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Novartis Research and Development

KJX839

Clinical Trial Protocol CKJX839A12402 / NCT05192941

Efficacy, safety, tolerability and quality of life of ongoing individually optimized lipid-lowering therapy with or without inclisiran (KJX839) – a randomized, placebo-controlled, double-blind multicenter phase IV study in participants with hypercholesterolemia

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List of abbreviations

ABI	Ankle-brachial index
ACL	adenosine triphosphate citrate lyase
ACS	Acute coronary syndromes
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Angina Pectoris
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate Aminotransferase
AxMP	Auxiliary Medicinal Product
CCS	chronic coronary syndromes
CHD	Coronary Heart Disease
CK	Creatine Kinase
cm	Centimeter
CMH	Cochrane-Mantel-Haenszel test
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTT	Clinical Trial Team
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DDE	Direct data entry
DILI	Drug-Induced Liver Injury
dL	Deciliter
DLT	Dose Limiting Toxicity
DM	Diabetes Mellitus
EAS	European Atherosclerosis Society
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
ESC	European Society of Cardiology
eSource	Electronic Source
ESS	Eligible screened set
EU	European Union
FAS	Full analysis set
FPG	Fasting plasma glucose
GCP	Good Clinical Practice

GGT	Gamma-glutamyl transferase
GSRS	Gastrointestinal Symptom Rating Scale
h	Hour
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
HRQoL	Health-Related Quality of Life
HTA	Heath technology assessment
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
IMNM	Immune-mediated necrotizing myopathy
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
kg	Kilogram
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LFT	Liver function test
LLT	Lipid-Lowering Therapy
mAb	monoclonal Antibody
MACE	Major adverse cardiovascular event
MALE	Major adverse limb event
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCS	Mental Component Score
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial infarction
Min	Minimum
mL	milliliter(s)
mmol	Millimoles
MMRM	mixed model for repeated measures
mRNA	messenger RNA
MTD	Maximum Tolerated Dose
NYHA	New York Heart Association
OHP	Off-site healthcare professional
PAD	Peripheral Arterial Disease
PCS	Physical Component Score
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PRO	Patient Reported Outcomes

PTA	Post-trial access
PV & PS	Pharmacovigilance and Pharma Safety
QLMI	Quality of Life after Myocardial Infarction
QMS	Quality Management System
RAN	Randomized set
RBC	Red blood cells
RD	Recommended Dose
RDO	Retrieved Drop Out Data
RIS	Run-in set
RISCs	RNA-induced silencing complexes
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
sCr	serum Creatinine
SCORE2	Systemic Coronary Risk Estimation 2
SCORE2-OP	Systemic Coronary Risk Estimation 2-Older Persons
SF-36	Short form health survey
SF-BPI	Short-form Brief Pain Inventory
siRNA	Small interfering RNA
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TFQ	Trial feedback questionnaire
TIA	Transient Ischaemic Attack
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
UNS	Unscheduled
US	United State
WBC	White blood cells
WHO	World Health Organization
WIQ	Walking impairment questionnaire
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 (IMP) (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
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.
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.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and eCRFs into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Estimand	As defined in the 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.
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 trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in 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).
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease.
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" 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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.
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.
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment).
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
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) / Opposition to use of data /biological samples	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. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 3 (02-Sep-2024)

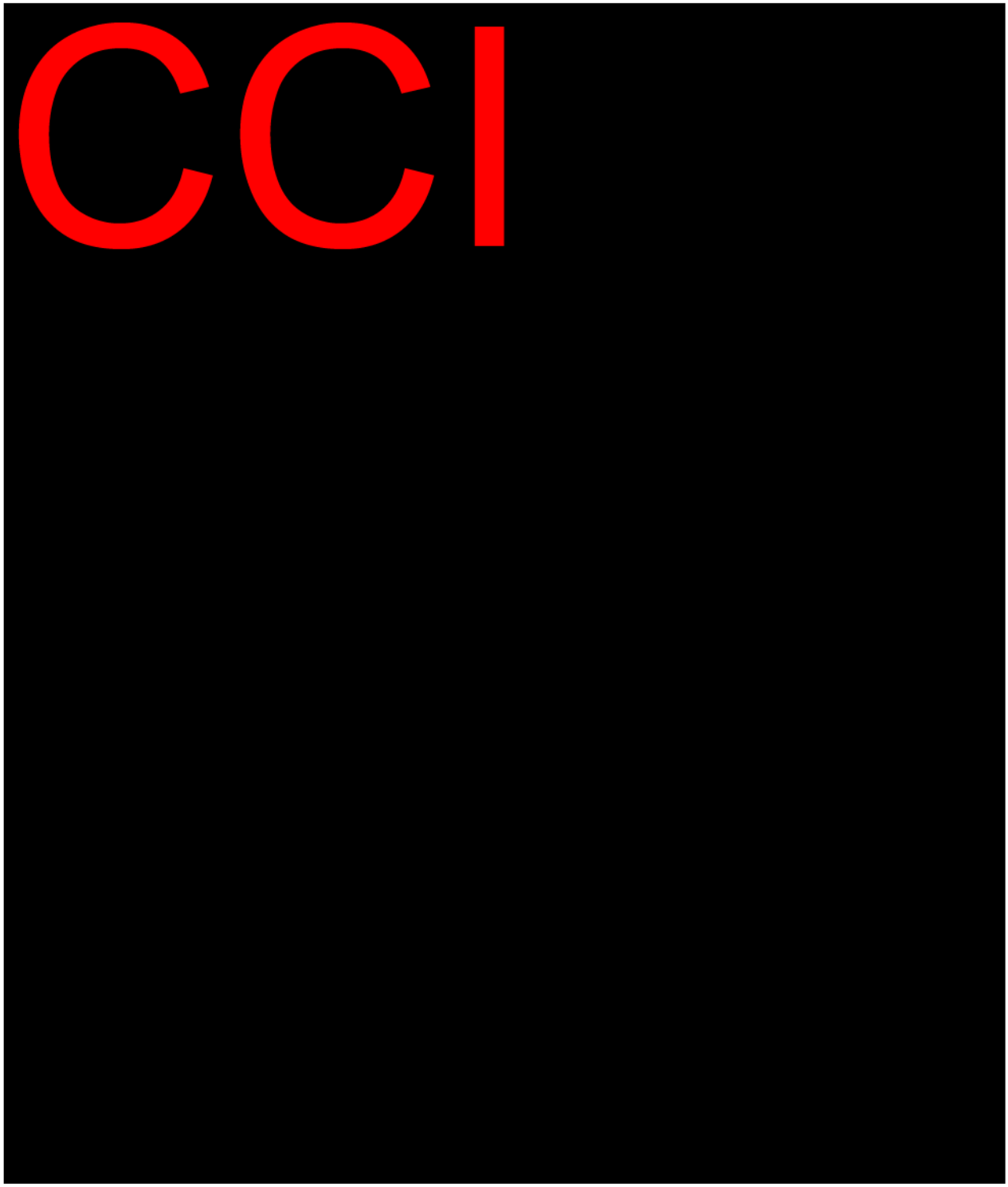
Amendment rationale

The purpose of this amendment is primarily to align the protocol with the current practice of issuing protocol deviations (PDs) for non-compliance with questionnaires that contribute to the secondary endpoints. In addition, as this study will have to adhere to EU-CTR standards, changes have been made across the protocol to fulfil key EU-CTR requirements.

Other minor points of clarification and alignment, editorial changes were made.

The amendment is being developed after the release of the protocol amendment version 02 which is already approved by the Health Authorities (HA) and Independent Ethics Committees (IEC) in all the 8 allocated study countries and has transitioned to EU-CTR. The study achieved Last Participant First treatment on 26-Feb-2024 with 1776 randomized participants. On 2-Sep-2024, 1391 participants had completed treatment.

Changes to the protocol


CCI

IRBs/IECs

The changes described in this amended protocol are non-substantial.

The changes herein are aligned to the trial specific model ICF.

Amendment 2 (01-Nov-2022)

Amendment rationale

The purpose of this amendment is to remove of mmol/L unit from inclusion criteria to be consistent with related endpoint, update the study discontinuation language, clarify starting dose for Rosuvastatin at Day 1, align with current approval status of inclisiran over the world, correct some timepoint in the schedule of assessment.

Other minor point of clarification and alignment, editorial changes were made.

The amendment is being developed after the release of the protocol amendment version 01 which is already approved by the Health Authorities (HA) and Independent Ethics Committees (IEC) in all the 8 allocated study countries.

Changes to the protocol

IRBs/IECs

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

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

The changes herein are aligned in the trial specific model ICF.

Amendment 1 (11-Nov-2021)

Amendment rationale

The purpose of this amendment is to update serious adverse event (SAE) reporting language to include stricter requirements for the reporting of SAEs, if required by local regulations. Additionally, warnings, precautions, follow-up for toxicities and prohibited medications were added for the study treatment, rosuvastatin. Other minor, editorial changes were made.

The amendment is being developed after the release of the original protocol version 00 but prior to the submission to Health Authorities (HA) and Independent Ethics Committees (IEC). Hence, Protocol Amendment Version 01 will be the first protocol submitted and implemented at all trial sites.

Changes to the protocol

IRBs/IECs

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

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

The changes herein are aligned in the trial specific model ICF.

Protocol summary

Protocol number	**CKJX839A12402**
Full Title	Efficacy, safety, tolerability and quality of life of ongoing individually optimized lipid-lowering therapy with or without inclisiran (KJX839) – a randomized, placebo-controlled, double-blind multicenter phase IV study in participants with hypercholesterolemia.
Brief title	Study of efficacy, safety, tolerability and quality of life of inclisiran (KJX839) vs placebo, on top of ongoing individually optimized lipid-lowering therapy, in participants with hypercholesterolemia.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this study is to demonstrate the superiority of inclisiran compared to placebo, both on top of ongoing individually optimized lipid-lowering therapy (LLT), on reaching a participant's LDL-C target (< 55 mg/dL or < 70 mg/dL, depending on the cardiovascular risk category, according to the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) as well as on patient-relevant safety, tolerability outcomes and quality of life.
Primary Objective(s)	The primary objective of this study is to demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on reaching a participant's individual LDL-C target as measured by the proportion of participants achieving individual LDL-C target (< 55mg/dL or < 70 mg/dL) at day 90.
Secondary Objectives	The secondary objectives of this study are to demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on: • Reducing mean LDL-C levels over the double-blind study period, as measured by the relative change (percentage from baseline to mean LDL-C level). • Muscle-related adverse events, as measured by the proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360. • Annualized number of days pain is experienced, as measured by the proportion of participants experiencing self-reported pain from baseline to day 360, using a pain diary. • Pain-related quality of life at day 360 using the Short-Form Brief Pain Inventory (SF-BPI) as measured by the change in the SF-BPI pain severity and interference scores from baseline to day 360 and the proportion of participants with clinically relevant change in SF-BPI pain severity and interference scores from baseline to day 360.
Study design	This study is a double-blind, placebo-controlled multicenter study in adult participants with very high or high cardiovascular risk (as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) who do not meet their individual LDL-C target despite being treated with their individual maximum tolerated dose (MTD) of a statin, and if applicable, further LLT. LDL-C target will be evaluated according to most recent assessment of cardiovascular risk category as determined by the investigator. This includes assessment of cardiovascular events and new-onset or worsening of cardiovascular risk factors as defined in the current guidelines throughout the trial. This is a treatment strategy study where the participants are both randomized to inclisiran versus placebo and also simultaneously switched to rosuvastatin, and then have their LLT individually optimized by investigators resulting in likely less intense LLT in the inclisiran arm and CCI [redacted] in the placebo arm. The study consists of:

	• A Screening period of approximately14 days for all participants. • An optional Run-in period of up to 120 days as individually applicable for statin or other LLT up titration. • An optional additional baseline period of approximately 10 days as individually applicable for required labs • A Treatment period of 360 days (excluding a safety follow-up call 30 days after the end of study (EOS) visit). All participants, who fulfill the inclusion/exclusion criteria, will be randomized at Day 1 (treatment period) in a 1:1 double-blind fashion to either inclisiran or placebo. In addition, at Day 1 all participants will be switched from their individual statin to rosuvastatin, which is considered open label study treatment in this trial. As per local SmPC, the recommended start dose for rosuvastatin at baseline is 5 mg/day or 10 mg/day. If a participant's LDL-C is not at target at day 30 and at the following visits, based on most recent LDL-C measurement, rosuvastatin should be individually titrated. If after the rosuvastatin titration to an individual MTD, a participant's individual LDL-C is not at target in either treatment arm, the LLT must be further escalated as per recommended process. The overall study duration is at least 360 days but can be longer depending on individual screening and run-in period time.
Rationale	Inclisiran is indicated, in the EU, in adults with primary hypercholesterolemia (heterozygous and non-familial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other LLTs in patients unable to reach LDL-C targets with the MTD of a statin, or alone or in combination with other LLTs in patients who are statin-intolerant, or for whom a statin is contraindicated. The aim of this study is to compare the efficacy, safety, tolerability and quality of life of a treatment strategy including inclisiran (on top of ongoing individually optimized LLT following a switch to Rosuvastatin at baseline) with a treatment strategy based on the current ESC/EAS guidelines, in participants whose LDL-C is not adequately controlled using the MTD of a statin for Health Technology Assessment.
Study population	This is a multi-center, multi-country study, expected to enroll 1760 participants, randomized 1:1 across two arms. Since 35% of participants are expected to be screening or run-in failures, approximately 2700 participants are anticipated to be screened. Participants eligible for this trial will include male and female participants age 18 years and older at very high and high risk for cardiovascular events as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) who do not meet their individual LDL-C target despite being treated with their individual MTD of a statin for at least 30 days, and if applicable, another LLT on top of statin stable for at least 30 days prior to screening (up to approximately 20% of randomized participants).

Key Inclusion criteria	• Male or female participants ≥18 years of age.
	• Participants meeting one of the following CV categories:
	• Very high risk participants with at least one of the following:
	  • Documented Atherosclerotic cardiovascular disease (ASCVD)
	  i Acute coronary syndrome: Unstable angina or myocardial infarction.
	  ii Stable angina.
	  iii Coronary revascularization.
	  iv Unequivocally documented ASCVD upon prior imaging.
	  v Stroke and TIA.
	  vi Peripheral artery disease (PAD).
	  • Diabetes mellitus (DM) with target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), or at least ≥ 3 major risk factors, or early onset of Type 1 DM of long duration (> 20 years).
	  • A calculated SCORE2 ≥ 7.5% for age <50 years; SCORE2 ≥10% for age 50-69 years; SCORE2-OP ≥15% for age ≥70 years to estimate 10-year risk of fatal and non-fatal cardiovascular disease (CVD).

	• Pre-existing diagnosis of heterozygous familial hypercholesterolemia (HeFH) with ASCVD or with another major risk factor. OR • High risk participants with at least one of the following: • Markedly elevated single risk factors, in particular total cholesterol >310 mg/dL, LDL-C > 190 mg/dL, or blood pressure ≥ 180/110 mmHg • Pre-existing diagnosis of HeFH without other major risk factors. • Diabetes Mellitus (DM) without target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), with DM duration ≥ 10 years or other additional risk factor. • Moderate chronic kidney disease (eGFR 30-59 mL/min/1.73m^2). • A calculated SCORE2 2.5 to <7.5% for age < 50 years, SCORE2 5 to < 10% for age 50-69 years; SCORE2-OP 7.5 to < 15% for age ≥70 years to estimate 10-year risk of fatal and non-fatal CVD.
	• LDL-C levels at screening and baseline: • in participants with very high cardiovascular risk: serum LDL-C ≥55 mg/dL. • in participants with high cardiovascular risk: serum LDL-C ≥70 mg/dL. • Participant on a stable dose of a statin for ≥ 30 days at screening. • Participants on the individual MTD of statin for ≥ 30 days at baseline. • Fasting triglyceride < 400 mg/dL at screening and baseline.
Key Exclusion criteria	• Participants on more than one other lipid-lowering drug on top of statin at screening visit. • Participants with a known intolerance to rosuvastatin at screening or baseline visit. • Previous (within 90 days of screening), current or planned treatment with a monoclonal antibody (mAb) directed towards PCSK9 (e.g. evolocumab, alirocumab) at screening or baseline visit. • Previous exposure to inclisiran or any other non-mAb PCSK9 targeted therapy, either as an investigational or marketed drug within 2 years prior to screening or baseline visit. • Previous, current or planned treatment with LDL-apheresis at screening or baseline visit. • Liver and CK: (a) Active liver disease defined as any current infectious, neoplastic, or metabolic pathology of the liver or (b) unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST) elevation >3x ULN, or total bilirubin elevation > 2x ULN (except for participants with Gilbert's syndrome), or (c) creatine kinase (CK) >5x ULN at screening or baseline visit. • Participant with severe renal impairment defined by eGFR <30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at screening or baseline visit. • Acute coronary syndrome, ischemic stroke or TIA, coronary revascularization or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease < 3 months prior to the screening or baseline visit. • Heart failure New York Heart Association (NYHA) class IV at screening or baseline visit. • Pregnant or nursing (lactating) women at screening or baseline visit. • Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing of study treatment.
Study treatment	• Double-blind investigational treatment inclisiran/placebo: subcutaneous injections of inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) or placebo, in 1.5 mL solution. • Open label study treatment rosuvastatin: all participants will receive rosuvastatin, starting at the lowest indicated dose and titrating up until they reach their individual LDL-C target or MTD, whichever occurs first. • Ongoing individual optimization of lipid-lowering background therapy if LDL-C is not yet at target.

