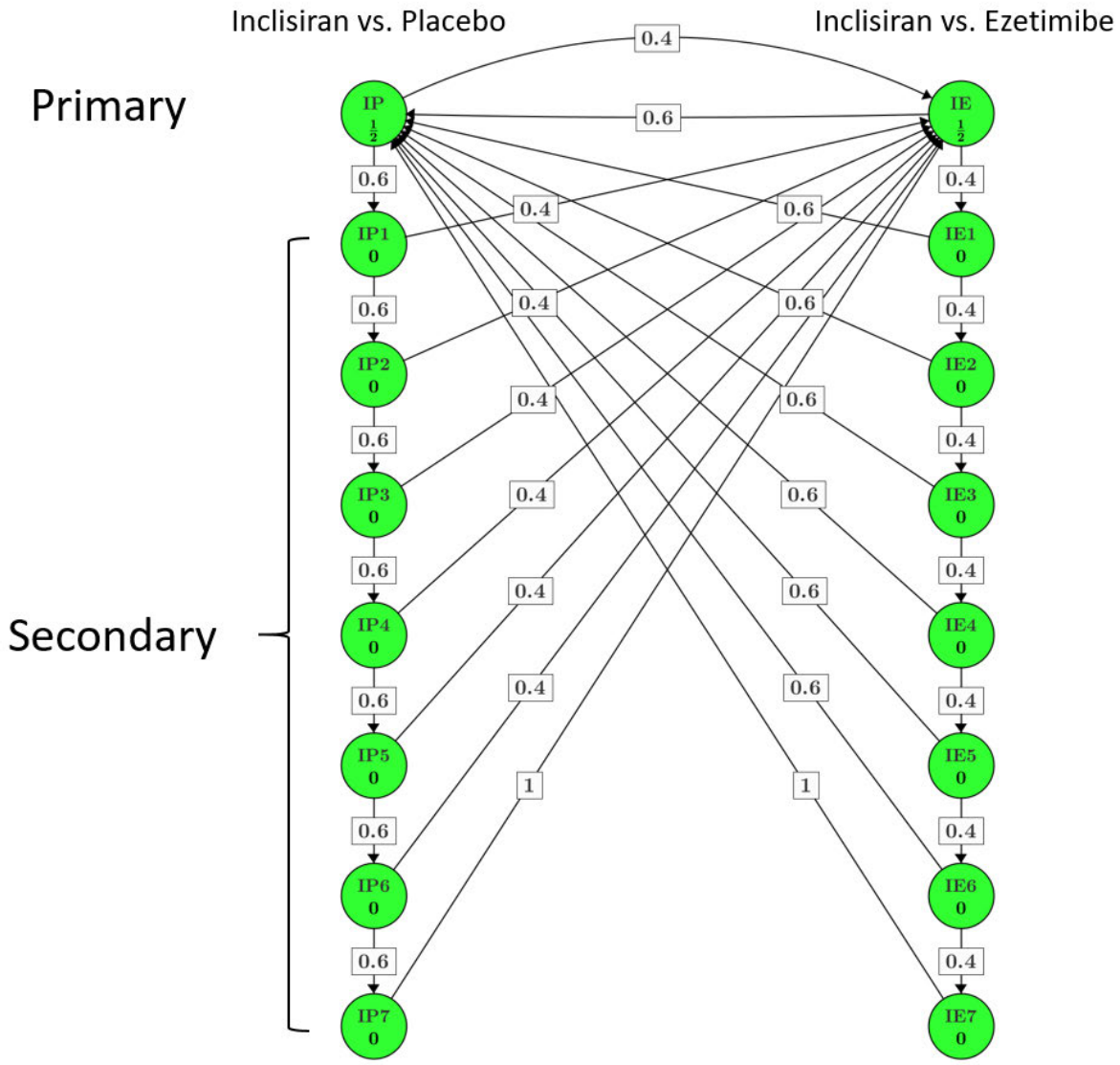
There are seven secondary efficacy endpoints defined, and fourteen secondary hypotheses to be tested for these seven secondary endpoints in the comparison between inclisiran and each comparator (placebo or ezetimibe) respectively:

1. Percentage change in PCSK9 from baseline to Day 150
2. Absolute change in LDL-C from baseline to Day 150
3. Percentage change in non-HDL-C from baseline to Day 150
4. Percentage change in TC/HDL-C ratio from baseline to Day 150
5. Percentage change in Apo B from baseline to Day 150
6. Percentage change in Apo B/Apo A-1 ratio from baseline to Day 150
7. Percentage change in Lp (a) from baseline to Day 150

For each of the secondary efficacy endpoints, the Treatment-policy Estimand and the Monotherapy Estimand will be defined in a similar way as for the primary endpoint. All secondary efficacy endpoints will be analyzed on FAS using the same ANCOVA model as for the primary efficacy endpoint as described in Section 12.4.2. Lipoprotein (a) will be log-transformed before modeling. The model will include treatment, stratification factor, and baseline value as fixed effects, and assume unequal variances between treatment groups. The least squares means for the difference between inclisiran and two comparators and corresponding unadjusted two-sided CIs will be provided separately.