Treatment of interest	The randomized treatment: blinded investigational treatment inclisiran (on top of presumably a less intense background LLT) or placebo (on top of a CCI [redacted] background LLT), And as background LLT: unblinded rosuvastatin 5 or 10 mg at baseline which is individually optimized on an ongoing basis.
Efficacy assessments	• LDL-C analysis, as performed by the Central Lab.
Key safety assessments	• Adverse event monitoring • Monitoring of laboratory markers in blood and urine

Other assessments	• Participant Reported Outcome (PRO) questionnaires to include:
	  • Daily Pain Diary
	  • Short Form Brief Pain Inventory
	  • Gastrointestinal Symptom Rating Scale
	  • SF-36
	  • Walking Impairment Questionnaire (in PAD subpopulation)
	  • Mac New Heart Disease Health Related Quality of Life (in Angina pectoris subpopulation)
	  • Treatment Satisfaction Questionnaire for Medication

Data analysis	The primary estimand is described by the following attributes: 1 Population: Adult participants categorized as very high risk or high risk as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) with elevated LDL-C despite being treated with the individual MTD of statin and, if applicable, also other LLT. 2 Endpoint: Proportion of participants achieving individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90. The individual LDL-C target of the participants is determined according to their individual cardiovascular risk category. 3 Treatment of interest: Inclisiran, compared to placebo, both on top of an ongoing participant-individually optimized LLT. Randomized treatments are the investigational treatment inclisiran or the placebo control treatment. In both treatment arms, participants receive an individually optimized rosuvastatin therapy for reaching the individual LDL-C target and tolerability. If required to achieve their LDL-C target, further participant-individually optimized LLT can be administered. 4 Summary measure: The odds ratio of achieving individual LDL-C target at day 90 compared between treatment arms. A larger proportion of participants indicates a superior outcome. The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures: 1 Relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits). 2 Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360. 3 Annualized number of days participants experiencing self-reported pain from day 1 to day 360. 4 Change from baseline in SF-BPI pain severity score from at day 360. 5 Change from baseline in SF-BPI pain interference score at day 360.
Keywords	Inclisiran, rosuvastatin, PCSK9, dyslipidemia, angina pectoris, peripheral artery disease, cardiovascular disease, LDL-C

1 Introduction

1.1 Background

Cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually (WHO 2017). Elevated low-density lipoprotein cholesterol (LDL-C) is a well-recognized major risk factor for the development of CVD (Grundy et al 2004, Baigent et al 2005, Mozaffarian et al 2015). Lowering LDL-C has been shown to reduce the risk of death or myocardial infarction (MI) or stroke and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005, Castilla-Guerra et al 2016).

Despite the availability of multiple therapeutic options for lipid lowering, including HMG -CoA reductase inhibitors (statins) and cholesterol absorption inhibitors (ezetimibe), over 50% of patients do not reach their LDL-C targets (Jones et al 2012, Jameson et al 2014, Barkas et al 2015, Fitzgerald et al 2017). This is particularly true in participants with pre-existing coronary heart disease (CHD) who are at the highest risk of major adverse cardiovascular events (MACE) and require the most intensive management (Davidson et al 2005). Furthermore, some observational studies demonstrated that more than 50% of participants did not adhere to statin therapy for more than six months, making poor compliance with statins one of the reasons for low treatment goal achievement (Poluzzi et al 2008, Mann et al 2010, Hirsh et al 2015).

The 2019 ESC/EAS Guidelines for the management of dyslipidemias defines cardiovascular risk categories and their corresponding LDL-C targets according to risk with a LDL-C target of < 55mg/dL for patients at very high risk and < 70mg/dL for patients at high risk for a cardiovascular event (Mach et al 2020). Statins are the first-choice pharmacological treatment for patients with hypercholesterolemia and at risk for CVD. However, a proportion of patients experience statin-associated muscle symptoms, including myopathy, myalgia and in very rare cases rhabdomyolysis. Statin-associated muscle symptoms with or without an elevation in creatine kinase are markedly more frequent at higher statin doses and are the most common cause of treatment discontinuation (Stroes et al 2015, Newman et al 2019, Ward et al 2019). Other lipid-lowering medications, such as ezetimibe, bile acid sequestrants, or bempedoic acid are associated with muscle-related symptoms or worsening of muscle-related symptoms when administered together with a statin or are associated with gastrointestinal side effects (Grundy et al 2019, Mach et al 2020, SmPCs). Consequently, in addition to efficiently lowering LDL-C, individual patient-relevant tolerability of lipid-lowering mono- or combination therapy options and quality of life needs to be considered.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is expressed and secreted into the bloodstream predominantly by the liver, binds to the LDL receptor (LDLR) both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, (Lakoski et al 2009, Mousavi et al 2009) thereby increasing the circulating LDL-C levels. Recently developed and approved PCSK9-blocking monoclonal antibodies (mAbs) reduce PCSK9 and lower LDL-C levels, and also significantly reduce the risk of CV events

(Sabatine et al 2017, Schwartz et al 2018). Currently approved PCSK9-blocking mAbs are administered every 2 or 4 weeks (Repatha® Package Insert; Praluent® Package Insert).

Beyond PCSK9-blocking mAbs, small interfering Ribonucleic Acids (siRNAs) can now be used to silence the expression of the PCSK9 gene in a sequence-specific way. This is done by catalytically silencing the translation of the complementary PCSK9 messenger RNAs (mRNAs) through the formation of effector RNA-induced silencing complexes (RISCs) and the use of a highly specific endogenous mechanism for regulating gene expression (Setten et al 2019). Inclisiran (KJX839) is a chemically-modified siRNA, conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate the specific uptake by hepatocytes (Khvorova 2017). In hepatocytes, the antisense strand is incorporated in the RISC and directs the catalytic breakdown of PCSK9 mRNAs. This prevents the subsequent production of PCSK9 protein. Reduced intrahepatic PCSK9 increases LDL-C receptor recycling and the expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation (Fitzgerald et al 2017).

The ORION-9, -10 and -11, confirmatory 18-months phase III clinical studies compared inclisiran versus placebo adjunctive to maximally-tolerated statin therapy in 3,660 participants with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalent, and/or heterozygous familial hypercholesterolemia (HeFH). An additional 681 participants were treated in phase I and phase II studies. In the phase III studies, treatment with inclisiran sodium 300 mg administered by subcutaneous (s.c.) injection on Day 1, Month 3 (Day 90) and every 6 months thereafter resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 48% to 52%, with time-adjusted average reductions of 44% to 54% sustained over 18 months (Investigator's Brochure (IB), Raal et al 2020, Ray et al 2020). The efficacy of inclisiran was consistent across phase II and phase III studies, with no differences observed across a broad range of subpopulations (IB).

The phase III and subsequent open-label extension trials have shown that there are 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. These injection site TEAEs were localized, predominantly mild, transient, and resolved without sequelae. Inclisiran is not associated with an increased risk for hepatic or renal dysfunction, hypersensitivity, neurologic events and neurocognitive disorders, or ophthalmological events and there is no difference from placebo in new onset or worsening of diabetes mellitus. The potential for immunogenicity of inclisiran is low. Additional details on the efficacy and safety of inclisiran are available in the IB.

Inclisiran is approved in the European Union (EU), United States, as well as other countries worldwide In the European Union, it is indicated for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C targets with the maximum tolerated dose (MTD) of a statin, or alone or in combination with other LLT in patients who are statin-intolerant, or for whom a statin is contraindicated.

1.2 Purpose

The purpose of this study is to demonstrate the superiority of inclisiran compared to placebo, both on top of ongoing individually optimized LLT, on reaching a participant's individual LDL-C target (< 55 mg/dL or < 70 mg/dL, depending on the cardiovascular risk category according to the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) as well as on participant-relevant safety, tolerability outcomes and quality of life.

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 on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on reaching a participant's individual LDL-C target as defined in 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020).	• Proportion of participants achieving individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on:	
• Reducing mean LDL-C levels over the double-blind study period.	• Relative change (percentage from baseline to mean LDL-C level over the double-blind treatment period.
• Muscle-related adverse events.	• Proportion of participants experiencing at least one muscle-related AE as defined in the Standardized MedDRA Queries (SMQ) rhabdomyolysis / myopathy from day 1 to day 360.
• Annualized number of days pain is experienced using pain diary.	• Proportion of participants experiencing self-reported pain. Annualized number of days participants experiencing self-reported pain from baseline to day 360.
• Pain-related quality of life at day 360 using the Short-Form Brief Pain Inventory (SF-BPI).	• Change from baseline in SF-BPI pain severity score to day 360. Change from baseline in SF-BPI pain interference score to day 360. Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to day 360. Proportion of participants with clinically relevant change in SF-BPI pain interference score from baseline to day 360.

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

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).

The primary clinical question of interest is: What is the effect of inclisiran versus placebo on top of an ongoing individually optimized LLT on achieving the individual LDL-C target at day 90 in very high risk and high risk participants as defined in the 2019 ESC/EAS guidelines for the treatment of dyslipidemias (Mach et al 2020).

The primary estimand is described by the following attributes:

1. Population: Adult participants categorized as very high risk or high risk as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) with elevated LDL-C despite being treated with the individual MTD of statin and, if applicable, also other LLT. Further details about the population are provided in Section 5.
2. Endpoint: Proportion of participants achieving individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90. The individual LDL-C target of the participants is determined according to their individual cardiovascular risk category.
3. Treatment of interest: Inclisiran, compared to placebo, both on top of an ongoing individually optimized LLT. Randomized treatments are the investigational treatment inclisiran or the placebo control treatment. In both treatment arms, participants receive an individually optimized rosuvastatin therapy for reaching the individual LDL-C target and tolerability. If required to achieve their LDL-C target, further individually optimized LLT can be administered. Additional information about the investigational treatment and control treatment are provided in Section 6.
4. Summary measure: The odds ratio of achieving individual LDL-C target at day 90 compared between treatment arms. A larger proportion of participants indicates a superior outcome.

Handling of intercurrent events:

1. **Discontinuation of study treatment:** Follow up information after permanent discontinuation of study treatment, Retrieved Drop Out Data (RDO) will be collected at regular study visits and will be included in the analysis, with treatments as assigned at randomization (treatment policy).
2. **Death**: For participants who die no subsequent LDL-C value can exist. Collected data should be analyzed before participants die. For deceased participants the last value measured before death will be included into the analysis (while alive strategy).

3. **Use of** PCSK9 **targeting non-study medication, or lipid apheresis**: It could occur that participants are switched to PCSK9 targeting therapy after discontinuation of study medication or receive lipid apheresis. For the primary endpoint, participants who use PCSK9 targeting non-study medication or lipid apheresis will be considered as not achieving their LDL-C target (composite strategy).
4. **COVID-19 pandemic impact on study**: For the primary endpoint, collected data will be included in the analysis and keep the treatment groups as assigned at randomization (treatment policy).

Change in background medication essentially concerns change in LLT during optimization. A change in background medication is therefore not considered as an intercurrent event because it is part of the treatment strategies that are compared.

2.2 Secondary estimands

The population and the treatment of interest associated with the secondary estimand are the same as for the primary estimand and we consider the same intercurrent events. Except one specific exception described below (the intercurrent event of death), the proposed approach for all secondary endpoints for the intercurrent events of discontinuation of study treatment, the use of PCSK9 targeting non-study medication or lipid apheresis or the impact of the COVID-19 pandemic, is the treatment policy strategy. For the intercurrent event of death a while alive strategy will be applied.

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures:

1. Relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits).
2. Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360.
3. Annualized number of days participants experiencing self-reported pain from day 1 to day 360.
4. Change from baseline in SF-BPI pain severity score from at day 360.
5. Change from baseline in SF-BPI pain interference score at day 360.
6. Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to Day 360.
7. Proportion of participants with clinically relevant change in SF-BPI pain interference score from baseline to Day 360.

However, the first secondary endpoint of relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits) will be handled differently for the use of PCSK9mAb or lipid apheresis. For this specific intercurrent event for this endpoint a hypothetical strategy as if no PCSK9mAb or lipid apheresis would have been administered will be applied.

3 Study design

This study is a double-blind, placebo-controlled multicenter study in adult participants with very high or high cardiovascular risk (as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020)) who do not meet their individual LDL-C target despite being treated with their individual MTD of a statin, and if applicable, further LLT.

LDL-C target will be evaluated according to most recent assessment of cardiovascular risk category as determined by the investigator. This includes assessment of cardiovascular events and new-onset or worsening of cardiovascular risk factors as defined in the current guidelines throughout the trial.

This is a treatment strategy study where the participants are both randomized to inclisiran vs placebo and also simultaneously switched to rosuvastatin, and then have their LLT individually optimized by investigators.

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

- A Screening period of approximately 14 days for all participants.
- An optional Run-in period of up to 120 days as individually applicable.
- An optional additional baseline period of approximately 10 days as individually applicable for required labs
- A Treatment period of 360 days.

The overall study duration is at least 360 days but can be longer depending on individual screening and run-in period time.

3.1 Screening period

At screening, in order to participate in the study, 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 obtained 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, she/he will have to return for the blood draw in a fasting state.

During the screening visit, the participant's individual cardiovascular risk will be categorized as very high risk or high risk, with corresponding LDL-C target < 55 mg/dL or < 70 mg/dL, respectively. This individual risk will be determined according to the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020).

The investigator must also ensure that each participant is on a stable dose (for ≥ 30 days prior to the screening visit) of a statin. To reflect current as well as prospective statin prescription patterns of everyday care among the study population, enrollment targets for statins are defined in Table 3-1.

In addition to ensuring that a participant is on a stable dose of a statin, the investigator must also determine if a participant's individual statin dose is considered to be the participant's MTD.

The participant's MTD of statin is defined as either the highest approved dose of a respective statin (as per local SmPC) or the other maximum dose of statin that can be taken by the participant on a regular basis

- without intolerable adverse event (AE) that requires dose adjustment, or
- without AE that requires a dose adjustment (e. g. elevated lab values as per local SmPC),

or

- without meeting any contraindication for a particular participant (as per local SmPC).

Any dose-limiting AEs and/or relevant contraindications must be documented in the eCRF.

Participants being treated with their MTD of statin at screening can directly undergo randomization at baseline, whereas participants treated with a statin dose that is not considered to be the participant's MTD will enter the run-in period.

The Interactive Response Technology (IRT) system will alert the investigator if the enrollment targets for any of the statins have already been met. If the enrollment target for a particular statin has been met, then enrollment for that group will be closed and the participant will not be screened.

Table 3-1 Percentages of statin use at screening in reference to the entire study population.*

statin	Up to approximately X% of all randomized participants can receive the respective statin at screening
simvastatin	70%
atorvastatin	70%
rosuvastatin	10%
pravastatin	5%
fluvastatin	5%
lovastatin	5%
pitavastatin	5%

*Percentages are based on current distribution of statins used in clinical practice in Germany according to the German report of drug prescription 2020 (Schwabe et al 2020). The thresholds have been set at least 50% higher than the current data to account for potential future adaptations in prescription patterns

At the screening visit, with the exception of PCSK9 mAbs or other PCSK9 targeting therapies, another LLT such as a cholesterol absorbing inhibitor or a bile acid sequestrant, as per European guideline recommendation, or alternatively, an adenosine triphosphate citrate lyase (ACL) inhibitor can be taken by a participant (stable for ≥ 30 days) on top of statin. In the DA VINCI study, 9% of European participants are being treated with ezetimibe in combination with moderate- or high-intensity statins (Ray et al 2020). The enrollment will be capped to approximately 20% of randomized participants being treated with a stable dose (for ≥ 30 days) of another LLT on top of a statin at the screening visit to reflect the current as well as the expected prospective prescriptions.

Screening period of approximately 14 days allow adequate time for the completion of all qualifying screening and eligibility evaluations.

A participant who enters screening and is determined not eligible will be considered as a screen failure. The Investigator may re-screen the participant at a later time if he/she thinks that the participant's condition can fulfill all the eligibility criteria. A participant may only be re-screened once and a minimum of 2 weeks must elapse between screen failure and re-screening visits.

3.2 Optional Run-in period

During the optional run-in-period, the participant's statin therapy will be up-titrated to reach their individual MTD. To do so, their screening statin dose will be increased to the next higher dose level according to the respective statin local SmPC. If the participant tolerates the next higher statin dose level for 30 days and LDL-C is still not at target, the participant's statin dose will undergo another up-titration according to the statin local SmPC. This procedure will be followed until:

a. The participant reaches the individual MTD. The MTD of a statin is defined as either the highest approved dose of a respective statin as per local SmPC or the maximum dose of statin that can be taken on a regular basis:
   - without an intolerable AE that requires dose adjustment, or
   - without an AE that requires dose adjustment (e. g. elevated lab values as per local SmPC),or
   - without meeting any contraindication for a particular participant (as per local SmPC).

Any dose-limiting AEs and/or relevant contraindications must be documented in eCRF.

b. The participant meets the individual LDL-C target.

The individual run-in period can take up to 120 days with visits every 30 days to optimize the participant`s individual statin therapy.

Participants who meet their individual LDL-C target in the run-in period will be considered a run-in failure. Also, participants who do not reach a MTD up to day 120 will be considered a run-in failure. These run-in failures will not be eligible for randomization or re-screening and will be discontinued from the study.

If the participant is treated with a further LLT at screening (Section 3.1), it is recommended during the run-in period to keep the participant under the same LLT, unless it is deemed medically necessary to change their LLT. It is also recommended not to add another LLT on top of the statin, while the statin is being titrated. The Investigator's LLT decision has to be documented on the respective eCRF pages.

Participants will be followed according to the Assessment Schedule for study-related assessments (Table 8-1).

The Investigator's statin titration decision will be based on the most current LDL-C value. For local decision making, the LDL-C value will be preferably measured using an LDL-C point of care device. In the event the assessment cannot be completed with the LDL-C point of care device, the LDL-C is to be assessed by the central lab.

If deemed necessary by the Investigator, unscheduled visits can take place at any time during the run-in period.

During the run-in period, all participants will be instructed to comply with lifestyle changes according to international recommendation (Mach et al 2020), and these instructions will be reinforced at every visit.

In addition, other risk factors for atherosclerotic disease such as high blood pressure and diabetes mellitus should be optimally treated during the run-in period according to local practice/guidelines.

Table 3-2 Approved statin dose ranges and recommended statin titration steps

statin	approved dose range* [mg/day]	maximum dose* [mg/day]	recommended titration steps* [mg/day]
simvastatin	5-80	80	5-10-20-40-80
atorvastatin	10-80	80	10-20-40-80
rosuvastatin	5-40	40	5-10-20-40
pravastatin	10-40	40	10-20-40
fluvastatin	20-80	80	20-40-80
lovastatin	10-80	80	10-20-40-80
pitavastatin	1-4	4	1-2-4

*according to local SmPC

3.3 Optional Baseline period (Day -10)

The Baseline visit is split into 2 visits, planned approximately 10 days apart (Day -10; Day 1).

The first visit on Day -10 will only apply for participants not randomized within 7 days of screening (see Section 8.1) and for participants coming from run-in.

The Day -10 visit will only consist of a lab draws, which will be sent to the Central Lab.

Following receipt of Central lab results and confirmation of eligibility, the investigator may then schedule the Baseline (Day 1) visit for randomization.

3.4 Double-blind treatment period

1) Baseline (Day 1)

All participants, who fulfill the inclusion/exclusion criteria (Section 5.1 and Section 5.2), will be randomized at baseline in a 1:1 double-blind fashion to either inclisiran or placebo. In addition, at baseline all participants will be switched from their individual statin to rosuvastatin, which is considered open label study treatment in this trial. Approximately 880 participants should be randomized per arm. Participants will be stratified by their cardiovascular risk.

At baseline, all participants will be instructed to comply with lifestyle changes according to international recommendation (Mach et al 2020), and these instructions will be reinforced at every visit.

In a double-blind setting, the participant will be subcutaneously injected with 300 mg inclisiran sodium or placebo at day 1, 90 and 270 during the treatment period (Figure 3-1) by a delegated healthcare professional at the study site.

At Day 1 visit, all participants will additionally be switched from their individual statin to rosuvastatin. As per local SmPC, the recommended start dose for rosuvastatin is 5 mg/day or 10 mg/day. Considering the local SmPC, the investigator will choose the appropriate rosuvastatin start dose level for a particular participant. Participants already treated with rosuvastatin prior to baseline will continue treatment with their individual MTD of rosuvastatin, if in accordance with the Investigator.

2) Post-Baseline

The Investigator's LLT decision will be based on the most current LDL-C value. For local LLT decision making, LDL-C value will be measured using an LDL-C point of care test device. In the event the assessment cannot be completed with the LDL-C point of care device, the LDL-C is to be assessed by the central lab.

Following randomization, if a participant's LDL-C is not at target at day 30 and at the following visits, based on most recent LDL-C measurement, rosuvastatin should be individually titrated at day 30 and at the following visits, until:

a. The participant reaches the individual MTD for rosuvastatin. The MTD of rosuvastatin is defined as either the highest approved dose of rosuvastatin or the maximum dose that can be taken on a regular basis:
   - without an intolerable AE that requires dose adjustment, or
   - without an AE that requires dose adjustment (e. g. elevated lab values as per local rosuvastatin SmPC), or
   - without meeting any contraindication for a particular participant (as per local rosuvastatin SmPC).

Any dose-limiting AEs and/or relevant contraindications must be documented in the eCRF.

b. The participant meets the individual LDL-C target.

Recommended titration steps for rosuvastatin are 5 mg/day, 10 mg/day, 20 mg/day up to a maximum dose of 40 mg/day, if indicated as referred to in the local SmPC. A dose adjustment to the next higher dose level every 30 days is in accordance with the local rosuvastatin SmPC. Rosuvastatin dose will not be blinded between the two treatment arms to enable ongoing individual LLT optimization by the investigator at his discretion. At day 90, it is assumed that rosuvastatin will be optimally titrated for most participants. In case further rosuvastatin titration is needed for a particular participant, there is an optional visit at day 120.

It is recommended not to add another LLT on top of rosuvastatin while it is being titrated. Further, if at screening and/or during the run-in period, as applicable, a participant is already treated with a non-statin lipid-lowering medication (Section 3.1), it is recommended to not to change it at baseline, and in parallel to the individual rosuvastatin titration, unless medically necessary.

For participants already taking rosuvastatin at screening and during the run-in period (if applicable), further lipid-lowering medication is recommended to be added after inclisiran/placebo injection on Day 1 and at earliest on Day 30. The Investigator's LLT decision has to be documented on the respective eCRF pages.

Following day 90, visits are scheduled every 60 days in order to follow the ESC/EAS guidelines for the management of dyslipidemias that recommends monitoring the participant's lipid level after starting LLT or after adjustment of LLT every 8 (±4) weeks (Mach et al 2020).

Recommended process in the treatment period in case LDL-C is still not at target after rosuvastatin titration:

If after the rosuvastatin titration to an individual MTD, a participant's individual LDL-C is not at target in either treatment arm, the LLT must be further escalated.

According to the current ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020), high-intensity statin therapy is the recommended first choice therapy for lipid lowering (Class I, Level A recommendation). If the LDL-C target is not achieved with the MTD of a high-intensity statin (implemented by using rosuvastatin in this study):

- The combination with ezetimibe is recommended (Class I, Level B recommendation).
- If the LDL-C target is still not achieved,
- consider also the use of bile acid sequestrant (Class IIb, Level C recommendation).
- Recently approved bempedoic acid may also be considered for LLT escalation, however, it is not depicted in the current guidelines and should thus be used secondarily after the aforementioned substances. Please refer to Figure 3-2.
- Then last, access to PCSK9 mAb as next escalation step will be handled according to the German prescribing restriction (Bundesausschuss 2021). The recommendation will be to use the latest version of the guidance and an English version will be made available.

PCSK9 mAb may be indicated in participants with a confirmed vascular disease (CHD, cerebrovascular disease, PAD) and regularly additional risk factors for cardiovascular events (e. g. diabetes mellitus, restricted renal function with eGFR < 60 mL/min/1.73m^2), or in participants with a confirmed diagnosis of HeFH taking the overall family predisposition into account, if LDL-C cannot be reduced sufficiently despite in principle a documented maximum dietary as well as lipid-lowering drug therapy over a period of 12 months.

To ensure that a participant is allowed to receive the PCSK9 mAb therapy according to the referenced guidance, the Steering Committee (members of the PCSK9 mAb decision board), will review the required participant's data and decide on the participant`s eligibility for such therapy (Section 10.3.1).

PCSK9 general decision:

In case a participant is deemed eligible, the participant will need to discontinue the blinded investigational treatment (inclisiran/placebo).

CCI is the preferred PCSK9 mAb to be used to enable consistency in therapy among trial countries and will be supported by the sponsor. The participant will remain in the study despite having discontinued blinded investigational treatment (inclisiran/placebo) and will be followed-up until the participant's end of study.

- If the participant is deemed ineligible for switch to PCSK9 mAb by the Steering Committee, the Investigator is encouraged to continue the participant's LLT escalation as recommended in Figure 3-2. If the investigator decides that a PCSK9-targeted therapy is indicated despite the decision of the SC, the participant will need to discontinue study treatment (inclisiran/placebo), and should be treated as per local standard of care and followed-up but should remain in the study until the participant end of study.

Particular attention should be paid to CCI: In the case where the investigator feels that a participant's condition warrants the use of PCSK9 mAb CCI, the blinded investigational treatment (inclisiran/placebo) should not be administered at CCI visit, but the participant's eligibility to PCSK9 mAb should first be assessed by the Steering Committee as below:

- If the participant is deemed eligible, blinded investigational treatment (inclisiran/placebo) must be discontinued, the participant will switch to PCSK9 mAb, preferably CCI and will be followed-up until the participant's end of study.
- If the participant is deemed not eligible by the Steering Committee following visit at CCI please refer to the procedure outlined above. In case the Investigator decides to continue the participant's LLT escalation, blinded investigational treatment (inclisiran/placebo) can be administered in an unscheduled visit, following CCI

For intractable cases with LDL-C still too high after LLT escalation as outlined above, if not already done, study treatment (inclisiran/placebo) will need to be discontinued and the participant should be treated as per local standard of care, e. g. also considering LDL-apheresis as 'ultima ratio'. The participant will remain in the study and will be followed-up until the participant's end of study.

For recommended LLT scheme based on ESC/EAS guideline in combination with relevant Health Technology Assessment (HTA) requirements, please refer to Figure 3-2. The Investigator's LLT decisions as well as possible deviations from the above described escalation algorithm have to be documented in detail on the appropriate eCRF pages. This includes formal contraindication as per respective local SmPC or prior intolerable AE.

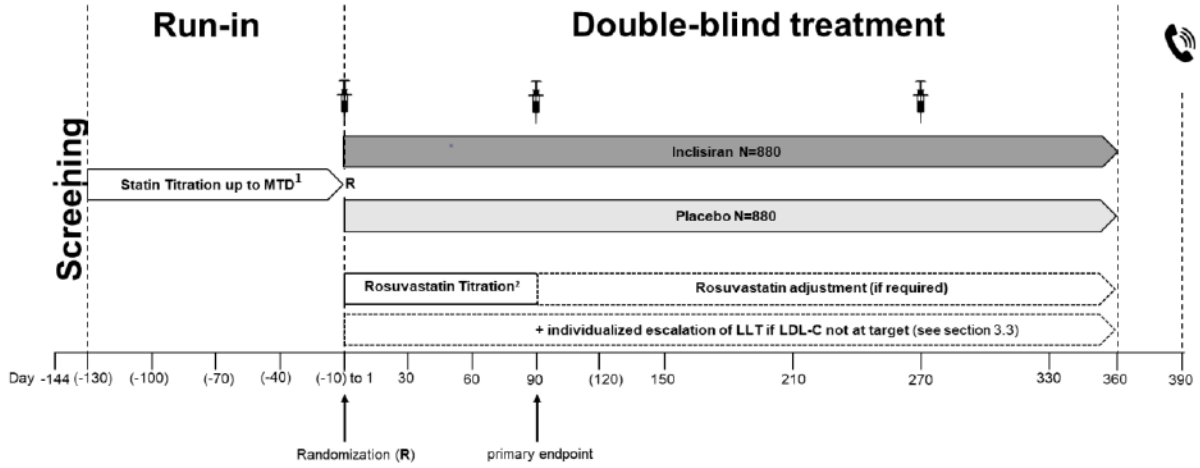
Participants will be followed according to the Assessment Schedule for study-related assessments (Table 8-1).

If deemed necessary by the Investigator, unscheduled visits can take place at any time during the treatment period.

In addition, other risk factors for atherosclerotic disease such as high blood pressure and diabetes mellitus should be optimally treated during the double-blind treatment period according to local practice/guidelines.

Every effort should be made to keep participants in the study, even in the case of study drug discontinuation (Section 9.1.1).

Figure 3-1 Study Design



[1] Duration of the Statin Titration period during the in run-in can be shorter than the depicted 120 days (see Section 3.2)

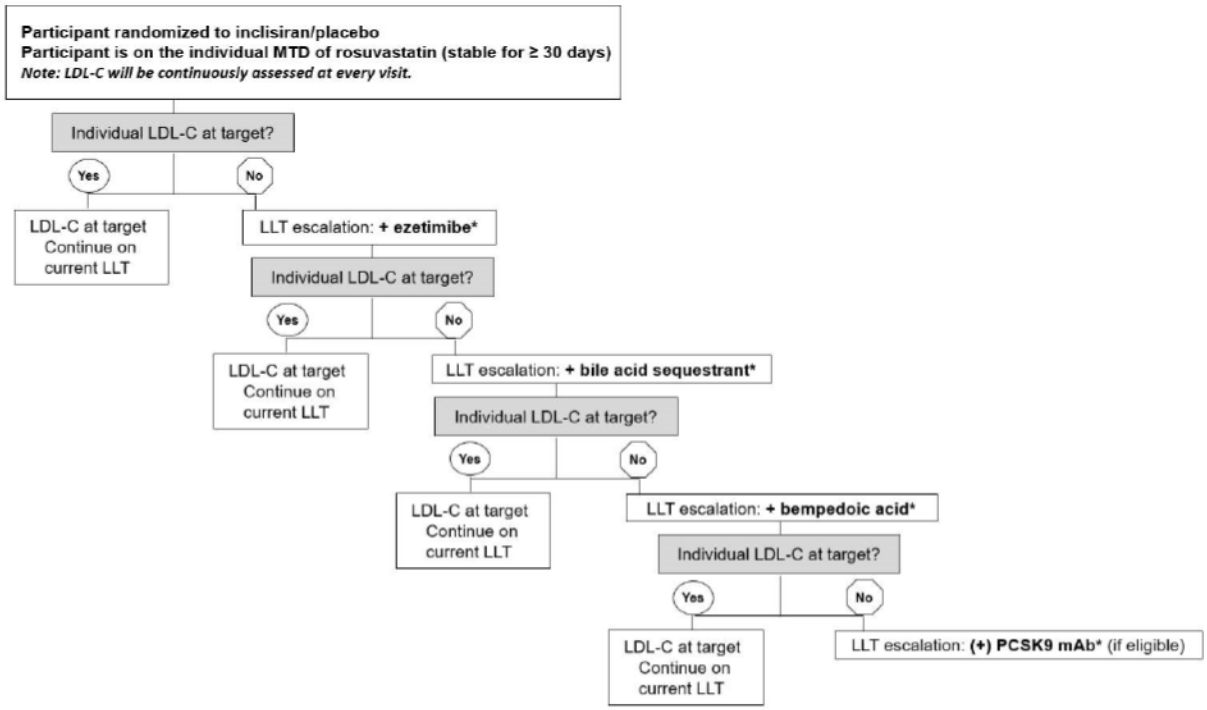
[2] Duration of the Rosuvastatin Titration period during the double-blind treatment period can be shorter or longer (broken line arrow) than the depicted 90 days in both treatment arms (see Section 3.4).

Notes:

All days in parenthesis represent optional visits.

A mandatory safety follow-up phone call must be given at day 390.

Figure 3-2 Recommended treatment scheme based on ESC/EAS guidelines in combination with relevant HTA requirements



(+) Please refer to Section 3.4
* If indicated as per (local) SmPC

3) End of Treatment (EOT) and End of Study (EOS) definition:

The EOT/EOS visit will be on Day 360. In addition, a safety follow-up call will be conducted 30 days after the EOS visit.

As inclisiran is a long-acting drug and the injections are administered 3 or 6 months apart the EOT is (1) the day the participant is not receiving the planned dose and not continuing with the study treatment or (2) the day planned EOS visit is achieved. Participants who premature discontinue from study treatment will have an EOT recorded and will remain in the study. They will be followed-up until the participant's end of study (EOS) as indicated in the Assessment Schedule (see Table 8-1).

If a participant discontinues the study early, the investigator must do their best to ensure the participant returns for an EOS visit.

4 Rationale

4.1 Rationale for study design

Approval by regulatory bodies worldwide is an essential first step to provide patients with innovative medical therapies. Subsequent health technology assessment (HTA) plays an

increasingly important role to provide patients with access to these therapies. It is not always possible to satisfy the requirements of both CCI in the same trial, as requirements may differ. For example, the CCI therapy required for CCI approval can be different to that required for a CCI, and the accepted clinical endpoints may differ. Inclisiran is approved or under regulatory review worldwide. Therefore, the focus of the current study is to generate the required CCI. The aim of this studyis to compare the efficacy, safety and tolerability as well as impact on quality of life, of a treatment strategy including inclisiran with a treatment strategy based on the current ESC/EAS guidelines, in participants whose LDL-C is not adequately controlled using the MTD of a statin, as required CCI.

The study design includes ongoing individual optimization of LLT throughout the trial, following randomization to inclisiran/placebo and a switch at randomization to rosuvastatin 5 or 10mg/day, to reach individual LDL-C target (as outlined in Section 3.4). It is therefore likely that intensity of background statin and other LLT in the CCI. The study design may result in CCI background therapy in the CCI group than in the CCI treated group, so that the treatment comparison is not simply between CCI placebo but rather between a treatment CCI of inclisiran plus (presumably lower use of) CCI and placebo plus (presumably CCI.

Access to PCSK9 mAbs is restricted in many countries. In this study, the CCI requirements applicable for Germany are used as a reference to provide homogeneity for the overall study.

Inclisiran is approved in EU, US, as well as other countries worldwide. In the EU, inclisiran is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C targets with the MTD of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

At screening, the participant's individual statin therapy will be considered along with the statin enrollment targets (refer to Table 3-1) to reflect current and prospective statin prescriptions in clinical routine.

The optional run-in period is specifically designed to continuously re-evaluate LDL-C and to titrate the participant’s individual statin prescribed at screening to the individual MTD.

Participants do not need to enter the run-in period if, at screening, they are already on the MTD of a statin as documented in the participant's medical history (refer to Section 3.1).

The treatment period is a randomized placebo-controlled, double-blind period. The present study aims to demonstrate the superiority of inclisiran compared to placebo, both with an ongoing individually optimized LLT, on the efficacy of lowering LDL-C as well as on safety, tolerability and other participant-relevant endpoints.

At baseline Day 1, among other inclusion/exclusion criteria, all participants, whose MTD of statin fails to sufficiently lower LDL-C to their target set at screening, will be randomized in a 1:1 double-blind fashion to either receive inclisiran or placebo.

In addition, at baseline Day 1 all participants will be switched from their individual statin to rosuvastatin. As per current ESC/EAS guideline, treatment with a high-intensity statin therapy is recommended (Mach et al 2020). Rosuvastatin is a highly potent and well-tolerated statin. Due to its hydrophilic nature it tends to be retained in the liver rather than to diffuse out of it in non-hepatic cells, including skeletal muscle, and this hydrophilic property is suggested to account for fewer AEs (Kones 2010, McTaggart 2003).

At baseline Day 1, a participant's individual statin therapy will be switched to rosuvastatin to ensure that all participants receive the same high-intensity statin during the treatment period. Up to approximately 10% of participants who are already taking rosuvastatin at screening can be enrolled in the trial. These participants can continue receiving their MTD of rosuvastatin at baseline if in accordance with the Investigator.

Rosuvastatin should be titrated to try to achieve target LDL-C level, or to an individual MTD according to investigator discretion.

If a participant's individual LDL-C is not at target in either treatment arm and after the rosuvastatin titration period, insufficient LLT must not be continued throughout the trial but be further escalated. To allow an ongoing individual LLT optimization as outlined above (Figure 3-2), LDL-C values will not be blinded.

This study design is appropriate to answer the clinical questions of interest on the use of inclisiran compared to placebo both on top of an ongoing individually optimized LLT in participants at very high or high cardiovascular risk according to the cardiovascular risk categories defined in the ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020).

4.1.1 Rationale for choice of background therapy

Statins are recommended first choice therapy for lipid lowering according to the ESC/EAS guideline (Mach et al 2020). At screening, it is required that all participants are receiving a stable dose of a statin (≥ 30 days). To further reflect current and prospective prescription of LLT in clinical routine among the study population, up to approximately 20% of participants treated with another LLT on top of statin can be enrolled in the present trial. With the exception of PCSK9 mAbs or other PCSK9 targeting therapies, such other lipid-lowering agents can be a cholesterol absorbing inhibitor or a bile acid sequestrant, both as per European guideline recommendation, or alternatively, an adenosine triphosphate citrate lyase (ACL) inhibitor, as indicated.

Prior to baseline, it is required that all participants are on their individual MTD of a statin for at least 30 days with which LDL-C is still not at target. The participant's individual statin will be switched to rosuvastatin at baseline. Rosuvastatin is a required open label baseline LLT during treatment period and defined as study medication.

Rosuvastatin should be titrated to try to achieve target LDL-C level, or to an individual MTD according to investigator discretion.

If the MTD of rosuvastatin fails to sufficiently lower LDL-C to target in either treatment arm, LLT must be further escalated throughout the trial to achieve a participant-individually optimized LLT. Lipid-lowering background therapy for treatment escalation should be aligned with the 2019 ESC/EAS guidelines for the management of dyslipidemias. If the LDL-C target is still not achieved with the MTD of a high-intensity statin, herein rosuvastatin, the combination with ezetimibe is recommended (Class I, Level B recommendation). If the LDL-C target is still not achieved, consider use of bile acid sequestrant (Class IIb, Level C recommendation) (Mach et al 2020). Bempedoic acid has recently been approved and may also be considered for LLT escalation, however, it is not depicted in the current European guidelines and should thus be used secondarily after the aforementioned treatments. If indicated, escalation to PCSK9 mAb, preferably CCI , may be considered for eligible participants (please refer to Section 3.4).