As stated in Section 12.4.2, the two families of secondary hypotheses H_{IPk} and H_{IEk} (k = 1, 2, ..., 7, following the order of the seven secondary endpoints as above) are included in the multiple testing procedure as presented in Figure 12-1. The hierarchical testing procedure will be used to test the seven secondary hypotheses within each family of the secondary endpoints (H_{IPk} or H_{IEk}). If one secondary hypothesis in the comparison between inclisiran and placebo H_{IPk} is rejected, a fraction of its significance level will be passed to the next hierarchy of secondary hypotheses under the same treatment comparison, while the remaining alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe, according to the pre-specified weights as indicated in the graph. If there is no next hierarchy of secondary hypotheses, then the whole alpha will be propagated to the primary hypothesis comparing inclisiran and ezetimibe. Vice versa for the alpha passing from H_{IEk}.

Figure 12-1 Testing procedure for primary and secondary endpoints



The intercurrent events and missing values will be handled following the same approach as described for the primary endpoints. Details of the analyses for secondary efficacy endpoints and sensitivity analyses if necessary will be specified in the SAP.

12.5.2 Safety endpoints

For all safety analyses, the SAF will be used. All tables and listings will be presented by treatment group.

Safety data will be summarized by treatment groups. Baseline data will be summarized where appropriate (for change from baseline summaries).

Adverse events

The number (and percentage) of participants with AEs and SAEs collected in the study as defined in Section 10.1.1 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 and preferred term.

Separate summaries by treatment, primary system organ class and preferred term will be provided for death.

A participant with multiple AEs within a primary system organ class will be only counted once towards the total of the primary system organ class.

Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit. Shift tables using the low, normal, or high classification will be used to compare baseline to the worst on-treatment value by treatment group. The number (and percentage) of participants meeting clinically significant criteria will be provided by treatment group.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

[redacted]

12.7 Interim analyses

No formal interim analysis will be performed in this study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation was based on a two sample t-test for the hypothesis that inclisiran is superior to either placebo or ezetimibe in terms of mean percentage change from baseline to Day 150 in LDL-C, at a one-sided significance level of 0.0125 (assuming a more conservative Bonferroni alpha split between the two primary hypotheses).

The sample size of 280 completers in total (with randomization ratio of 2:1:1 to inclisiran, placebo, and ezetimibe arms) will provide at least 99% power to detect a 40% difference between inclisiran and placebo or a 20% difference between inclisiran and ezetimibe at significance level of 0.0125 (one-sided test) assuming 30% for the standard deviation. Adjusted for 6% potential dropouts, approximately 300 participants in total will be randomized with a 2:1:1 ratio, i.e., 150 participants in the inclisiran arm, and 75 participants in both the placebo and ezetimibe arm.

12.8.2 Secondary endpoint(s)

Statistical power will not be assessed for secondary endpoints.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

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 or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The Investigator will be responsible for the following:

Signing 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.

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

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 European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) or EMA's Clinical Trials Information System (CTIS) public website. In addition, after study completion (defined as last patient 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 or CTIS public website 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.

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

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

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.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication
- Trial Feedback Questionnaires (TFQ) - start and end of trial

13.6 Data Protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

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

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Section 16.2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

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

Table 16-1 Liver laboratory trigger definitions

Liver laboratory triggers	Definition/ threshold
If ALT, AST and TBL normal at baseline:	● ALT or AST > 3.0 × ULN ● TBL > 1.5 × ULN ● ALP > 2.0 × ULN (in the absence of known bone pathology)
If ALT, AST, or TBL abnormal at baseline:	● ALT or AST > 2 x baseline or > 300 U/L, whichever occurs first ● TBL > 2 x baseline and > 2.0 x ULN

Table 16-2 Follow-up requirements for liver laboratory triggers - ALT, AST, TBL

ALT or AST	TBL	Liver Symptoms	Action
ALT or AST increase without TBL increase:			
If normal at baseline: ALT or AST > 3.0 x ULN **If elevated at baseline:** ALT or AST > 2 x baseline	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBL, PT/INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If normal at baseline: ALT or AST > 5.0 x ULN for more than two weeks **If elevated at baseline:** ALT or AST > 3 x baseline for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** • Measure ALT, AST, ALP, GGT, TBL, PT/INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline. • If no cause can be identified to explain the elevation in liver enzymes, then study treatment must be discontinued.
If normal at baseline: ALT or AST > 8.0 x ULN	Normal	None	
ALT or AST increase with TBL increase:			
If normal at baseline: ALT or AST > 3.0 x ULN **If elevated at baseline:** ALT or AST > 2 x baseline	TBL > 2.0 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT or AST > 3.0 x ULN **If elevated at baseline:** ALT or AST > 2 x baseline	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-3 Follow-up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia or elevated ALP

Criteria	Actions required	Follow-up monitoring
Elevated TBL (isolated)		
> 1.5 – 3.0 x ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 (≤ 1.5 x ULN) or to baseline
> 3.0 - 10.0 x 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. concomitant medications, medical history, lab) in the appropriate eCRF	Monitor LFTs weekly until resolution to ≤ Grade 1 (≤ 1.5 x ULN) or to baseline (ALT, AST, TBL, albumin, CK, GLDH, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10.0 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g. concomitant medications, medical history, lab) in the appropriate eCRF	ALT, AST, TBL, albumin, CK, GLDH, PT/INR, ALP and GGT until resolution (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., concomitant medications, medical history, lab) in the appropriate eCRF	Investigator discretion
Elevated ALP (isolated)		
> 2.0 x ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

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: Specific Renal Alert Criteria and Actions and Event Follow-up

Refer to Section 10.2.2.