For intractable cases with LDL-C still too high after LLT escalation as outlined above, the investigator can decide to have the participant discontinue all study treatment (inclisiran/placebo + rosuvastatin) and to have the participant switched to local standard of care, e.g. considering LDL-apheresis as 'ultima ratio'.

Final treatment decision regarding escalation of LLT is based on the discretion of the Investigator considering the respective local SmPCs and above recommended LLT scheme based on ESC/EAS guideline in combination with relevant HTA requirement. The Investigator's LLT decisions as well as possible deviations from the above described escalation algorithm have to be documented in detail in eCRF. This includes formal contraindication as per local SmPC or prior intolerable AE.

4.2 Rationale for dose/regimen and duration of treatment

The established dose regimen for inclisiran sodium for adults is 300 mg s.c. administered at Day 1, Month 3 (Day 90) and every 6 months thereafter. This dose and dose regimen were extensively studied in the phase III clinical program, and will be used in the present study to provide maximum efficacy with an acceptable safety profile. Furthermore, a 300 mg dose of inclisiran sodium has been studied in participants with mild, moderate and severe renal impairment and mild and moderate hepatic impairment, with no clinically meaningful differences in LDL-C and PCSK9 lowering compared to that observed in other participant populations, and with no dose adjustment required (IB).

Three large pivotal phase III clinical trials (ORION-9. -10, -11) (Wright et al 2021) in adults with ASCVD, ASCVD risk equivalents, and HeFH demonstrated that the dose regimen used in the present study (300 mg inclisiran sodium s.c. on Day 1, Month 3 (Day 90), and (every) 6 months thereafter) resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 48% to 52%, with time-adjusted average reductions of 44% to 54% sustained over 18 months (Raal et al 2020, Ray et al 2020). This dose and regimen has been shown to be

well tolerated, with a safety profile similar to placebo, with the exception of more injection site reactions associated with inclisiran compared to placebo.

The primary endpoint at day 90 of the 1 year-treatment period will CCI of action of the test treatment. Further, the rationale for the 1-year duration of the placebo-controlled treatment period is that it also allows a reasonable number of 3 injections per participant (given the twice yearly dosing regimen) and is suitable to assess longer-term efficacy as well as safety, tolerability and quality of life.

The high-intensity open label statin rosuvastatin will be used according to local SmPC with recommended start dose level of 5mg/day or 10mg/day followed by an individual titration based on tolerability and required LDL-C lowering. At day 90, it is assumed that rosuvastatin is optimally titrated for most participants.

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

This trial is placebo-controlled to provide robust evidence on the effect of inclisiran in combination with an ongoing individually optimized LLT on clinical efficacy, safety and tolerability as well as on quality of life. The use of placebo as a comparator for inclisiran is justified since all enrolled participants will be treated with their individually optimized LLT (including rosuvastatin and other lipid-lowering (background) treatment, if indicated) throughout the study. All participants will be on standard of care including, but not limited to, dietary advice, antihypertensives, anti-diabetic therapies, and antiplatelet therapies provided by the Investigator, as clinically appropriate.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

LDL-C plays a major role in the initiation and progression of ASCVD. Lowering LDL-C has been shown to reduce the risk of death or MI or stroke and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005, Castilla-Guerra et al 2016). Therefore, elevated LDL-C levels need to be carefully controlled. The current ESC/EAS guidelines for the management of dyslipidemias recommend a LDL-C target of < 55 mg/dL in very high risk patients and a LDL-C target of < 70 mg/dL in high risk patients as defined by the cardiovascular risk categories (Mach et al 2020). Furthermore, an LDL-C reduction $\geq 50\%$ from baseline is recommended for these participant populations. Despite the availability of multiple options of lipid-lowering drugs, current therapies still do not provide sufficient control for many patients with elevated LDL-C (Fitzgerald et al 2017, Barkas et al 2015, Jameson et al 2014, Jones et al 2012, Ray et al 2020 (DA VINCI)). This is particularly true in patients with pre-existing CVD who are at the highest risk of MACE and require the most intensive management (Davidson et al 2005). Recent data from the DA VINCI study, an 18 country, cross-sectional,

observational study across Europe in patients prescribed with LLT for primary and secondary prevention, show that only 33% achieved their risk-based goal according to 2019 ESC/EAS guideline (Ray et al 2020, Mach et al 2020). For very high risk primary and secondary prevention patients, the 2019 ESC/EAS guideline defined LDL-C target was achieved in 17% and 22% of patients, respectively (Ray et al 2020).

Inclisiran is approved in EU, US, as well as other countries worldwide. In the EU, it is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C targets with the MTD of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

In Phase III studies, in adults with ASCVD, ASCVD risk equivalents, and/or HeFH, inclisiran, given on Day 1, Month 3 (Day 90) and every 6 month thereafter on top of maximally-tolerated statin therapy with or without other LLT, lowered LDL-C by ~50% versus placebo. The effect was persistent over time and reversible on stopping inclisiran.

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 and inclisiran did not show evidence of embryo lethality, 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.

Safety data obtained from three large pivotal studies (ORION-9, -10, -11, Wright et al 2021) that included 1,833 participants treated with inclisiran for up to 18 months (mean treatment duration on inclisiran was 526 days) showed that the overall safety profile of inclisiran was similar to placebo. Treatment-emergent adverse events (TEAEs) leading to study discontinuation were balanced between inclisiran and placebo. The only adverse reactions associated with inclisiran were AEs at the injection site (8.2% for inclisiran-treated participants vs. 1.8% for placebo-treated participants), but these adverse reactions were localized, mild or moderate in severity, transient and resolved without sequelae. The proportion of participants who discontinued treatment due to this AE was low: 0.2% for inclisiran and 0.0% for placebo.

Inclisiran is not associated with an increased risk for hepatic or renal dysfunction, hypersensitivity, neurologic events and neurocognitive disorders, or ophthalmological events and there was no difference from placebo in new onset or worsening of diabetes. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of inclisiran were observed in the participants who were tested positive for anti-inclisiran antibodies.

For the risk and benefit assessment of approved rosuvastatin please consider the information provided in this protocol and always refer to the local SmPC.

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 (Section 5.2). If there is any question that the participant will not reliably comply, they should be considered as not eligible to the study.

In general, the risk of participants in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring of safety parameters.

The benefit a participant might have by participating in the study is the close monitoring of their condition and close adherence as well as an ongoing individual optimization of LLT.

4.5.1 Covid-19 impact on risk-benefit

The coronavirus disease 2019 (COVID-19) pandemic may continue to affect countries participating in study CKJX839A12402. While participants with underlying CV disease have an increased risk for unfavorable outcomes (e.g., respiratory failure, death) after contracting COVID-19, the risk of being exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be mitigated if the measures recommended or enforced by national and/or local authorities are followed. Should local (e.g. community-based) or general (e.g. country-or-state based) lock-down be required by authorities, due to COVID-19, the study participants must follow the guidance/requirements applicable to the general population, as well as any specific guidance/requirement applicable to their underlying condition. If the study-level and the population-level requirements are followed, the pandemic-related risk of a participant participating in the study should not exceed the risk of a participant with a similar condition not participating in the study.

4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g.. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the Public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by Local or Regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

The study population consists of adult participants at very high and high risk for cardiovascular events as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) who do not meet their individual LDL-C target despite being treated with their individual MTD of a statin for at least 30 days, and if applicable, another LLT on top of statin stable for at least 30 days prior to screening (up to approximately 20% of randomized participants).

Among the defined study population, treatment with inclisiran on top of an ongoing individually optimized LLT is suggested to be especially beneficial for subpopulations suffering from PAD and CHD with stable angina pectoris (AP). These participants have been shown to respond to

LLT with improved functional capacity and quality of life (Mohler 2003, Mondillo et al 2003, Kabaklić and Fras 2017, Manfrini et al 2020).

AP or 'chest tightness' describes a thoracic or retrosternal pain that occurs frequently in the form of attacks and is triggered by myocardial ischemia. AP is the cardinal symptom of CHD and can be distinguished into stable and unstable AP periods, categorized as either chronic syndromes (CCS) or acute coronary syndromes (ACS). Stable AP is characterized by chest pain that can be reproduced by physical or psychological stress and that disappears at rest or after administration of nitroglycerine (Knuuti et al 2020).

PAD is a restriction in blood flow of the arteries supplying the extremities or, more rarely, the aorta. Blood flow can be restricted gradually (through a stenosis) or complete (occlusion) (Aboyans et al 2018). PAD is evidenced by intermittent claudication with an ankle-brachial index (ABI) ≤ 0.90 prior peripheral arterial revascularization procedure, or, amputation due to atherosclerotic disease. Thromboangiitis obliterans is not a qualifying event.

Around 1760 participants who meet the eligibility criteria will be randomized 1:1 at baseline. Participants will be stratified by their cardiovascular risk, very high risk or high risk as defined in the inclusion criteria (Section 5.1 and Section 16.4). Participants will continue to be screened until approximately 1760 participants are randomized to the trial. Since 35% screening and run-in failure rate is expected, approximately 2700 participants are anticipated to be screened.

5.1 Inclusion criteria

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

At Screening:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female participants ≥18 years of age.
3. Participants categorized as very high or high CV risk, as defined below:
   - **Very high risk participants** with at least one of the following:
     1. Documented ASCVD
        ACS: Unstable angina or myocardial infarction
        Stable angina
        Coronary revascularization
        Unequivocally documented ASCVD upon prior imaging
        Stroke and Transient Ischaemic Attack (TIA)
        PAD
     2. Diabetes mellitus (DM) with target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), or at least ≥ 3 major risk factors, or early onset of Type 1 DM of long duration (> 20 years)
     3. A calculated SCORE2 ≥ 7.5% for age < 50 years; SCORE2 ≥ 10% for age 50-69 years; SCORE2-OP ≥ 15% for age ≥ 70 years to estimate 10-year risk of fatal and non-fatal CVD

4. Pre-existing diagnosis of heterozygous familial hypercholesterolemia (HeFH) with ASCVD or with another major risk factor.

OR

- **High risk participants** with at least one of the following:
  1. Markedly elevated single risk factors, in particular total cholesterol > 310 mg/dL, LDL-C > 190 mg/dL, or blood pressure ≥ 180/110 mmHg
  2. Pre-existing diagnosis of HeFH without other major risk factors
  3. DM without target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), with DM duration ≥ 10 years or other additional risk factor
  4. Moderate chronic kidney disease (eGFR 30-59 mL/min/1.73m^2)
  5. A calculated SCORE2 2.5 to <7.5% for age under 50 years; SCORE2 5 to <10% for age 50-69 years; SCORE2-OP 7.5 to <15% for age ≥70 years to estimate 10-year risk of fatal and non-fatal CVD

as defined by the cardiovascular risk categories in the 2019 ESC/EAS guideline (Mach et al 2020), [Note: Table 4, page 15: High risk and very high risk only] and updated SCORE2 and SCORE2-OP (according to Hageman et al 2021, de Vries et al 2021, Visseren et al 2021). Further details for documented ASCVD are provided in Section 16.4.

4. LDL-C levels:
   a. in participants with very high cardiovascular risk: serum LDL-C ≥55 mg/dL.
   b. in participants with high cardiovascular risk: serum LDL-C ≥70 mg/dL
5. Participant on a stable dose of a statin for ≥ 30 days. (Please refer to Table 3-1 for statin enrollment targets.). [The investigator must ensure that the participant's individual statin therapy does not meet any contraindication for that participant and does not interfere with the listed eligibility criteria as stated in the local SmPC of the respective statin.].
6. Up to approximately 20% of total participants can be on a stable dose (for ≥ 30 days prior to screening) of another LLT on top of statin such as a cholesterol absorbing inhibitor or a bile acid sequestrant, or alternatively, an adenosine triphosphate citrate lyase (ACL) inhibitor, as indicated.
7. Fasting triglyceride < 400 mg/dL.

At Baseline:

8. Fasting triglyceride < 400 mg/dL.
9. Before randomization, despite being treated with the individual MTD of a statin for ≥ 30 days and, if applicable, with another LLT on top of statin (stable for ≥ 30 days),
   a. in participants with very high cardiovascular risk: serum LDL-C ≥ 55mg/dL.
   b. in participants with high cardiovascular risk: serum LDL-C ≥ 70mg/dL.

5.2 Exclusion criteria

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

1. Severe concomitant non-CV disease that is expected to reduce life expectancy to less than 2 years at screening or baseline visit.
2. Participants on more than one other lipid-lowering drug on top of statin at screening visit.
3. Pre-existing diagnosis of homozygous familial hypercholesterolemia at screening or baseline visit.
4. Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome at screening or baseline visit.
5. Previous (within 90 days of screening), current or planned treatment with a monoclonal antibody (mAb) directed towards PCSK9 (e.g. evolocumab, alirocumab) at screening or baseline visit.
6. Previous exposure to inclisiran or any other non-mAb PCSK9 targeted therapy, either as an investigational or marketed drug within 2 years prior to screening or baseline visit.
7. Previous, current or planned treatment with LDL-apheresis at screening or baseline visit.
8. Participants with known intolerance to rosuvastatin at screening or baseline visit.
9. History of hypersensitivity to any of the study treatments, inclisiran or rosuvastatin, or its excipients or to drugs of similar chemical classes at screening or baseline visit.
10. Participants taking gemfibrozil at screening or baseline visit.
11. Liver and CK: (a) Active liver disease defined as any current infectious, neoplastic, or metabolic pathology of the liver or (b) unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST) elevation >3x ULN, or total bilirubin elevation > 2x ULN (except for participants with Gilbert's syndrome), or (c) creatine kinase (CK) >5x ULN at screening or baseline visit.
12. Participant with severe renal impairment defined by eGFR <30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at screening or baseline visit.
13. Acute coronary syndrome, ischemic stroke or TIA, coronary revascularization or peripheral arterial revascularization procedure or amputation due to atherosclerotic disease < 3 months prior to the screening or baseline visit.
14. Planned or expected cardiac, cerebrovascular or peripheral artery surgery or coronary revascularization within the study duration.
15. Heart failure New York Heart Association (NYHA) class IV at screening or baseline visit.
16. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy (excluding systemic adjuvant therapies given to prevent cancer recurrence eg: hormonotherapy for prostate or breast cancer) during the 3 years prior to screening or baseline visit.
17. Participant with myopathy at screening or baseline visit.
18. Participant receiving concomitant ciclosporin at screening or baseline visit.

19. Participants that are predisposed to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).
20. Participants with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose-malabsorption.
21. Unwillingness or inability (e.g. physical or cognitive) to comply with study procedures (including study visits, fasting blood draws and compliance with study treatment regimens), and medication administration (injections) and schedule. Participant should be able and willing to read, understand and answer questionnaires.
22. Any surgical or medical condition, which in the opinion of the investigator, may place the participant at higher risk from his/her participation in the study, or is likely to prevent the participant from complying with the requirements of the study or completing the study at screening or baseline visit.
23. Use of other investigational drugs within 5 half-lives, 30 days or until the expected pharmacodynamic effect has returned to baseline (e.g. biologics), whichever is longer or longer if required by local regulation, prior to screening visit.
24. Pregnant or nursing (lactating) women at screening or baseline visit.
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment, which includes rosuvastatin, and for 5 days (= 5 times the terminal half-life of rosuvastatin) after stopping medication. Highly 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 study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

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 deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the local ICF.

6 Treatment

6.1 Study treatment

Participants will be randomized 1:1 to double-blind s.c. injections of inclisiran sodium 300 mg or placebo. Investigational and control drugs will not be dispensed to the participants but administered by qualified, delegated healthcare personnel at the study site on Day 1, Day 90 and Day 270 of the study.

The open label study treatment, rosuvastatin, will be delivered to the participants at randomization and next visits for daily intake, and participants will be asked to return all unused rosuvastatin treatment and its packaging at each study visit.

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

Treatment Title	Inclisiran[1]	Placebo
Treatment Description	Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL	Placebo in 1.5 mL
Types	Drug	Drug
Dose Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)	Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL	Placebo in 1.5 mL
Dosage Level(s)	Inclisiran sodium 300 mg as 1 injection of 1.5 ml at each of the timepoints specified in Table 8-1	Placebo as injection in 1.5 ml at each of the timepoints specified in Table 8-1
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
IMP	Yes	Yes
Sourcing	Provided centrally by the Sponsor (global)	Provided centrally by the Sponsor (global)
Packaging and Labeling	Study treatment will be provided in pre-filled syringes. Each syringe will be labeled as required per country requirement.	Study treatment will be provided in pre-filled syringes. Each syringe will be labeled as required per country requirement.
1 Inclisiran is also referred to as KJX839		

During the treatment period, a participant can become eligible for PCSK9 mAb treatment. Please refer to Section 3.4 for decision on eligibility.

If, during the course of the study, as per assessment by the Steering Committee, a participant's condition warrants the use of a PCSK9 mAb, preferably CCI the participant will need to discontinue the blinded investigational treatment, inclisiran/placebo, but will remain in the study and will be followed-up until the participant's end of study.

In cases where the Steering Committee deems a participant not eligible for PCSK9 mAb and the Investigator decides to treat the participant as per local standard of care, the participant will need to discontinue study medication (inclisiran/placebo), but will remain in the study and will be followed-up until the participant's end of study.

For intractable cases with LDL-C still too high after LLT escalation (refer to Section 3.4), the Investigator can decide to have the participant discontinue study treatment (inclisiran/placebo) and to be treated as per local standard of care, e.g. considering LDL-apheresis as 'ultima ratio'. The participant will remain in the study and will be followed-up until the participant's end of study.

6.1.2 Additional study treatments

Rosuvastatin is regarded as an Auxiliary Medicinal Product (AxMP) according to the EU Clinical Trial Regulation (EU CTR) refer to Table 6-2.

Table 6-2 Auxilliary Medicinal Products

Treatment Title	**Rosuvastatin**
Treatment Description	Rosuvastatin, 5 mg, 10 mg, 20 mg, 40 mg*
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	Rosuvastatin, 5 mg, 10 mg, 20 mg, 40 mg*
Dosage Level(s)	Dosage and frequency to be determined by the investigator as per local regulations
Route of Administration	Oral use
Use	Background intervention
Authorization status of the AxMP in EEA	Yes
Sourcing	Provided locally by the country or study site
Packaging and Labeling	Will be labeled as required per country requirement and local regulations.
* as commercially available	

At baseline, all participants will be switched from their individual statin to rosuvastatin with a starting dose of 5 mg/day or 10 mg/day according to the local SmPC and at the discretion of the Investigator. Participants who are already treated with rosuvastatin prior to baseline will continue treatment with their individual MTD of rosuvastatin at the discretion of the Investigator.

In addition to the treatment with inclisiran/placebo, rosuvastatin should be sequentially titrated to the MTD, if a participant's individual LDL-C is not at target (refer to Section 3.4).

6.1.3 Treatment arms/group

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

a. Inclisiran sodium 300 mg s.c.
b. Corresponding placebo

Each participant will receive one injection of blinded inclisiran or placebo on Day 1, a second injection of blinded inclisiran or placebo on Day 90 and a subsequent injection of blinded inclisiran or placebo on Day 270, unless there is a need for discontinuing inclisiran/placebo in the course of the study (refer to Section 3.4 and Section 10.2).

In addition at Day 1, each participant will be switched to open label study treatment, rosuvastatin, and receive one dose of rosuvastatin every day from Day 1 to Day 360 during the treatment period, as per individual titration, unless there is a need for discontinuing rosuvastatin in the course of the study (refer to Section 3.4 and Section 10.2).

6.1.4 Treatment duration

Participants who complete participation in this trial and continue to derive clinical benefit from the study treatment based on the investigator's evaluation may receive post-trial access. Post-Trial Access (PTA) means the provision of study treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues study treatment, launch or reimbursement (where applicable), CCI [redacted].

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition participants onto locally available alternative treatment, or standard of care.

The planned study treatment duration is 360 days. In addition, a safety follow-up call will be conducted 30 days after the EOS visit.

Participants may be discontinued from the trial 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 safety recovery or until EOS as per Assessment Schedule (Table 8-1).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

LLT used by the participant in the 6 months prior to screening must be recorded on the appropriate eCRF pages.

All other medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) used by the participant in the 3 months prior to screening must be recorded on the appropriate eCRF pages, independent of whether they will be continued during the study or not. Each concomitant drug must be individually assessed against all exclusion criteria.

Concomitant lipid-lowering therapy

In addition to the treatment with inclisiran/placebo and MTD of rosuvastatin, a participant's individual LLT has to be further escalated throughout the trial, if LDL-C is not at target. The participant's individual LLT should be complemented with ezetimibe (guideline recommendation Class I, Level B). If the LDL-C target is still not achieved, consider use of bile acid sequestrants (guideline recommendation Class IIb, Level C) (Mach et al 2020). Recently approved bempedoic acid may also be considered to be used, however, it is not depicted in the current guidelines and should thus be used secondarily after the aforementioned substances for further escalation of LLT. Concomitant PCSK9 mAb can be considered if a participant is deemed eligible by the Steering Committee. If the participant is deemed eligible for PCSK9 mAb treatment, then the blinded investigational treatment (inclisiran/placebo) will need to be discontinued. The Investigator's treatment decision as well as deviation from the above recommended LLT escalation need to be well documented on the appropriate eCRF pages. (See Figure 3-2)

A new concomitant lipid-lowering drug must be assessed against all prohibited medications prior to its initiation.

Other concomitant therapy

All other medication, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRF pages. A new concomitant drug must be assessed against all prohibited medications prior to its initiation.

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.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Concomitant use of SARS-CoV-2 (COVID-19) vaccines is allowed among participants in this trial. There is no evidence to suggest that participants receiving either inclisiran/placebo or rosuvastatin are at increased risk for adverse events following a COVID-19 vaccination. However, since both inclisiran/placebo and COVID-19 vaccines are administered subcutaneously, it is recommended that the COVID-19 vaccine is administered +/- 7 days from inclisiran/placebo administration. Further, it is recommended that a different anatomical location is used for COVID-19 vaccine and inclisiran/placebo to help differentiate potential

local adverse reactions. Both COVID-19 vaccination administrations that occur prior to entering the study, and during the course of this study should be documented on the eCRF.

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; please refer to local rosuvastatin SmPC for full details). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing rosuvastatin therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered.

Other co-medication increasing the incidence of myositis, myopathy or rhabdomyolysis including fibric acid derivatives, nicotinic acid, azole antifungals, protease inhibitors, macrolide antibiotics and ezetimibe should be used with caution.

The initiation of treatment or dosage up-titration of rosuvastatin in participants treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalized Ratio (INR).

Oral contraceptive: Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel. These increased plasma levels should be considered when selecting oral contraceptive doses.

Please always refer to the local rosuvastatin SmPC.

6.2.2 Prohibited medication

The simultaneous administration of the blinded investigational treatment, inclisiran/placebo, and PCSK9 mAb, CCI [redacted], is prohibited.

In case a PCSK9 mAb is planned to be administered, either based on the eligibility assessment by the Steering Committee or based on the investigator's decision to treat as per local standard of care, blinded investigational treatment (inclisiran/placebo), as outlined in Section 3.4 and Section 6.1.1 must be discontinued.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Any investigational product	Full study duration	Discontinue all study treatment
Lomitapide	Full study duration	Discontinue all study treatment
Mipomersen	Full study duration	Discontinue all study treatment
Niacin	Full study duration	Discontinue all study treatment

Medication	Prohibition period	Action taken
Gemfibrozil	Full study duration	Discontinue all study treatment
Following medications are contraindicated to receive concomitantly with rosuvastatin		
• sofosbuvir/velpatasvir/voxilaprevir	Full study duration	Discontinue all study treatment
• ciclosporin	Full study duration	Discontinue all study treatment

Precautions and warnings:

Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. Rosuvastatin therapy may be re-introduced 7 days after the last fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

The 40 mg dose of rosuvastatin is also contraindicated in patients with pre-disposing factors for myopathy/ rhabdomyolysis, including concomitant use of fibrates.

6.2.3 Rescue medication

Not applicable for the blinded investigational treatment, inclisiran/placebo. For the open label study treatment, rosuvastatin, please always refer to the local SmPC.

6.3 Preparation and dispensation

Blinded investigational treatment, inclisiran/placebo:

- Each study site will be supplied with study drug in packaging as described in Section 6.1.1.
- A unique medication number is printed on the study medication label.
- Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). Study medication (inclisiran/placebo) accountability and reconciliation data are recorded in the IRT system. The study medication has a 2-part label (base plus tear-off label), immediately before 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

Open label study treatment rosuvastatin:

- Commercially available rosuvastatin will be sourced locally and supported by the sponsor.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Blinded investigational treatment, inclisiran/placebo, must be received by a designated person at the study site, handled, stored and kept safely and properly in a secured location to which only the investigator and the designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

For open label study treatment, rosuvastatin, the above is also applicable when stored at the site. In case rosuvastatin is supplied by another facility, e. g. local pharmacy, it needs to be ensured all processes regarding the proper handling of the open label study medication are followed.

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

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

For open label study treatment, rosuvastatin, that is administered at home, participants will be asked to -bring all used/unused study treatment and its packaging at each study visit.

The investigator must maintain an accurate record of the shipment and dispensing of all study treatment (including open label study treatment, rosuvastatin) in a drug accountability log. Monitoring of the drug accountability of both of the study treatments, blinded inclisiran/placebo and open label rosuvastatin, will be performed by field monitors during site or remote visits, and at the completion of the trial, as described in the Monitoring Plan.

The site may destroy and document the 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 blinded investigational 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

The following non-study treatments have to be monitored specifically, as described in the Monitoring Plan:

- All lipid-lowering therapies

6.3.2 Instructions for prescribing and taking study treatment

Blinded investigational treatment, inclisiran/placebo, will not be dispensed to the participants. Study drug injections will be performed exclusively at the study site by qualified clinical study site staff under the supervision of the investigator or designee.

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

Participants will be administered one subcutaneous injection of blinded investigational treatment, inclisiran/placebo, at pre-defined visits, as specified in the Schedule Visit (Table 8-1).

Injections will be administered after all other study assessments have been completed for the visit.

Blinded investigational treatment, inclisiran/placebo, assigned by the IRT will be recorded in the IRT system. All injections to the participant as well as study drug interruptions/discontinuations (i.e. no injection at a designated dosing visit) during the study must be recorded on an appropriate eCRF and within IRT.

Open label study treatment, rosuvastatin, will be commercially sourced locally. Rosuvastatin should be taken by the participant at a certain dose level and time of day as instructed by the investigator and according to the local SmPC. Drug reconciliation of open label study treatment, rosuvastatin, needs to be performed and documented to capture the dispensing and daily intake of rosuvastatin on participant level. Rosuvastatin dispensing or accountability will not be captured within IRT. For this reason, it is important that any drug interruptions, or discontinuations for rosuvastatin during the study be recorded in the eCRF.

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 ICF, the participant is assigned to the next sequential Participant No. available.

6.4.2 Treatment assignment, randomization

At screening, the investigator or his/her delegate will contact the Interactive Response Technology (IRT) and record the current statin and LLT, if applicable, in the system in order to manage the population according to eligibility criteria. Once the participant's full eligibility has been confirmed, the investigator or his/her delegate will indicate in IRT and eCRF in which subsequent period the participant will be assigned (run-in or treatment period).

The investigator or his/her delegate will contact the IRT again at the baseline/randomization visit (Day 1). All eligible participants will be randomized via IRT to one of the two treatment arms. The IRT will assign a randomization number to the participant, which will be used to link

the participant to a treatment arm 1:1 and will specify a unique medication number for the first package of blinded investigational treatment, inclisiran or placebo, to be assigned 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, or by a delegate under Novartis/Sponsor supervision, 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.

Randomization will be stratified by cardiovascular risk category as outlined in the 2019 ESC/EAS guidelines for the management of dyslipidemia (Mach et al 2020) and defined in the inclusion criterion a) very high risk participant and b) high risk participant.

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 blinded to the identity of the treatment (inclisiran/placebo) from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding. The independent statistician and programmer will not be involved in any other trial activities. (2) The treatment identity will be concealed by using identical packaging, labelling, schedule of administration and appearance of the blinded investigational treatment.

Unblinding via randomization codes will only occur in the case of participant emergencies and after the end of the study. Unblinding a single participant at a site by revealing the randomization code 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 blinded investigational treatment, inclisiran/placebo.

The rosuvastatin dose will not be blinded.

6.6 Dose escalation and dose modification

Blinded investigational treatment, inclisiran/placebo, dose adjustments are not permitted, for interruptions, please refer to Section 9.1.1.

For open label study treatment, rosuvastatin, dose adjustments please refer to Section 3.4 and Section 6.6.2. For rosuvastatin dose interruptions please refer to Section 9.1.1 and Section 10.2.

6.6.1 Dose escalation guidelines

Dose adjustments of blinded investigational treatment, inclisiran/placebo, are not permitted.

For open label study treatment, rosuvastatin, dose adjustments please refer to Section 3.4.

6.6.1.1 Starting dose

Not applicable for blinded investigational treatment, inclisiran/placebo.

At the baseline visit (Day 1), all participants will be switched from their individual statin to open label study treatment, rosuvastatin. Participants can start rosuvastatin treatment either with 5 mg/day or 10 mg/day according to the local SmPC.

Start dose of 5 mg/day is recommended in patients:

- 70 years
- with moderate renal impairment (creatinine clearance < 60 mL/min)
- of Asian ancestry
- with predisposing factors to myopathy.

Considering the local SmPC, rosuvastatin starting dose will be chosen for a particular participant by the investigator. Participants already treated with rosuvastatin prior baseline visit will continue treatment with their individual MTD of rosuvastatin, if in accordance with the investigator.

Rosuvastatin should be used with caution in participants with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment (severe renal impairment is an exclusion criterion (Section 5.2))
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age > 70 years
- situations where an increase in plasma levels may occur
- concomitant use of fibrates.

6.6.1.2 Provisional dose levels

During visits at Day 30, Day 60 and Day 90, open label study treatment, rosuvastatin, will be sequentially titrated every 30 days until the participant's individual LDL-C is at target or until the participant achieves the MTD of rosuvastatin, whichever occurs first. For MTD definition please refer to Section 3.4.

Dose adjustments have to follow the local SmPC, and recommended titration steps for rosuvastatin are 5 mg/day, 10 mg/day, 20 mg/day, and up to a maximum dose level of 40 mg/day, if indicated. In case rosuvastatin is not optimally titrated by Day 90, there is an optional visit at Day 120 for further optimizing rosuvastatin dose.

6.6.2 Definitions of dose limiting toxicities (DLTs)

DLTs are not applicable for blinded investigational treatment, inclisiran/placebo.

For open label study treatment, rosuvastatin, please refer to Section 10.2 and local SmPC.

6.6.3 Dose modifications

Blinded investigational treatment, inclisiran/placebo, dose adjustments and modifications are not permitted throughout the trial.

For open label study treatment, rosuvastatin, dose adjustments please refer to Section 3.4 and Section 10.2.

The 40 mg rosuvastatin dose is contraindicated in participants with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- moderate renal impairment (creatinine clearance < 60 mL/min)
- hypothyroidism
- personal or family of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in plasma levels may occur
- Asian patients
- Concomitant use of fibrates.

In situations where co-administration of medicinal products causing an increase in systemic exposure of rosuvastatin or increased risk of myopathy is unavoidable, the maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products (always refer to local rosuvastatin SmPC).

Generally, rosuvastatin should be prescribed with caution in participants with pre-disposing factors for myopathy/rhabdomyolysis.

Please note, specific types of genetic polymorphisms are known that can lead to an increased rosuvastatin exposure. For participants who are known to have such specific types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

The initiation of treatment or dosage up-titration of rosuvastatin in participants treated concomitantly with vitamin K antagonists (e.g., warfarin or another coumarin anticoagulant) may result in an increase in International Normalized Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR.

6.6.4 Follow-up for toxicities

Not applicable for blinded investigational treatment, inclisiran/placebo.

For follow-up of toxicities of open label study treatment, rosuvastatin, please refer to Section 10.2.

All AEs will be followed up appropriately, see Section 10.1.1.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by informing the participant that compliance is necessary for the participant's safety and the validity and the integrity of the study. The investigator should also instruct the participant to adhere closely to the scheduled study visits. Blinded investigational treatment, inclisiran/placebo, will not be dispensed to the participant but administered at designated study visits at the study site, by qualified personnel. Inclisiran/placebo dosing information should be captured within each designated visit on an appropriate eCRF page.

For open label study treatment, rosuvastatin, the investigator must promote compliance by instructing the participant to take the study treatment 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 treatment as prescribed.

Compliance for open label study treatment, rosuvastatin, 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 at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

All additional LLT dispensed must be recorded in eCRF and compliance should be instructed accordingly.

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.

AEs related to the open label study treatment, rosuvastatin, should be treated in reference to the respective local SmPC.

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

6.7.3 Emergency breaking of assigned treatment code

Code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most of the time, the study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the IRT 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 unblinding can be performed at any time.

After an emergency unblinding, blinded investigational treatment, inclisiran/placebo, 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 EOS 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), IRB/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 ICF that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found either in the Investigator's Brochure (IB), or in the local SmPC. 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 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, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study.
- Pregnancy Outcomes Reporting Consent for female participants.

Women of childbearing 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.

As per Section 4.6, 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.).

Data protection measures

Participants will be assigned a unique identifier. 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.

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment will be followed-up until the end of the study 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 (EOS) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications not previously reported must be recorded on the eCRF.

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.

PRO measure(s) are strongly recommended to be completed before any clinical assessments are performed at any given visit (with the exception of the pain diary which should be completed as described in Section 8.5.1.2).

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

- Fasted for all visits with LDL-C assessment and assessment of other lipid samples.
- Must refrain from unaccustomed strenuous physical exercise for 48 hours before the screening and any study visit until the double-blind treatment period has been completed.

As per Section 4.6, 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	Run-In				Baseline		Treatment											Follow-up call
Visit Name	Screening[1]	Run-In Period[2]				Baseline[3]		Treatment								Prior to PCSK9mAb switch[5]	Unscheduled	EOT/EOS[22]	Follow-up call +30 days
Days	-144 to -130	-130	-100	-70	-40	-10	1	30	60	90	120[4]	150	210	270	330	UNS	UNS	360	390
Informed consent	X																		
Inclusion / Exclusion criteria	X						X												
Demography	X																		
Medical history/current medical conditions	X																		
CV Disease, Alcohol and COVID-19 Vaccination History	X																		
Smoking status	X	X	X	X	X		X	X	X	X	X[4]	X	X	X	X				
(Other) prior/concomitant medications	X	X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	
Prior/Concomitant lipid lowering therapies (types and doses)	X	X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	
Surgical/medical procedures[6]		X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	
Lifestyle instructions	X	X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	
Enter patient visit into IRT	X						X	X	X	X	X[4]	X	X	X	X		X	X	

Period	Screening	Run-In				Baseline		Treatment											Follow-up call
Visit Name	Screening[1]	Run-In Period[2]				Baseline[3]		Treatment								Prior to PCSK9mAb switch[5]	Unscheduled	EOT/EOS[22]	Follow-up call +30 days
Days	-144 to -130	-130	-100	-70	-40	-10	1	30	60	90	120[4]	150	210	270	330	UNS	UNS	360	390
Randomization							X												
Dispense inclisiran/placebo							X			X				X					
Dispense rosuvastatin							X	X	X	X	X[4]	X	X	X	X		X		
Rosuvastatin compliance								X	X	X	X[4]	X	X	X	X		X	X	
AEs/SAEs	X	X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	S[7]
Pregnancy Test (serum)[8]	X																		
Pregnancy Test (urine)[9]		X	X	X	X		X	X	X	X	X[4]	X	X	X	X		X	X	
Physical Examination	S[7]						S[7]			S[7]				S[7]				S[7]	
Body Height	X																		
Body Weight	X						X												
Vital Signs	X			X			X	X		X		X	X	X	X		X	X	
Fasting LDL-C assessment[10]			X	X	X			X	X	X	X[4]	X	X	X	X		X		
Fasting Lipid Profile[11]	X					X			X	X		X			X			X	
Fasting Lp(a)[12]	X					X				X								X	
PCSK9 levels[13]							X									X		X	
Clinical Chemistry[14]	X			X		X				X		X	X	X	X			X	
Limited chemistry[15]		X	X		X			X	X		X[4]						X		

Period	Screening	Run-In				Baseline		Treatment										Follow-up call
Visit Name	Screening[1]	Run-In Period[2]				Baseline[3]		Treatment								Prior to PCSK9mAb switch[5]	Unscheduled	EOT/EOS[22]	Follow-up call +30 days
Days	-144 to -130	-130	-100	-70	-40	-10	1	30	60	90	120[4]	150	210	270	330	UNS	UNS	360	390
Hematology[16]	X					X						X						X	
Urinalysis[17]	X					X						X						X	
Pain Diary[18]							X	X	X	X	X	X	X	X	X		X	X	
SF-BPI[19]	X						X	X	X	X	X[4]	X	X	X	X		X	X	
GSRS[19]							X	X	X	X	X[4]	X	X	X	X		X	X	
SF-36[19]	X						X			X			X					X	
WIQ[19,20]							X			X								X	
Mac New[19,21]							X			X								X	
TSQM[19]							X			X								X	
Safety Follow up Call																			S[7]

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Central Lab results will be needed to confirm eligibility at the screening visit.
[2] Optional visit only for participants that require a statin up-titration after screening in order to reach their individual MTD, run-in-period
[3] The Baseline visit may be split into 2 visits, planned approximately 10 days apart. Participants not randomized within 7 days of screening or coming from run-in will have Day -10 visit which will only consist of Central lab draws. The investigator may schedule the Baseline (Day 1) visit, after Central lab results are received and eligibility confirmed.
[4] Only if necessary, Optional visit for titration of rosuvastatin, treatment period
[5] This is not required to be a stand-alone visit: This is a reminder to investigators to draw a blood sample, to measure levels of PCSK9, prior to switching a participant to a PCSK9 mAb. Timing for this visit will vary, depending on the timing of treatment switching and will not be applicable for all participants. In case PCSK9 samples were taken at an unplanned visit, the sampling can be recorded at this visit
[6] Record any surgeries or medical procedures since the prior visit.
[7] S: Record in Source Document only (send paper SAE form to safety when SAE is reported)
[8] Only in women of childbearing potential. Serum tests will be sent to the Central lab for analysis.
[9] Only in women of childbearing potential. Performed locally, prior to any dosing, using central laboratory kit supplies.
[10] LDL-C can be assessed locally at the site via a provided LDL-C point of care device. These local results will be used for LLT decision making. In the event the assessment cannot be completed with the LDL-C point of care device, LDL-C will be assessed by central lab (unscheduled visit).
[11] LDL-C, ApoB, non-HDL-C, total cholesterol, triglycerides, and HDL-C. Performed by the central lab.

Period	Screening	Run-In				Baseline		Treatment										Follow-up call
Visit Name	Screening[1]	Run-In Period[2]				Baseline[3]		Treatment								Prior to PCSK9mAb switch[5]	Unscheduled	EOT/EOS[22]	Follow-up call +30 days
Days	-144 to -130	-130	-100	-70	-40	-10	1	30	60	90	120[4]	150	210	270	330	UNS	UNS	360	390

[12] Lp(a) will only be tested at screening, baseline, Day 90 and EOS. From this sample,triplicate serum aliquots will be made to allow Lp(a) testing in both nmol/L and mg/dL; a third aliquot will be made to allow testing of LDL-C and/or Lp(a) using novel methods currently in development.
[13] A blood draw for PCSK9 levels will also be performed prior to participant switch to PCSK9 mAb, ~~preferably once this switch is granted~~. The PCSK9 results will remain blinded and will not be used to influence treatment decisions. A plasma aliquot from tthe PCSK9 blood draw (e.g. SOMA) may also be used to profile proteins related to study drug or dyslipidemia.
[14] AST, ALT, ALP, GGT, total bilirubin, CK, creatinine, creatinine clearance, eGFR, chloride, sodium, potassium, fasting glucose, HbA1C. Performed by the central lab.
[15] ONLY: AST, ALT, ALP, GGT, CK, Total bilirubin. Performed by the central lab.
[16] Hematocrit, Hemoglobin, Red Blood Cell (RBC) Count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Platelets, Erythrocyte Cell Morphology, White Blood Cell (WBC) count with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands). Performed by the central lab.
[17] Urinalysis to include: specific gravity, pH, glucose, protein (total), ketones, bilirubin, urobilinogen, nitrite, hemoglobin (blood), leukocytes esterase. If dipstick measurement results are positive (abnormal), microscopic examination will be performed.
[18] Done every day during the treatment period, using a digital hand-held device. Participant is to complete the diary everyday at home and the diary will be checked by the investigator at each site visit.
[19] Training for each questionnaire should be completed with each participant prior to the first individual participant questionnaire completion.
[20] The Walking Impairment Questionnaire will only be completed by participants diagnosed with peripheral artery disease (PAD) at Baseline.
[21] The Mac New Heart Disease Health Related Quality of Life Questionnaire will only be completed by participants diagnosed with Angina Pectoris (AP) at Baseline.
[22] Theoretically, EOT and EOS happen on day 360, but if EOT occurs before the EOS visit, it is recommended that the participant remains in the study until the scheduled EOS. The assessments listed for this visit should only be conducted if the End of Treatment (EOT) and End of Study (EOS) occur simultaneously. An "early Exit" (premature discontinuation from study treatment and study on the same day before day 360) is considered as an EOS visit, and the assessments should be performed as they would be on EOS visit day 360. In case of premature treatment discontinuation, the assessments for the scheduled visit day should be performed (for details refer to Section 8.5.1 and Section 9.1.1).

8.1 Screening

Screening activities (Table 8-1) must be initiated only after the ICF (and assent if applicable) has been signed. A participant may go directly from the screening visit to the baseline visit, if they meet the criteria, as outlined in Section 3.1. In this case the screening period may last up to 14 days. If the time between the screening labs and randomization is less than or equal to 7 days, then the labs do not need to be repeated and the screening labs will function as both the screening and baseline labs.

A participant who enters screening but is determined not eligible will be considered a screen failure. The investigator may consider re-screening the participant at a later time if he/she believes that the participant's condition has changed and they may potentially be eligible. In this case, a new participant number will be allocated to the participant and he/she will need to re-perform all Screening Visit procedures. A participant may be re-screened once. A minimum of 2 weeks must elapse between screen failure and re-screening. The participant must provide new written informed consent before being re-screened.

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, reported AEs related to Auxiliary Medicinal Product (AxMP) and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data is 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 SAE 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 that the participant was not randomized.

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

8.2 Participant demographics/other baseline characteristics

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

Participant demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity, relevant medical history, CV disease history, alcohol history, COVID-19 vaccination information and current medical condition present before informed consent was signed (where possible, diagnoses and not symptoms will be recorded), concomitant LLT, as well as relevant laboratory tests.

Participant race and ethnicity are collected and analyzed to assess the diversity of the study population as required by certain Health Authorities and may be used to identify variations in safety or efficacy due to these factors.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate eCRF page.

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

The investigator will record in the eCRF in which cardiovascular risk category the participants is allocated at screening, run-in period (if applicable) and during the treatment period for analysis purpose, and also in IRT at screening for stratification.

8.3 Efficacy

The LDL-C and other exploratory biomarker assessments are specified below, with the Assessment Schedule (Table 8-1) detailing when each assessment is to be performed. Participants will be in a fasted state for all of these laboratory assessments. Details regarding the collection, processing, shipping and storage of the samples for central lab will be provided in a Laboratory Manual.

8.3.1 LDL Cholesterol

The primary efficacy assessment will be LDL-C, as tested and reported by the central lab as part of the full Lipid Panel at the frequency shown in Table 8-1 .

In addition, where a recent LDL-C measurement is required in order to decide for LLT escalation, LDL-C will be measured locally at sites using a LDL-C point of care device at the frequency shown in Table 8-1. In the event the assessment cannot be completed with the LDL-C point of care device, the LDL-C is to be assessed by the central lab.

Participants need to be fasting for all LDL-C assessments. LDL-C values will not be blinded for the investigator to enable an ongoing individual optimization of LLT if necessary to achieve a participant's LDL-C target. The investigator is encouraged to not disclose the LDL-C value to the participant.

If participants gain eligibility and receive LDL-apheresis in the course of study (refer to Section 3.4), LDL-C must be measured immediately before the scheduled apheresis treatment.

8.3.2 Appropriateness of efficacy assessments

Inclisiran is a siRNA which acts to reduce LDL-C. 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 (Ference et al 2017). Laboratory tests related to the endpoints are in line with the expected efficacy of inclisiran. It is the primary endpoint of the study.

Exploratory endpoints are hypothesis generating and exploratory in nature.

8.4 Safety

The safety profile of inclisiran has been well characterized in the Phase III LDL-C lowering studies (ORION-9, -10 and -11) (Wright et al 2021) which included over 3,600 participants with similar demographic and baseline characteristics to the population expected to be included in the current study.

The safety profile of rosuvastatin has been well characterized and is outlined in the local SmPC.

As per Section 4.6, 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.

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

For details on AE collection and reporting, refer to the AE Section 10.1.

A complete physical examination will be performed at the visits, as outlined in Table 8-1. Details on what is included in the complete physical exam and the requirements to perform vital signs assessment and height/ weight measurements are provided in Table 8-2.

Table 8-2 Assessments & Specifications

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 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

As per Section 4.6, 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.

Specimens will be obtained at the time points detailed in the Assessment Schedule (Table 8-1). Details on what is included in hematology, chemistry, lipids/lipoproteins and urinalysis laboratory evaluations are provided in Table 8-3.

Central laboratory will be used for analysis of all specimens collected, with the exception of urine pregnancy tests, which will be done locally (using testing materials supplied by the central laboratory). Serum pregnancy tests at screening will be done by the central laboratory.

For immediate and local action on statin up/down-titration or other LLT escalation, LDL-C value will be measured using a LDL-C point of care device and recorded in the eCRF accordingly. In the event the assessment cannot be completed with the LDL-C point of care device, the LDL-C is to be assessed by the central lab.

LDL-C will also be centrally analyzed at the visits as outlined in Table 8-1, as part of the full Lipid Panel.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in a Laboratory Manual.

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

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Red Blood Cell (RBC) Count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Platelets, Erythrocyte Cell Morphology*, White Blood Cell (WBC) count with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands**)
Chemistry	**Full chemistry:** AST, ALT, ALP, GGT, total bilirubin, direct and indirect bilirubin (if total >2ULN), CK, creatinine, creatinine clearance, eGFR*, sodium, potassium, chloride, glucose (fasting)***, HbA_{1c}*** **Limited chemistry:** ONLY: AST, ALT, ALP, GGT, total bilirubin (fractioned bilirubin (if total bilirubin >2ULN), CK
Lipids/Lipoproteins/ Biomarkers	LDL-C, ApoB, Lp(a), non-HDL-C, total cholesterol, triglycerides, and HDL-C. PCSK9 levels, see Table 8-1.
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)
Urinalysis	Dipstick measurements for: specific gravity, pH, glucose, protein (total), ketones, bilirubin, urobilinogen, nitrite, hemoglobin (blood), leukocytes esterase If dipstick measurement results are positive (abnormal), microscopic examination will be performed

*Reflex testing only in event of abnormal result from absolute count/ differentials

**eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) eGFR formula as follows:

175 x [standardized serum creatinine (mg/dL)]$^{-1.154}$ x [age] $^{-0.203}$ x [1.212 if race=black/African American] x [0.742 if female]

***Diagnosis of diabetes based on HbA1c ≥_6.5% (48 mmol/mol) or FPG two consecutive values ≥126 mg/dL (7.0 mmol/L).

8.4.2 Electrocardiogram (ECG)

Not Applicable.

8.4.2.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not Applicable.

8.4.2.2 Cardiac enzymes

Not Applicable.

8.4.3 Pregnancy

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment, which includes rosuvastatin, and for 5 days (= 5 times the terminal half-life) of rosuvastatin) after stopping medication. Highly 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 study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

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 childbearing 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 childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the local ICF.

All woman of child-bearing potential will have a serum pregnancy test performed at the Screening Visit. A urine pregnancy test will be performed at all subsequent visits. A positive urine pregnancy test should be confirmed with a serum pregnancy test. Participants with a positive urine/serum pregnancy at any time in the study must be excluded.

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

As per Section 4.6, 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, urine pregnancy test kits may be used at the participant's home. 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).

8.4.4 Other safety evaluations

8.4.4.1 Hyperglycemia-related events

AEs of new onset of diabetes mellitus should follow the criteria accepted in recent diabetes guidelines (ESC 2019 Guideline on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the European Association for the Study of Diabetes (EASD)) and be reported in participants with no medical history of diabetes mellitus and only in the context of the local standard of care follow-up if:

- Either an HbA1c with a diagnostic threshold of ≥6.5% (48 mmol/mol) or a FPG 2 consecutive values ≥126 mg/dL (7.0 mmol/L) is documented. A diagnosis of new onset diabetes mellitus can only be confirmed if two abnormal test results, either from the same sample or in two separate test samples, can be retrieved.).
- Addition of a new concomitant medication for control of plasma glucose.
- Evidence of classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose of ≥200 mg/dL (11.1 mmol/L).
- A plasma glucose of ≥200 mg/dL (11.1 mmol/L) 2 hours after a 75-gram oral glucose load.

Details for AEs of new onset of diabetes mellitus will also be collected.

'Worsening of glycemic control' should be reported as an AE on the eCRF in participants with a medical history of disease (HbA1c ≥6.5% at baseline) when both conditions are met:

- HbA1c increases from baseline >0.5%.
- New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of the plasma glucose level.

8.4.4.2 Major Adverse Cardiovascular Event (MACE)

Participants in the investigated population are at risk to the occurrence of major cardiovascular events (MACE). On a participant level this may appear in diverse types of events. Therefore, in this trial a broad approach to the evaluation of MACE events is deemed appropriate. A 5P-MACE will be evaluated as a composite of CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic), urgent coronary revascularization. The components of MACE will be reported as diagnosed by the investigator. Details on these events will be collected on an appropriate eCRF page.

8.4.4.3 CCI

8.4.4.4 Hospitalization due to a cardiovascular reason

Every hospitalization due to a cardiovascular (CV) reason as primary diagnosis of admission will be recorded on an appropriate eCRF page by the investigator.

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.5.1 Clinical Outcome Assessments (COAs)

As per Section 4.6, 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, PRO data may be collected remotely according to local regulation.

Patient reported outcomes (PRO)

Completion of Questionnaires

Participant should complete the PROs at the scheduled visit before any clinical assessments are conducted (with the exception of the pain diary which should be completed as described in Section 8.5.1.2). Missing PROs should not be captured as a protocol deviation with the exception of PROs included in the secondary endpoints (SFBPI and pain diary).

The participant should be given sufficient space and time to complete the PROs .

Under special circumstances, such as but not limited to illiteracy and poor vision, the completion of the questionnaires can be done with assistance, by a caregiver or a study coordinator not directly involved in the care of the participant, if a participant is unable to complete it on their own. This situation should be clearly noted both in source documents.

Participant questionnaires should be completed in the language most familiar to the participant.

All participants will complete the PRO questions via an electronic handheld device. If participants experience any difficulties with submission after they complete the Patient Reported Outcome (PROs), the study staff should assist them with submitting their responses. In case participants discontinue treatment prior to the study completion, they should be asked to complete the PROs as indicated in the schedule of assessments.

The site personnel should check the PRO measures for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file.

Completed PROs as well as pain diary, including any unsolicited comments written by the participant, must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs or use of pain-relieving medication before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigator should not encourage the participant to change responses reported in the completed questionnaire or diary. Study investigators must follow reporting instructions outlined in Section 10.1.

8.5.1.1 Short-Form Brief Pain Inventory (SF-BPI)

The SF-BPI is a self-administered standardized fifteen items questionnaire that assesses how pain interferes with or influences a participant's life. The query period covers the past 24 hours and takes 5 minutes for the participant to complete. The first item is a screening question about the participant's pain on the day. The questionnaire is then composed of pain drawing diagrams, four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on pain relief treatment or medication, and one item on pain interference, with seven sub-items (general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life). The SF-BPI includes two main scores: a pain severity score and a pain interference score. The pain severity score combines the information of the four items about pain intensity, which are rated from 0, no pain, to 10, pain as bad as you can imagine. To derive the pain severity score the average of the four items will be taken The pain interference is calculated similarly using the seven items regarding pain interference, which are rated from 0, does not interfere, to 10, completely interferes. The pain interference score will be the average of these seven items. Both scores will be between 0 and 10. The remaining items if the questionnaire do not contribute to the scoring. Higher scores correspond to a poorer condition of the participant. The first item, pain drawing diagrams (painful and most painful areas) and the items on pain relief treatment or medication (list of the treatments and amount of relief) do not contribute to the scoring. It has been validated (Tan et al 2005, Keller et al 2004) for use with non-malignant pain populations and has been used in statin trials (Cleeland 2009).

The SF-BPI will be recorded as outlined in the Assessment Schedule (Table 8-1).

8.5.1.2 Pain Diary

The Pain Diary is based on item-3 of SF-BPI. Daily pain will be rated on a numeric scale from 0 (no pain) to 10 (pain as bad as you can imagine) by the participants describing their pain at its worst in the last 24 hours. All participants will complete the diary via a handheld an electronic device. Investigators should instruct the participants to fill in the diary on a daily basis and to adhere to a certain routine for completing the diary.

8.5.1.3 SF-36 Version 2

The Short-Form Health Survey (SF-36) is a generic health-related quality of life (HRQoL) instrument which comprises of 36 questions across 8 domains: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or

emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); 8) general health perceptions (Ware and Sherbourne 1992). Two overall summary scores, the physical component summary (PCS) and the mental component summary (MCS) will be computed (Ware 1994). An increase in the scale values reflects an improvement in the quality of life (Ware and Sherbourne 1992). The SF-36 is considered to be a valid, reliable, concise generic measure of state of health and has demonstrated to detect clinical treatment benefits across medical conditions including chronic disorders such as dyslipidemia (Hyttinen et al 2008). The SF-36 is regularly used as a generic questionnaire in clinical studies in the field of cardiology (Müller-Nordhorn et al 2004) and is the most frequently used generic questionnaire in clinical studies with peripheral arterial disease (PAD) participants (Poku et al 2016). In the cardiovascular participant population, especially those with Coronary Heart Disease (CHD), it is considered to be the most reliable and change-sensitive generic questionnaire (Dempster and Donnelly 2000). The SF-36 has been validated at the international level for the chronically ill, including cardiac participants (Ware and Gandek 1998, Alonso et al 2004). In addition, the Health-related quality of life (HRQoL) project resulted in international reference values for the SF-36 for heart participants (Huber et al 2016). SF-36 will be recorded as outlined in Table 8-1.

8.5.1.4 Gastrointestinal Symptom Rating Scale (GSRS)

The self-administered GSRS questionnaire contains 15 items for gastrointestinal syndromes, which are composed of 5 dimensions (abdominal pain, reflux syndrome, indigestion, diarrhea and constipation) and use a Likert scale with 7 units (1 being no discomfort to 7 being very severe discomfort) (Svedlund et al 1988, Chan et al 2006, Kulich et al 2003). The subscores of individual domains are calculated by averaging the scores of the associated items. The average of all subscores gives the total score, which ranges from 1 to 7 points. The lower the value, the better the gastrointestinal condition. The reliability and validity of the GSRS are well-documented (Revicki et al 1998, Kulich et al 2008, Samaha et al 2008), and norm values for a general population are available (Kulich et al 2003, Dimenäs et al 1995). The GSRS has been taken isolated into account in the present indication (Samaha et al 2008) and therapeutic area of "metabolic diseases".

Data will be collected as outlined in the Assessment Schedule (Table 8-1).

8.5.1.5 Treatment Satisfaction Questionnaire for Medication (TSQM v. II)

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a validated participant reported outcome instrument (Atkinson et al 2004, Atkinson et al 2005) used to assess participant satisfaction with treatment. All subjects will be provided with the TSQM v. II, an 11-item multiple choice questionnaire validated to assess convenience and global satisfaction with treatment.

TSQM is a widely used generic measure, including dyslipidemia (Mulchandani et al 2019, Rodríguez Arroyo et al 2014), to assess the major dimensions of patients' satisfaction with medication and has been psychometrically validated in a heterogeneous sample (Atkinson et al 2004, Atkinson et al 2005). TSQM v. II is comprised of 11 questions that

provide scores on four scales: effectiveness (2 items), side effects (4 items), convenience (3 items) and global satisfaction (2 items) over the previous 2–3 weeks, or since the participant's last use. With the exception of item 4 (presence of side effects; yes or no), all items have five or seven responses, scored from one (least satisfied) to five or seven (most satisfied). Item scores are summed to give four domain scores, which are in turn transformed to a scale of 0–100. The higher the value, the higher is the participant's satisfaction with the treatment.

Data will be collected as outlined in the Assessment Schedule (Table 8-1).

8.5.1.6 Walking Impairment Questionnaire (WIQ)

The Walking Impairment Questionnaire (WIQ) measures self-reported walking distance, walking speed, and stair-climbing ability in men and women with lower extremity peripheral arterial disease (PAD) (Regensteiner et al 1996). The modified WIQ records a total of 16 items in four categories: pain (2 questions), walking distance (7 questions), walking speed (4 questions), and stair climbing (3 questions). In the WIQ distance score, the participant records the degree of difficulty walking specific distances (ranging from walking indoors to 1,500 feet or 5 blocks) on a graded Likert- scale from 0 to 4. A score of 0 represents the inability to walk the distance in question and a score of 4 represents no difficulty. In the WIQ speed score, the participant is asked to assess the degree of difficulty walking 1 block at specific speeds ranging from walking slowly to jogging on a graded scale ranging from 0 to 4. In the WIQ stair climbing score, the participant reports the degree of difficulty climbing 1, 2, and 3 flights of stairs. This graded score is multiplied by a pre-specified weight for each distance, speed, or number of stair flights. The products are summed and divided by the maximum possible score to obtain a percent score, ranging from 0 (representing the inability to perform any of the tasks) to 100 (representing no difficult with any of the tasks) (Regensteiner et al 1990). The WIQ scores have been shown to improve in response to lower extremity revascularization (Nicolaï et al 2009) and supervised exercise therapy (McDermott et al 2009). The WIQ has been validated several times in PAD participants (McDermott et al 1998, Sagar et al 2012, Coyne et al 2003, Nicolaï et al 2009) and also provides good predictions of cardiovascular risk in other cardiovascular diseases (Nead et al 2013).

The WIQ will only be completed by participants diagnosed with PAD at Baseline. WIQ will be collected as outlined in the Assessment Schedule (Table 8-1).

8.5.1.7 MacNew Heart Disease Quality of Life Questionnaire (MacNew)

The MacNew Heart Disease HRQoL questionnaire (Mac-New) is a self-administered modification of the original Quality of Life after Myocardial Infarction (QLMI) instrument (Lim et al 1993, Valenti et al 1996). It was specially developed to measure the quality of life of participants with cardiovascular diseases. The MacNew consists of 27 items which fall into three domains (physical limitations, emotional and social function domain scale). There are 5 items that inquire about symptoms: angina/chest pain, shortness of breath, fatigue, dizziness, and aching legs. The participants answer the questions using a seven-point Likert scale from 1 ("worst feeling") to 7 ("best feeling"). The scores of the three individual domains are calculated by averaging the point values in the associated items. The average value of all 27 items gives the global total score. A higher total score corresponds to a better quality of life. The validity, reliability and change sensitivity of the MacNew have been demonstrated in various participant

groups, including participants with myocardial infarction, with AP and with ischemic heart failure (Höfer et al 2004, Höfer et al 2012).

The Mac New questionnaire will only be completed by participants diagnosed with Angina Pectoris at Baseline. The query period covers the past 14 days. The MacNew questionnaire will be administered as outlined in Table 8-1.

8.5.2 Other exploratory biomarkers

Other exploratory biomarkers to be collected will include:

- Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, and HDL-C, to be collected as per assessment Table 8-1.
- PCSK9 levels will be collected from all participants at the baseline and the EOS visits. In the case that a PCSK9 mAb treatment is indicated for a particular participant in the escalation process, a blood draw for PCSK9 levels must be performed prior to starting on the PCSK9 mAb. The results from the PCSK9 testing will be blinded to all site staff and Novartis team members.

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 administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment (inclisiran/placebo) or rosuvastatin for a given participant if, he/she believes that continuation of the respective study treatment would negatively impact the participant's well-being.

Discontinuation from study treatment (inclisiran/placebo) or rosuvastatin is required under the following circumstances:

- Participant/guardian decision.
- Pregnancy.
- Use of prohibited treatment as per recommendations in the prohibited treatment (Section 6.2.2).
- Any situation in which continued study participation might result in a safety risk to the participant (Section 10.2).

- Following emergency unblinding.
- Any 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 (Section 10.2).
- Participant is switched to a PCSK9 mAb (Section 3.4).
- Intractable cases with LDL-C still too high after the recommended LLT escalation (Figure 3-2 of Section 3.4) and participant is required to be treated per local standard of care.

If a participant is required to discontinue from Inclisiran/Placebo, they should remain on open label study treatment (rosuvastatin) and continue following the protocol recommended escalation scheme as applicable (Section 3.4 and assessment schedule (Table 8-1).

If a participant is required to discontinue from open label treatment rosuvastatin, they should be switched to an alternative well tolerated statin, as per local standard of care and at the discretion of the investigator, and continue following the protocol recommended LLT escalation scheme as applicable (Section 3.4) and assessment schedule (Table 8-1).

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 in eCRF.

Participants who discontinue from study treatment (Inclisiran/placebo) or rosuvastatin should be followed-up and return to the visits as outlined in the Assessment Schedule (Table 8-1), or at a minimum agree to return for the end of study visit or have the safety phone call indicated in the Assessment Schedule (refer to Table 8-1).

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 Assessment Schedule.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment (for inclisiran/placebo only).

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

In case a participant discontinues blinded investigational treatment inclisiran/placebo due to a switch to PCSK9 mAb (refer to Section 3.4), the participant will remain in the study and be followed-up until the participant's end of study according to the Assessment Schedule.

9.1.2 Discontinuation from study

Discontinuation from study occurs 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 Schedule (EOS) (refer to Table 8-1).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, 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 participant's end of study.

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

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples).

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 in writing (depending on local regulations) and recorded in the source documentation.

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/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the Assessment Schedule (refer to Table 8-1).

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

9.3 Study completion and post-study treatment

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

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last study visit (EOS) or at least 90 days after last study treatment in case of early study discontinuation. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

At the end of the study (EOS), every effort will be made to continue provision of study treatment outside this study through an alternative setting to participant who in the opinion of the Investigator are still deriving clinical benefit.

Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up. This care may include modification of the background LLT and control of other CV risk factors, as it would normally be done in standard clinical practice.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. 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 participants 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 also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments including PROs and diary (refer to Section 8.5.1).

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. The causality the investigator is obligated to assess the relationship between any treatment (study medication or AxMPs) used in the study and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. 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 inclisiran/placebo, or rosuvastatin.
   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased for rosuvastatin
   - Drug interrupted/permanently discontinue
6. Its outcome can be:
   - not recovered/not resolved;
   - recovered/resolved;
   - recovering/resolving,
   - recovered/resolved with sequelae;
   - fatal;
   - or unknown

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

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

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB) or local SmPC.

Information about adverse drug reactions for rosuvastatin can be found in the local SmPC.

Abnormal laboratory values or test results constitute AEs 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.

Reporting of AEs related to AxMP(s)

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points mentioned in the paragraph above.

If a suspicion that medical occurrence could be related to AxMP cannot be ruled out, the reporting rules for study treatment apply.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered 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 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but 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 occurring before EOS visit is collected and recorded on the eSAE page with paper backup and as paper during the 30 days safety follow-up period after EOS; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAE reporting time frames are as follows:

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 occurring between time participant signs ICF until time that participant is determined to be a run-in failure must be reported to Novartis.
3. SAEs occurring between time participant signs ICF until 30 days after EOS must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a PV & 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, or European Clinical Trial Regulation 536/2014, or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day follow-up period after EOS should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Reporting of SAEs related to AxMP(s)

All SAEs related to any auxiliary medicinal product (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

10.1.4 Pregnancy reporting

Pregnancies

If a 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 Chief Medical Office and Patient Safety (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 and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

Study treatment errors are unintentional errors in the prescribing, dispensing, administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of a study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol. including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) eCRF and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

Always refer to the local rosuvastatin SmPC.

10.2.1 Liver safety monitoring

Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is > 3x ULN (always refer to the local SmPC).

Hepatic Serious Adverse Event(s)

Hepatic SAEs will be specifically collected and assessed throughout the trial to identify the potentially rare cases of drug-induced liver injury (DILI), none of which have been seen so far with inclisiran.

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. Hepatic AEs will be assessed as serious under "medically significant" even if other seriousness criteria are not met, using the following criteria:

- ALT or AST ≥5x ULN
- ALP ≥2x ULN in the absence of known bone pathology
- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN (meeting the criteria for a potential Hy's Law case)
- For participants with elevated AST or ALT or total bilirubin value at baseline: AST or ALT > 2 x baseline AND >3x ULN combined with total bilirubin > 2 x baseline AND > 2.0 x ULN (meeting the criteria for a potential Hy's Law case)

For potential Hy's Law cases an expedited reporting is required, and will be handled as a serious unexpected adverse event associated with the use of the study treatment (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

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. The required clinical information will be collected in specific eCRF forms to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The evaluation of these elevated LFTs may include a detailed history, as well as relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, laboratory tests, imaging and pathology assessments that would have been performed to elucidate the etiology of these hepatic SAEs.

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.

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

Permanent discontinuation from study treatment should be the rule if causality assessment indicates that DILI is probable. Please refer to Section 9.1.1 for more details on discontinuation from study treatment.

10.2.2 Renal safety monitoring

For the open label study treatment (rosuvastatin) renal function should be monitored and assessments are outlined in the Assessment Schedule (Table 8-1). Rosuvastatin is contraindicated:

- in participants with severe renal impairment (creatinine clearance <30 mL/min) regardless of the dose,
- in participants with moderate renal impairment (creatinine clearance <60 mL/min) with 40 mg dose rosuvastatin.

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease.

10.2.3 Skeletal muscle safety monitoring

Participants should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever.

Rosuvastatin therapy should be discontinued if CK levels are markedly elevated (> 5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin at the lowest dose with close monitoring (always refer to the rosuvastatin SmPC). Investigators are encouraged to identify early signs and symptoms of muscle-related adverse events and may CCI rosuvastatin dosage to prevent severe muscular symptoms. In case the participant does not tolerate the lowest dose of rosuvastatin, the participant must discontinue rosuvastatin, be treated as per local standard of care and followed-up until the participant's end of study as outlined in the Assessment Schedule (Table 8-1).

10.2.4 Severe cutaneous reaction monitoring

At the time of rosuvastatin prescription, participants should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appear, rosuvastatin should be discontinued immediately. Participant should be treated as per local standard of care and followed-up until the participant's end of study as outlined in the Assessment Schedule (Table 8-1). If the participant has developed a serious reaction such as Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms with the use of rosuvastatin, treatment with rosuvastatin must not be restarted at any time.

10.2.5 Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. If a participant is suspected to have developed interstitial lung disease, the participant must discontinue rosuvastatin, be treated as per local standard of care and followed-up until the participant's end of study as outlined in the Assessment Schedule (Table 8-1).

10.2.6 Immune-mediated necrotizing myopathy (IMNM)

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

10.2.7 Prothrombin time and International Normalized Ratio

The initiation of treatment or dosage up-titration of rosuvastatin in participants treated concomitantly with vitamin K antagonists (e.g., warfarin or another coumarin anticoagulant) may result in an increase in International Normalized Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

10.3 Committees

10.3.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, experts in their respective fields and Novartis representatives from the CTT.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the CTT, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

Some of the SC members will be part of a group to decide on eligibility of participants for receiving PCSK9mAb following the escalation process in the treatment period. The investigator will ensure all relevant data, to support the decision to switch the participant's treatment to a PCSK9mAb, has been entered into the eCRF. The SC members will alert the investigator on the decision, in a timely manner. Please also refer to Section 3.4.

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 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

Novartis personnel or designated 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 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, run-in failures and study completion, as well as randomization codes and data about the study treatment (s) dispensed (only Inclisiran/placebo) to the participant 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 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.

Data quality assurance

Monitoring strategy methods, responsibilities, and requirements are provided in the monitoring plan/contracts. Details may include definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

11.3 Site monitoring

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

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, 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

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

12.1 Analysis sets

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 **run-in set (RIS)** consists of all patients who enter the run-in phase.

The **randomized set (RAN)** consists of all participants who received a randomization number, regardless of receiving trial medication.

The **full analysis set (FAS)** consists of all randomized participants who received at least one dose of double-blind study medication. Following the intent-to-treat principle, participants will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS.

The **safety set (SAF)** includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received. The SAF will be used for the analyses of safety and tolerability variables.

The **AP set** is a subset of the FAS and includes participants with a diagnosis of angina pectoris at baseline.

The **PAD** set is a subset of the FAS and includes participants with a diagnosis of peripheral artery disease at baseline.

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

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

The number of participants screened, randomized and included in FAS will be presented by treatment group and overall for the screened set. In addition, the reasons for discontinuation prior to randomization will be provided for the screened and run-in set. The number and proportion of participants who completed the study, who discontinued the study and the reason for discontinuation from study will be presented in a study disposition table for each treatment group and overall based on the randomized set. The frequency (%) of participants with major protocol deviations as well as the criteria leading to data exclusion from analysis will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized participants by region as well as the number of participants enrolled and randomized per region and country will be presented descriptively for the randomized set.

Baseline values corresponding to laboratory measurements in the lipid panel refer to assessments collected on Day 1 of the study (before the first administration of study drug). Other biochemistry measurements included in the subset of safety laboratory measurements as well as other background baseline characteristics should be collected prior to randomization or Day 1.

The demographic and background characteristic variables will be summarized using descriptive summary statistics. Continuous variables will be summarized using n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to inclisiran / placebo and to rosuvastatin will be summarized by means of descriptive statistics.

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

12.3.1 Study drug

The duration of the double-blind treatment will be computed as the time from randomization to the first out of

- a) the last contact to the participant or b) the date of the last diary entry obtained from the participant, what ever comes later
- the participant's death
- or the participant's study completion visit (EOS).

The duration of the on-treatment period will be computed as the time from the first injection to the first out of

- the last injection plus exposure attributable time length of 180 days
- the participant's death
- or the participant's study completion visit (EOS).

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

The number of participants with dose adjustments (interruption or permanent discontinuation) and the reasons will be summarized by treatment and all dosing data will be listed.

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

12.3.2 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 ATC class. 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 ATC class.

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.

Furthermore, the classes of medications at time of randomization and during the double-blind period will be summarized separately.

12.4 Analysis supporting primary objectives

The primary aim of the study is to demonstrate the superiority of inclisiran on top of a participant-individually optimized LLT in reaching participant-individual LDL-C targets compared to placebo on top of a participant-individually optimized LLT.

12.4.1 Definition of primary endpoint(s)

The primary endpoint for this study is the proportion of participants achieving their individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90. The participant-individual LDL-C target depends on their cardiovascular risk category as defined in the 2019 ESC/EAS guidelines for the management of dyslipidemia (Mach et al 2020). The individual LDL-C target (< 55 mg/dL or < 70 mg/dL) will be evaluated according to the most recent assessment of the cardiovascular risk category as determined by the investigator. Accordingly, the achievement of the participant-individual LDL-C target forms a binary response variable for LDL-C target. The primary endpoint will be analyzed based on the FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

For the primary analysis the odds ratio between inclisiran vs placebo of the participants achieving their individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90 will be estimated using a logistic regression model. Treatment and cardiovascular risk category (stratification factor: very high risk, high risk) will be included as factors in the model. The odds ratio and its 95% confidence interval (CI) and p-value will be estimated. The null hypothesis of equal odds will be rejected if the 1-sided p-value from the logistic regression model for the factor "treatment" is <0.025.

The primary null hypothesis to be rejected is that the odds regarding participants achieving their individually optimized LDL-C target (< 55 mg/dL or < 70 mg/dL) at day 90 are equal between treatment groups. Let p_1 and p_0 denote the proportion of participants achieving their individually optimized LDL-C target in the inclisiran or placebo group, respectively.

The primary null hypothesis tested can be described as:

H_{01}: $OR := (p_1/(1-p_1)) / ((p_0/(1-p_0)) \leq 1$ vs. H_A: $OR := (p_1/(1-p_1)) / ((p_0/(1-p_0)) > 1$.

Additionally, the relative risk as well as absolute risk difference and their 95% confidence intervals will be estimated supplementary.

12.4.3 Handling of intercurrent events of primary estimand

The general strategy to account for different intercurrent events is summarized in Table 12-1. For specific intercurrent events analysis will additionally follow the explanation below:

1. **Discontinuation of study treatment**: Follow up information after permanent discontinuation of study treatment, Retrieved Drop Out data (RDO) will be collected at regular study visits and will be included in the analysis, with treatments as assigned at randomization (treatment policy).
2. **Death**: For participants who die no subsequent LDL-C value can exist. Collected data should be analyzed before participants die. For deceased participants the last value measured before death will be included into the analysis (while alive strategy).

3. **Use of PCSK9 targeting non-study medication or lipid apheresis**: It could occur that participants are switched to PCSK9 targeting therapy after discontinuation of study medication or receive lipid apheresis. For the primary estimand participants who use PCSK9 targeting non-study medication or lipid apheresis will be considered as not achieving their LDL-C target (composite strategy).
4. **COVID-19 pandemic impact on study**: For the primary estimand collected data will be included in the analysis and keep the treatment groups as assigned at randomization (treatment policy).

Table 12-1 Account for different post randomization events for the primary endpoint reaching LDL-C target at day 90

Intercurrent event	Strategy
Permanent discontinuation of study treatment	Treatment policy strategy
Death	While alive strategy
Use of PCSK9-inhibitor antibodies	composite strategy
COVID-19 pandemic impact on study	Treatment policy strategy

Change in background medication essentially concerns change in LLT during optimization. A change in background medication is therefore not considered as an intercurrent event because it is part of the treatments compared.

12.4.4 Handling of missing values not related to intercurrent event

Missing values will be handled using multiple imputation. In a first step the continuous LDL-C level will be imputed by m=100 imputations based on FAS. From the imputed continuous LDL-C level the primary endpoint will be derived against the set LDL-C target and analyzed with the methods described in regarding section. Results will be combined according to Rubin's rules on the log scale. The imputation model will impute missing values based on all observed data taking the intercurrent event strategy into account. The imputation model will include randomized treatment arm and the stratification factor.

12.4.5 Sensitivity analyses

Not applicable.

12.4.6 Supplementary analysis

With a supplementary analysis the impact of allowing the use of PCSK9 mAb will be investigated. For this supplementary analysis the primary analysis will be repeated but LDL-C values observed during or after the use of a PCSK9 mAb will be included as measured.

12.4.7 Supportive analyses

Subgroup analyses for the following subgroups will be conducted:

- Age group
- Gender

- Cardiovascular risk category before randomization (very high risk, high risk) as stratification factor.

12.5 Analysis supporting secondary objectives

The population and the treatment of interest associated with the secondary estimand are the same as for the primary estimand and we consider the same intercurrent events. Except one specific exception described below, the proposed approach for all secondary endpoints for the intercurrent events of discontinuation of study treatment, the use of PCSK9mAb or lipid apheresis or the impact of the COVID-19 pandemic is the treatment policy strategy. For the intercurrent event of death a while alive strategy will be applied.

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures:

1. Relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits)
2. Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360
3. Annualized number of days participants experiencing self-reported pain from day 1 to day 360
4. Change from baseline in SF-BPI pain severity score from at day 360
5. Change from baseline in SF-BPI pain interference score at day 360
6. Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to Day 360
7. Proportion of participants with clinically relevant change in SF-BPI pain interference score from baseline to Day 360

However, the first secondary endpoint of relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits) will be handled differently for the use of PCSK9mAb or lipid apheresis. For this specific intercurrent event for this endpoint a hypothetical strategy as if no PCSK9mAb or lipid apheresis would have been administered will be applied.

The following four secondary endpoints will be included in the confirmatory testing framework in addition to the primary endpoint with corresponding hypothesis tested:

1. Relative change (percentage change) from baseline in LDL-C level over the double blind study period (averaged over all post baseline visits)
2. Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360
3. Annualized number of days participants experiencing self-reported pain from day 1 to day 360
4. Change from baseline in SF-BPI pain severity score at day 360
5. Change from baseline in SF-BPI pain interference score at day 360

12.5.1 Control of Familywise type I error rate

The null hypothesis to be rejected for the relevant secondary endpoints are:

- H_{02}: The mean relative changes from baseline in LDL-C level, averaged over all post baseline visits during the double-blind treatment period, are equal between treatment groups.
- H_{03}: The odds regarding participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360 are equal between treatment groups.
- H_{04}: The annualized mean number of days pain is experienced is equal between both groups.
- H_{05}: The mean change from baseline in SF-BPI pain severity score from day 1 to day 360 is equal between treatment groups.
- H_{06}: The mean change from baseline in SF-BPI pain interference score from day 1 to day 360 is equal between treatment groups.

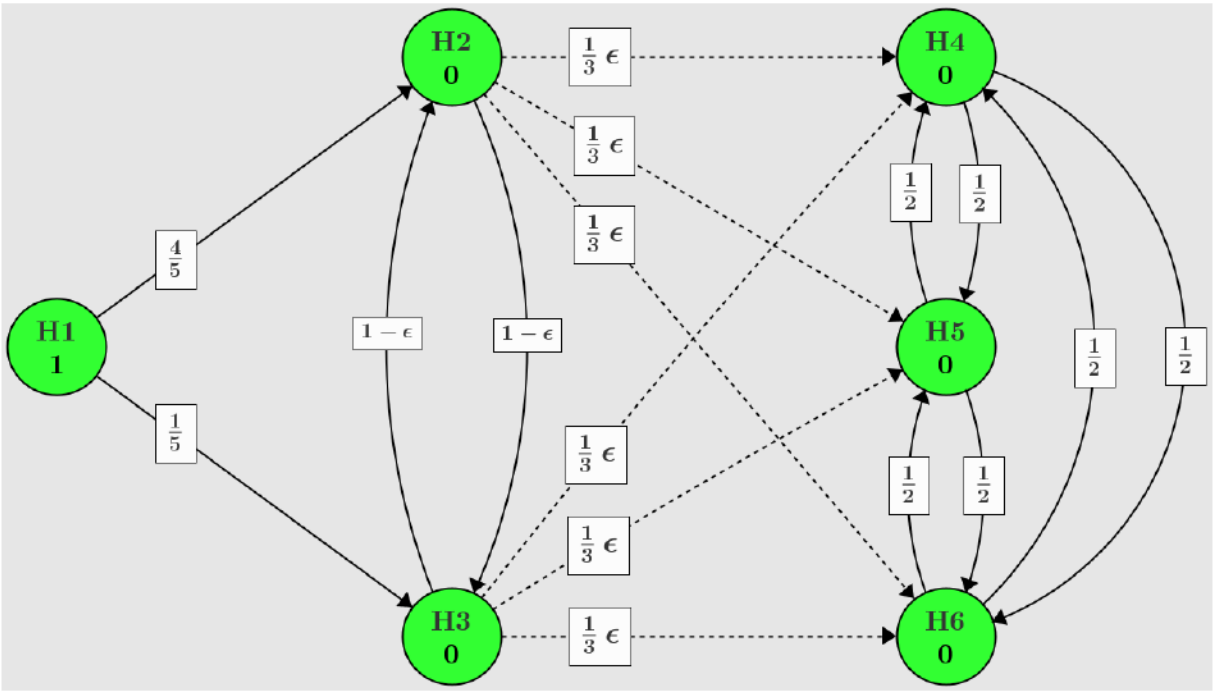
Hypotheses are grouped into three families. The first family contains the primary hypothesis H01. The second family contains two secondary hypotheses H02 and H03. The third family contains the rest of secondary hypotheses H04, H05 and H06. The hierarchical testing strategy is applied to these three families. First H01 is tested at level alpha. If it is rejected, we test the second family using a closed test at level alpha. If both H02 and H03 are rejected, we test the third family using the Hommel procedure at level alpha. When not all hypotheses in a family can be rejected, testing stops at the corresponding family and does not proceed to test the next family.

Within the second family, a closed test procedure based on weighted Simes tests is applied with 80% weight for H02 and 20% weight for H03. First the two nominal p-values for H02 and H03 are simultaneously compared to alpha. If both nominal p-values are $\leq$ alpha, the two null hypotheses are rejected. Otherwise compare the individual nominal p-values to the weighted alpha with the pre-specified weights (0.8/0.2) separately. If the p-value for H02 is $\leq 0.8*$alpha, H02 is rejected; If the p-value for H03 $\leq 0.2*$alpha, H03 is rejected.

Within the third family, the Hommel procedure is applied. Let the ordered p-values for H04, H05, H06 be $p(1) \leq p(2) \leq p(3)$ and the corresponding hypotheses H(1), H(2) and H(3). First if $p(3) \leq$ alpha, we can reject all three hypotheses. Otherwise, if $p(2) \leq$ alpha / 2, reject H(2) and H(1). Otherwise, if $p(1) \leq$ alpha / 3 or ($p(1) \leq$ alpha / 2 and $p(2) \leq 2$alpha / 3), reject H(1).

This testing procedure controls the familywise error rate at level alpha in the strong sense. Figure 12-1 below shows the applied testing procedure.

Figure 12-1 Applied testing procedure



12.5.2 Efficacy endpoints

For muscle-related AE / SMQ rhabdomyolysis / myopathy the SAF will be used for analysis. For all other secondary efficacy analyses the Full Analysis Set (FAS) will be used.

12.5.2.1 Relative change (percentage) from baseline to mean LDL-C level over the double-blind treatment period

The relative change (percentage change) from baseline in LDL-C level averaged over the double-blind treatment period will be analyzed using a mixed model for repeated measures (MMRM) including treatment group, stratification factor (cardiovascular risk category: very high risk, high risk), scheduled visit and the interaction of treatment group with scheduled visit as factors and baseline LDL-C level and the interaction of baseline LDL-C level with scheduled visit as covariates. Visit will be included as a categorical variable, and an unstructured covariance matrix will be used for the model. The null hypothesis of equal mean changes between both groups to the average over all post baseline visits will be tested by an appropriate linear contrast of the variable treatment and treatment by visit interaction. The null hypothesis will be rejected within the confirmatory testing framework, if the 1-sided p-value is <0.025. The adjusted mean change from baseline and its corresponding 95% confidence interval will be presented.

For this endpoint a graphical presentation of the course of the regarding variable over time will be shown additionally to the analysis. Further details for this graphical presentation and for the analysis of secondary endpoints will be provided in the statistical analysis plan (SAP).

12.5.2.2 Muscle-related AE / SMQ rhabdomyolysis / myopathy

The proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360 will be analyzed in a logistic regression model. Treatment and determined LDL-C target at screening will be included as factors in the model. The LDL-C targets depend on the participants' CV risk category and will be attributed directly from the CV risk category eCRF entries. Therefore, the CV risk category will be included in the model as the stratification factor ("very high risk", "high risk"). The odds ratio and its 95% confidence interval (CI) and p-value will be estimated. The null hypothesis of equal odds will be rejected within the confirmatory testing framework if the 1-sided p-value from the logistic regression model for the factor "treatment" is <0.025.

Additionally, the relative risk as well as absolute risk difference and their 95% confidence intervals will be estimated from a Cochrane-Mantel-Haenszel test (CMH) stratified for the determined LDL-C target before randomization based on the Score statistic.

In case of missing values muscle-related AE / SMQ rhabdomyolysis / myopathy will not be imputed but analyzed according to last known status of the occurrence of an event. To investigate the sensitivity to missing values or potentially different observation times in the two study arms, a time to the first experience of at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy will be conducted.

12.5.2.3 Number of days participants experiencing self-reported pain from day 1 to day 360

The number of pain days experienced will be analyzed using a negative binomial model (P. McCullagh and J.A. 1989) with the number of observed pain days as the dependent variable and treatment group and stratification factor (cardiovascular risk category: very high risk, high risk) as fixed-effect factors and log (follow-up duration in years) as the off-set. The annualized incidence rates and their 95% confidence intervals estimated from the model will be provided by treatment group. The treatment comparison will be performed through the estimated incidence rates. The incidence rate ratio and its 95% confidence interval will be provided.

12.5.2.4 Mean change from baseline in SF-BPI pain severity score and pain interference score at day 360

Mean change from baseline in SF-BPI pain severity score and SF-BPI pain interference score at day 360 will be analyzed using a mixed model for repeated measures (MMRM). Treatment group, stratification factor (cardiovascular risk category: very high risk, high risk), scheduled visit, and the interaction of treatment group with scheduled visit will be included as fixed factors in model, baseline SF-BPI value and the interaction of baseline SF-BPI value with scheduled visit will be included as a fixed covariate. Beyond that visit will be included as a repeated factor nested within participant and an unstructured covariance matrix will be used for the model.

The adjusted mean change from baseline at day 360 and its regarding 95% confidence interval will be presented. The null hypothesis of equal mean changes will be rejected based on the treatment contrast at regarding visits according to a 1-sided p-value <0.025 within the confirmatory testing framework.

For this endpoint a graphical presentation of the course of the regarding variable over time will be shown additionally to the analysis. Further details for the analysis and the graphical presentation will be provided in the statistical analysis plan (SAP).

12.5.3 Safety endpoints

The Safety Set (SAF) will be used for safety analyses, including the secondary safety endpoint.

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Safety summaries (tables, figures) include all data from the double-blind treatment period and baseline data. In particular, summary tables for AEs will summarize all events obtained during double-blind treatment period, with a start date during the double-blind treatment period. Additionally, all summary tables for AEs will be repeated for on-treatment AEs only (TEAEs). A separate summary for death will be provided.

12.5.3.1 Adverse events

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

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

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation

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

AEs which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

12.5.3.2 Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time. Change in SBP/DBP from baseline to day 360.

12.5.3.3 Clinical laboratory evaluations

The Safety Set (SAF) will be used for safety analyses, including the secondary safety endpoint.

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Safety summaries (tables, figures) include all data from the double-blind

treatment period and baseline data. In particular, summary tables for AEs will summarize all events obtained during double-blind treatment period, with a start date during the double-blind treatment period. Additionally, all summary tables for AEs will be repeated for on-treatment AEs only (TEAEs). A separate summary for death will be provided.

12.5.4 Patient reported outcomes

Patient reported secondary endpoints are the number of days participants experience self-reported pain from day 1 to day 360 as reported in the eDiary and the mean change from baseline in SF-BPI at day 360. Regarding analyses of these endpoints are described in the order of the testing procedure in Section 12.5.2.3 and Section 12.5.2.4, respectively. Other patient reported outcomes are exploratory endpoints. The analysis of exploratory endpoints will be described in the statistical analysis plan (SAP).

12.6 Analysis of exploratory endpoints

Exploratory endpoints are listed in the study objectives. The analysis of exploratory endpoints will be described in the statistical analysis plan (SAP).

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The assumption for the occurrence of LDL-C target attainment on day 90 in the inclisiran-arm is based on the ORION study data set. In CCI of participants achieved an LDL-C level CCI mg/dl target at day 90 CCI of participants achieved an LDL-C level CCI mg/dl at day 90 CCI (Ray et al 2020). Assuming CCI approx. CCI of participants achieve their individual LDL-C target at day 90. For the assumption of LDL-C target attainment at day 90 in the placebo arm, the EXPLORER trial reports response rates for CCI (Ballantyne et al 2007): CCI of participants achieved an LDL-C level CCI mg/dl at day CCI). Mean LDL-C level at day CCI was CCI so it can be estimated that approx. CCI of participants may have reached the CCI target. Based on the study population and treatment regime herein, day CCI of EXPLORER trial likely relates to day 90 of the present study. With the above stated assumption of a CCI among the participant population, CCI of participants are considered to reach their LDL-C target at day 90. Considering the high LDL-C levels at baseline in the EXPLORER trial compared to ORION trials, herein, a slightly higher goal attainment rate of approx. CCI at day 90 for participants in the comparator arm is assumed. Under these assumptions, CCI participants per arm are required based on a chi-square test of proportions to achieve 90% power on a two-sided, 5% significance level. In order to compensate for missing

values and other protocol deviations, approximately 880 participants per arm (approximately 1760 participants in total) should be enrolled/randomized into this trial.

12.8.2 Secondary endpoint(s)

For the secondary endpoint "Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360", the following deliberations apply: Due to the potent LDL-C lowering effect of inclisiran and the CCI in both treatment-arms depending on the achievement of the individual LDL-C target of the participant, it is expected that the mean and the median statin doses will be CCI. Based on the CCI of action of inclisiran, it is estimated that the CCI of participants in the CCI will require CCI rosuvastatin CCI in the treatment period. Thus, most participants in the CCI will remain on the lower doses of rosuvastatin throughout the trial. In contrast, in the CCI, most participants will require CCI of rosuvastatin CCI to CCI the LDL-C.

Various studies have shown that statins at high dosages are associated with CCI ranging between CCI for atorvastatin 80 mg/day (Parker et al 2013) to CCI for various statins (Bruckert et al 2005), while there is evidence from double-blind clinical trials that CCI statins are not associated with a CCI than placebo with an overall incidence of CCI (Gupta et al 2017). For the sample size calculation, we assume a rather conservative approach of an occurrence of CCI in the CCI and CCI in the CCI. Pain can be of different CCI. Assuming CCI are CCI in a conservative approach, according to the methodology defined CCI to CCI AEs will only be CCI if the CCI interval of the risk ratio stays below the threshold of CCI. A sample size of CCI participants per arm will result in 90% power to obtain a confidence interval of the risk ratio fulfilling this condition. For a considerable additional benefit, the respective threshold is defined by the CCI. Under the assumptions above, the power to meet this condition as well would be CCI. The power calculations were performed with SAS Software by simulating and analyzing 1000 studies with the assumed AE rates.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including 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

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the

investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in CTIS. 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, CTIS etc.).

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

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

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

- Thank You Letter
- Participant Card
- Plain Language Trial Summary - after Clinical Study Report (CSR) publication
- Trial Feedback Questionnaire (TFQ) - up to 3 times during the trial

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.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Not applicable

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

Not applicable.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Please refer to Section 10.2.2.

16.4 Documented ASCVD

Documented ASCVD (clinical/imaging):

a. Acute coronary syndrome:
    1. Unstable angina (defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis)
    2. Myocardial infarction: Spontaneous MI (either ST-elevation MI or non-ST-elevation MI), which was not the result of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), and which occurred in the period 3 months prior to screening. Confirmation of MI is a participant history/participant recollection of signs or symptoms consistent with presentation of MI, and at least one of the following (adapted from Thygesen et al., 2019):
        1. Documentation of cardiac biomarkers that exceed the diagnostic threshold of a local laboratory for MI
        2. Pathological Q waves on ECG or other ECG changes as defined in Appendix 16.5
        3. Imaging evidence of loss of viable myocardium or regional wall motion abnormality in a pattern consistent with an infarction or ischemic etiology
        4. Identification of a coronary thrombus by angiography at the time of presentation with myocardial infarction
b. Stable angina
c. Coronary revascularization (PCI, CABG, and other arterial revascularization procedures)
d. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having > 50% stenosis), or carotid ultrasound
e. Stroke and TIA: History of ischemic stroke (an acute episode of focal cerebral, spinal, or visual dysfunction caused by infarction of central nervous system tissue) or TIA having occurred in the period ≥ 3 months prior to screening documented by computerized tomography (CT) scan, Magnetic Resonance Imaging (MRI) or other visualization method

f. PAD, as evidenced by either intermittent claudication with ankle brachial index (ABI) < 0.9 prior peripheral arterial revascularization procedure, or, amputation due to atherosclerotic disease. Thromboangiitis obliterans is not a qualifying event

16.5 ECG findings supporting diagnosis of myocardial infarction

Electrocardiographic manifestations suggestive of acute myocardial ischaemia (in the absence of left ventricular hypertrophy and bundle branch block) (Thygesen et al 2019).

ST elevation

New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age.

When the magnitudes of J-point elevation in leads V2 and V3 are registered from a prior electrocardiogram, new J-point elevation ≥1 mm (as compared with the earlier electrocardiogram) should be considered an ischemic response.

ST-depression and T wave changes

New horizontal or downsloping ST-depression ≥0.5 mm in two contiguous leads and/or T inversion >1 mm in two contiguous leads with prominent R wave or R/S ratio >1

Pathological Q waves

Any Q wave in leads V2–V3 >0.02 s or QS complex in leads V2–V3.

Q wave ≥0.03 s and ≥1 mm deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF).