NOVARTIS

Novartis Research and Development

KJX839

Clinical Trial Protocol CKJX839A1US01 / NCT04873934

A randomized, controlled, multicenter, open-label trial comparing a hospital post-discharge care pathway involving aggressive LDL-C management that includes inclisiran with usual care versus usual care alone in patients with a recent acute coronary syndrome (VICTORION-INCEPTION)

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List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CHD	Coronary heart disease
CK	Creatinine Kinase
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EHR	Electronic Health Record
FDA	Food and Drug Administration
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GPP	Good Pharmaceopidemiology Practice
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein Cholesterol
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
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

IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection Site Reaction
IUD	intrauterine device
IUS	intrauterine system
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
LFT	Liver function test
LLN	lower limit of normal
LNP	lipid nanoparticle
Lp(a)	Lipoprotein(a)
MACE	Major adverse cardiovascular events
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial Infarction
mL	milliliter(s)
MMRM	Mixed-effects model repeated measures
mRNA	Messenger RNA
No.	Number
NOACs	novel or non-Vitamin K oral anticoagulants
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PFS	Pre-Filled Syringe
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	prothrombin time
QMS	Quality Management System
RBC	red blood cell(s)
RISC	RNA-Induced Silencing Complex
RNAi	Ribonucleic acid interference
RU	Resource Utilization
s.c.	subcutaneous
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
sCR	serum creatinine
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
siRNA	small interfering ribonucleic acid
SUSAR	Suspected Unexpected Serious Adverse Reaction

TBL	Total Bilirubin
[redacted]	[redacted]
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
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.
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms 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 or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	Electronic source (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 case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate

Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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
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 a nurse, phlebotomist or 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 a newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued, and no further assessments are planned

Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet, or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or videoconference, 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 it might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 04

Amendment rationale

The purpose of the clinical study amendment is to clarify the use of inclisiran, which is now commercially available as LEQVIO®. Exclusion criteria #11 and 15 has been modified. Similarly, the study design has been modified to reflect the same. The number of sites was increased from 40 to up to approximately 130.

Changes to the protocol

- Section 3 Study Design: Added "Commercially available inclisiran may be used for appropriate patients in the usual care arm at the sole discretion of the treating physician, without any influence from the PI." Deleted "If and when…treating physician"
- Section 5 Study Population: The number of sites was increased from 40 to up to approximately 130
- Section 5.2

o Exclusion criteria #15: Added "Treatment with monoclonal antibodies directed towards PCSK9 or inclisiran within 90 days of screening."

o Exclusion criteria #11: Added "Approved vaccines or vaccines used under Emergency Use Authorization should not be considered part of this exclusion criteria. Patients can receive COVID vaccines during inclisiran trials.

While use of COVID anti-viral therapies approved for use under Emergency Use Authorization would need to adhere to the washout period outlined above prior to screening, they would not be considered as criteria for trial termination/discontinuation.

Amendment 03

Amendment rationale

The purpose of the clinical study amendment is to clarify the understanding of what is meant by patients being hospitalized for an acute coronary syndrome (ACS). The term "hospitalization" applies to patients who are either admitted to the hospital as an in-patient or in an out-patient setting (i.e., not requiring admission for an overnight hospital stay).

Some of the inclusion and exclusion criteria have been modified. The criteria for glomerular filtration rate has been reduced from a calculated value greater than 30 ml/min to a value greater than 20 ml/min. The exclusion criteria for heart failure (HF) has been changed from class III or IV HF to now only excluding participants with class IIIb or IV HF or a left ventricular ejection fraction less than 25%. The exclusion criteria for The protocol amendment has also removed the requirement for participants to be randomized within 5 weeks of being discharged for an ACS. Screening of participants needs to occur withing 5 weeks of an ACS but the site does not have to randomize the patient within the 5 week window as they still have 30 days following screening to randomize a participant into the trial.

Changes to the protocol

- Protocol Summary
    - Purpose and rationale: added "… with a previous hospitalization (in-patient/out-patient) for an ACS …"
    - Primary Objective: added "… in participants with a recent hospitalization (in-patient/out-patient) for an ACS ..."
    - Study population: added "… with a recent hospitalization (in-patient/out-patient) for an ACS …"
    - Inclusion criteria #2: Added "Recent ACS (in-patient/out-patient) within 5 weeks of screening), …"
    - Inclusion criteria #3: Added "Serum LDL-C ≥70 mg/dL or non-HDL ≥100 mg/dL"
    - Inclusion criteria #5: Modified "calculated glomerular filtration rate >20 ml/min …"
    - Inclusion criteria #7: Added "… following hospitalization (in-patient/out-patient) for an ACS."
    - Exclusion criteria #1: Modified "New York Heart Association (NYHA) class IIIb …" and "… last known left ventricular ejection fraction <25%."
    - Exclusion criteria #6: Modified "Treatment with monoclonal antibodies directed towards PCSK9 within 90 days of screening."
- Section 1.1 Background: added "… with inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS …"

- Section 1.2 Purpose: added "a recent ACS (in-patient/out-patient) within 5 weeks of screening." and added "… initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS …"
- Table 2-1 under Primary objectives: added "initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) …"
- Section 2.1 Primary estimands: removed "within 5 weeks" and added "… implementation pathway in participants following a recent ACS, …"
- Section 3 Study Design: deleted "and randomization" to now state: "Screening of participants must take place within 5 weeks after discharge."
- Section 4.1 Recruitment: added "… recently hospitalized for an ACS (in-patient/out-patient), …"
- Section 5 added "… with a recent hospitalization (in-patient/out-patient) for an ACS (within 5 weeks) …"

- Section 5.1
  - Inclusion criteria #2: Added "Recent ACS (in-patient/out-patient) within 5 weeks of screening, …"
  - Inclusion criteria #3: Added "Serum LDL-C ≥70 mg/dL or non-HDL ≥100 mg/dL"
  - Inclusion criteria #5: Modified "…calculated glomerular filtration rate >20 ml/min …"
  - Inclusion criteria #7: Removed "discharged" and added "in-patient/outpatient" to "Participants are required to be on statin therapy, or have documented statin intolerance, as determined by the investigator, following hospitalization (in-patient/outpatient) …".

- Section 5.2
  - Exclusion criteria #3: Modified "New York Heart Association (NYHA) class IIIb …" and "… last known left ventricular ejection fraction <25%."
  - Exclusion criteria #15: Modified "Treatment with monoclonal antibodies directed towards PCSK9 within 90 days of screening."

Amendment 02

Amendment rationale

The purpose of the clinical study amendment is to update the protocol in order to be aligned with other ongoing inclisiran Phase III studies with respect to the documentation of statin intolerance, definition of hyperglycemia-related events and assessment of injection site reactions. The protocol has also removed any reference to the need to contact and obtain consent from the female partner of any male participant when the female partner becomes pregnant during the study in order to obtain pregnancy outcome information.

This protocol amendment, finalized prior to study start, will be the initial protocol version submitted to regulatory authorities, including the FDA, and Site IRBs for study approval.

Changes to the protocol

- Updated list of abbreviations to include Injection Site Reaction
- Protocol Summary
    - Data Analysis section updated efficacy variables being analyzed
- Section 3 added language, “if and when inclisiran becomes commercially available”
- Section 6.5.1 removed “not applicable” and provided guidance with respect to drug interruptions and/or drug discontinuation
- Section 6.5.2
    - Removed not applicable
    - Added Section 6.5.2.1 follow up on potential drug-induced liver injury (DILI) cases
- Section 6.7.1.1 removed language that participants will be asked to return all unused study medication
- Section 7 removed pregnant partner information
- Section 8
    - Included language for required 8 hour fasting prior to laboratory evaluations
    - Included language that blood donations are prohibited during study participation
- Table 8-1
    - Added “Medical History: Statin Intolerance”
    - Added footer for “Weight” to be captured at visits 3, 4 and 5
    - Updated “Pulse Rate” and “Blood Pressure” to be captured at visits 3 and 4
    - Added “prior or” to concomitant medications
    - Added “Surgical / Medical procedures”

  - Added “Injection Site Reaction Assessment”
  - Updated footer numbers
  - Provided clarification of biobanking collection at Visits 2-5
- Section 8.2 removed “date of birth”
- Table 8-3 removed “Lactate” from full serum chemistry
- Section 8.4.4 added “Injection site reactions” and “Hyperglycemia-related events” information
- [redacted]
- Section 8.5.3
  - Added analysis of proteins.
  - Updated language to indicate all measures of Lp(a) and hsCRP are blinded to participants and staff and to allow for any lab measures from the biobank samples to be analyzed *during* or after study close
- Section 10.1.4 removed the word “pregnancies” at the start of the paragraph and pregnant partner information
- Section 10.2 removed “not applicable”
- Section 10.2.1 removed test for unexplained increases in transaminases or total bilirubin, as well as instructions on follow-up, as this is now captured in section 6.5.2.1, Appendix 2 and in the remainder of the paragraph
- Section 11.1 removed Integrated data acquisition approach, Direct EHR Data Capture and Linked Pharmacy & Medical Claims Data information
- Section 12.5.1 updated efficacy variables being analyzed

Amendment 01

Amendment rationale

The purpose of the clinical study amendment is to modify the protocol to be in alignment with it being a Phase IIIb trial instead of a Phase IV. As a result, the protocol is now more closely aligned with the other Phase III studies with inclisiran, particularly with respect to the timing and frequency of some of the laboratory assessments.

The protocol amendment also added two new exclusion criteria in the protocol to clearly define the situation regarding a recurrent ACS event and the scheduling or occurrence of a coronary revascularization procedure.

The patient reported outcomes to be used in the study have been updated to remove the Belief about Medication Questionnaire (BMQ).

The protocol updated the sections with respect to the capture of EHR and claims data into the database to state that it may not be possible in all patients.

The protocol was also updated according to the most recent version (4.0) of the clinical trial protocol template, issued on 15-Feb-2021.

Changes to the protocol have also been made to align with another ongoing Phase IIIb clinical study with inclisiran (KJX839A1US02). Other changes to the protocol included the addition of a study name and other necessary spelling and grammatical corrections.

Changes to the protocol

- Title page study name "VICTORION-INCEPTION" added to title.
- List of abbreviations were updated to include EHR, GPP, HBcAb, HBsAb, hCG, HDL-C, VLDL, [redacted]
- Glossary of terms were updated to include Clinical Outcomes Assessment (COA), Clinical Trial Team, Coded Data, Discontinuation from study, Discontinuation from study treatment, off-site, off-site healthcare professional (OHP), Patient-Reported Outcomes (PRO), Randomization, Re-screening, Remote and Tele-visit.
- Glossary of terms were updated to remove cycles and run-in failure
- Protocol Summary
    - Full title "VICTORION-INCEPTION" was added
    - Clinical Phase was updated to Phase IIIb
    - Study type was updated to interventional
    - Key Exclusion criteria was added.
        - Recurrent ACS event within 2 weeks prior to randomization.
        - Coronary angiography and revascularization procedure (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)

surgery) performed within 2 weeks prior to the randomization visit or planned after randomization

- Study treatments was updated to include (KJX839), 284 mg, 1.5 ml Liquid in a single-use prefilled syringe (PFS) for s.c. administration
- Key safety assessments: removed following statement: "Safety assessments include adverse event monitoring, physical examinations, monitoring of laboratory markers in blood and urine and assessment of standard 12-lead ECG at screening."
- Other assessments: Removed Belief about Medication Questionnaire PRO
- Data Analysis: Updated statement: "If the p-value based on a two-sided test for treatment at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ([inclisiran + usual care] - usual care) is less than 0, statistical significance in favor of inclisiran is shown" and definition of Discontinuation of statin therapy changed to: "no statin use $\geq$ 30 days before the end-of-study visit"

- Section 2 title "Objectives and endpoints" has been updated to "Objectives, endpoints and estimands"
- Table 2-1 updated the definition of secondary efficacy variable, Discontinuation of statin therapy: "no statin use $\geq$ 30 days before the end-of-study visit" [redacted]
- Section 2.1 updated to include the statement: "The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during the trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment)".
- Section 3 updated to include the statement: "The collection of data from trial sites through eCRFs may also be complemented with EHR data and claims data (e.g., lipid measurements and concomitant medications), if available." Other minor administrative changes and a section on Remote procedures has been added.
- Section 4.1.1 minor administrative changes
- Section 4.2 minor administrative changes
- Section 4.4 added the statement: "After all participants complete their baseline visit, the demographic and baseline characteristics may be summarized to help design new studies"
- Section 4.6 Rationale for Public Health Emergency mitigation procedures added
- Section 5 minor administrative changes
- Section 5.2 Exclusion criteria - added: i) Recurrent acute coronary syndrome event within 2 weeks prior to randomization and ii) Coronary angiography and

revascularization procedure (PCI or CABG surgery) performed within 2 weeks prior to the randomization visit or planned after randomization as exclusion number 6 and 7

- Section 6.1 minor administrative changes
- Section 6.2.1 minor administrative changes
- Section 6.2.2 administrative clarification
- Section 6.6.1 Treatment compliance section added
- Section 6.7 has been updated with Public Health emergency information
- Table 6-4 minor administrative changes
- Section 7 Informed consent procedures - minor administrative changes
- Section 8 Visit schedule and assessments - administrative changes and updated with Public Health emergency information
- Table 8-1 has been updated to include separate sections for i) ACS Medical History, ii) smoking status, iii) Full Clinical Chemistry, iv) Limited Clinical Chemistry, v) Hepatitis Markers, vi) Lipids and lipoproteins, vii) coagulation to streamline data collection and laboratory assessment procedures. [redacted]
- Section 8.2 updated to include relevant medical history
- Section 8.3 Efficacy has been updated to revise the secondary efficacy variable: Discontinuation of statin therapy to: "no statin use ≥ 30 days before the end-of-study visit" [redacted]
- Section 8.3.4 concomitant medications section was removed. Duplicate information from section 6.2.1
- Section 8.4 updated to include Public Health emergency information
- Table 8-2 updated vital signs to be measured by standard sphygmomanometer or an automated BP device
- Section 8.4.1 Minor administrative changes and updated to include Public Health emergency information
- Table 8-3 Clinical Laboratory Assessments - updated test names under each category and added Coagulation as a test category
- Section 8.4.3 updated to include Public Health emergency information
- Section 8.4.5 minor administrative changes
- [redacted]
- Section 8.5.4 Patient Reported Outcomes - updated to include Public Health emergency information

[redacted]

[redacted]

- Section 9.2 Study completion and post-study treatment - changed to "For study participants who have successfully completed the study, further guidance will be provided separately concerning continuation of treatment and access to investigational drug. This guidance will be provided to sites prior to the completion visit of the first patient (first patient last visit). For study participants who terminate prior to the end of the study or who withdraw from treatment, continuing treatment should be managed by the investigator and/or referring or primary physician."
- Section 11.1 Data collection - minor administrative changes
- Section 12.1 added "in the inclisiran + usual care group (i.e., excludes patients in the inclisiran + usual care group who missed one or more doses) and all participants in the usual care group." and "where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received."
- Section 12.4 title updated to Analysis supporting primary objectives
- Section 12.4.2 added "2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis." and "All efforts will be made to follow up participants until the end of the study. Participants will be expected to follow the visit schedule and assessments even after discontinuation of study treatment. Data after participants discontinued study treatment will be used in the analysis ("retrieved dropout")."
- Section 12.4.3 title updated to Handling of intercurrent events of primary estimands and updated to include "Discontinuation of study treatment. This intercurrent event will be ignored in the analysis."
- Section 12.4.5 title updated to Sensitivity analysis and include "Discontinuation of study treatment. This intercurrent event will be ignored in the analysis."
- Section 12.4.6 Supplementary analysis – added information on supplementary analysis of the primary efficacy variable
- Section 12.5 title updated to Analysis supporting secondary objectives
- Section 12.5.1 Efficacy endpoints – updated the secondary efficacy variable, Discontinuation of statin therapy: "no statin use ≥ 30 days before the end-of-study visit"
- Section 12.5.2 Safety endpoint - removed 12 Lead ECG

[redacted]

- Section 12.7 Interim analyses - added "After all participants complete their baseline visit, the demographic and baseline characteristics may be summarized to help design

new studies. No analysis will be performed using post-baseline data. Thus, there is no need to adjust the level of significance for such interim analysis of baseline data."

- Section 12.8.1 added "trial since changes in lipid-lowering therapy are allowed in both treatment groups."
- Section 15 updated references
- [redacted]

Other typographical corrections were also included.

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

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Protocol summary

Protocol number	CKJX839A1US01
Full Title	A randomized, controlled, multicenter, open-label trial comparing a hospital post-discharge care pathway involving aggressive LDL-C management that includes inclisiran with usual care versus usual care alone in patients with a recent acute coronary syndrome(VICTORION-INCEPTION)
Brief title	Management of LDL-cholesterol with inclisiran + usual care compared to usual care alone in participants with a recent acute coronary syndrome
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional clinical trial
Purpose and rationale	The purpose of this study is to study the effectiveness of implementation of a systematic LDL-C management pathway including treatment with inclisiran in participants who have experienced a recent acute coronary syndrome (ACS) and have an increased LDL-cholesterol (≥70 mg/dL) despite being treated with a statin drug. In this context, we aim to assess the LDL-C lowering effects of aggressive LDL-C management with inclisiran on top of usual care in patients with a previous hospitalization (in-patient/out-patient) for an ACS compared to patients receiving usual, care without inclisiran.
Primary Objective(s)	The primary objective of this study is to assess the effect on LDL-C of implementation of an LDL-C management care pathway that includes initiation of inclisiran on top of usual care in participants with a recent hospitalization (in-patient/out-patient) for an ACS with LDL-C ≥70 mg/dL despite being on statin therapy compared to usual care without inclisiran at Day 330.
Secondary Objectives	The secondary objectives in this study include the following: To assess (1) the absolute change from baseline in LDL-C level at Day 330, and (2) average of absolute and percent changes from baseline in LDL-C levels to each post-baseline visit, in the inclisiran + usual care group compared to usual care group at Day 330 To assess the proportion of participants reaching pre-specified LDL-C targets in the inclisiran + usual care group compared to usual care group at Day 330 To assess plasma lipoproteins and triglycerides in the inclisiran + usual care group compared to usual care group at Day 330 To assess changes in and adherence to background lipid-lowering therapy in the inclisiran + usual care group compared to usual care group at Day 330 To assess overall safety and tolerability of inclisiran
Study design	The study design will be a randomized, parallel-group, open-label, controlled, multicenter study comparing an LDL-C management strategy including inclisiran with usual care.
Study population	Male or female participant's ≥18 years of age with a recent hospitalization (in-patient/out-patient) for an ACS and elevated LDL-C (≥70 mg/dL) despite being

	treated with statin therapy by their health care practitioner. We plan to randomize approximately 384 participants at up to approximately 130 US sites.
Key Inclusion criteria	Participants eligible for inclusion in this study must meet **all** of the following criteria: 1. Males and females ≥18 years of age 2. Recent ACS (in-patient/out-patient) within 5 weeks of screening, defined as: Ischemic symptoms with unstable pattern, occurring at rest or minimal exertion within 24 hours of an unscheduled hospital admission or emergency department visit, due to presumed or proven obstructive coronary disease AND at least one of the following: a. Elevated cardiac biomarkers (cardiac troponin (cTn) or the MB fraction of creatinine kinase (CKMB)) with at least one value above the 99th percentile of the upper reference limit (URL) or defined by the local laboratory MI diagnosis cut-off values OR b. Resting ECG changes consistent with ischemia or infarction AND additional evidence of obstructive coronary disease 3. Serum LDL-C ≥70 mg/dL or non-HDL ≥100 mg/dL 4. Fasting triglycerides <4.52 mmol/L (<400 mg/dL) at screening 5. Calculated glomerular filtration rate >20 mL/min by estimated glomerular filtration rate (eGFR) 6. Participants must be willing and able to give informed consent before initiation of any study related procedures and willing to comply with all required study procedures 7. Participants are required to be on statin therapy, or have documented statin intolerance, as determined by the investigator, following hospitalization (in-patient/out-patient) for an ACS. Statin intolerant patients are eligible if they had intolerable side effects on at least 2 different statins, including one at the lowest standard dose.
Key Exclusion criteria	• New York Heart Association (NYHA) class IIIb or IV heart failure or last known left ventricular ejection fraction <25%. • Significant cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation at the time of screening. • Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years. • Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer. • Planned use of other investigational products or devices during the course of the study. • Treatment with monoclonal antibodies directed towards PCSK9 or with inclisiran within 90 days of screening. • Recurrent ACS event within 2 weeks prior to randomization. • Coronary angiography and revascularization procedure (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery) performed within 2 weeks prior to the randomization visit or planned after randomization. • Approved vaccines or vaccines used under Emergency Use Authorization should not be considered part of this exclusion criteria. Patients can receive COVID vaccines during inclisiran trials. While use of COVID anti-viral therapies approved for use under Emergency Use Authorization for would need to adhere to the washout period outlined

	above prior to screening, they would not be considered as criteria for trial termination/discontinuation.
Study treatments	• Inclisiran (KJX839), 284 mg, 1.5 ml Liquid in a single-use prefilled syringe (PFS) for s.c. administration plus usual care • Usual care alone
Treatment of interest	To compare the LDL-C lowering effects of inclisiran on top of usual care compared to usual care alone, in participants who have a recent ACS.
Efficacy assessments	The primary efficacy assessment will be LDL-C, from which the two primary efficacy variables (percent change from baseline in LDL-C; achieving LDL-C < 70 mg/dL [yes, no]) are derived. Other efficacy assessments will include measurement of ApoB, Lp(a), non-HDL-C, very-low-density lipoprotein (VLDL), total cholesterol, triglycerides, HDL-C, discontinuation of statin therapy, and changes in other background lipid lowering therapy. Assessment of lipid lowering medications may also be conducted with data complemented by EHR and claims data to assess adherence to background therapy.
Key safety assessments	Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.
Other assessments	[redacted]
Data analysis	The primary efficacy variables are the following: 1. Percent change from baseline in LDL-C 2. Achieving LDL-C <70 mg/dL (yes, no) The primary analysis time point for both primary efficacy variables is at Day 330. Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction as explanatory variables. An unstructured working correlation matrix will be assumed for this model. Least-squares mean of each treatment group, least-squares mean treatment difference, two-sided 97.5% confidence interval for the treatment difference, and p-value based on the fitted MMRM will be reported for each applicable visit (day). If the p-value based on a two-sided test for treatment at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ([inclisiran + usual care] - usual care) is less than 0, statistical significance in favor of inclisiran is shown. Primary efficacy variable 2 will be analyzed at each post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables. The odds ratio, two-sided 97.5% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. If the p-value based on a two-sided test for inclisiran + usual care versus usual care at Day 330 is < 0.025 and the corresponding odds ratio is greater than 1, statistical significance in favor of inclisiran + usual care is shown. The secondary efficacy variables are the following: 1. Absolute change from baseline in LDL-C

	2. Average percent change from baseline in LDL-C levels to each post-baseline visit 3. Average absolute change from baseline in LDL-C levels to each post-baseline visit 4. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline) 5. Achieving ≥ 50% reduction from baseline in LDL-C (yes, no) 6. Achieving LDL-C < 55 mg/dL (yes, no) 7. Percent change from baseline in apoB 8. Absolute change from baseline in apoB 9. Percent change from baseline in VLDL 10. Absolute change from baseline in VLDL 11. Percent change from baseline in non-HDL-C 12. Absolute change from baseline in non-HDL-C 13. Percent change from baseline in total cholesterol 14. Absolute change from baseline in total cholesterol 15. Percent change from baseline in Lp(a) 16. Absolute change from baseline in Lp(a) 17. Percent change from baseline in HDL-C 18. Absolute change from baseline in HDL-C 19. Percent change from baseline in triglycerides 20. Absolute change from baseline in triglycerides 21. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose) 22. Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days) 23. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no) Analyses of secondary efficacy variables 1 and 7 - 20 will be similar to the primary analysis of primary efficacy variable 1 (using MMRM, but with a two-sided 95% confidence interval for the treatment difference). Secondary efficacy variables 2, 3, and 22 will be analyzed using a linear model with treatment and baseline LDL-C as explanatory variables. Secondary efficacy variables 4 - 6 and 23 will be analyzed at each post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables. Secondary efficacy variable 21 will be analyzed at each post-baseline visit using a proportional odds model with treatment and baseline LDL-C as explanatory variables.
Key words	Hyperlipidemia, Acute Coronary Syndrome (ACS), Secondary Cardiovascular Prevention, Atherosclerotic Cardiovascular Disease (ASCVD), Hypercholesterolemia, Lipid lowering therapies

1 Introduction

1.1 Background

Inclisiran is a novel synthetic small interfering ribonucleic acid (siRNA) therapeutic for subcutaneous (SC) injection for the treatment of hypercholesterolemia. Inclisiran has been shown to lower low density lipoprotein cholesterol (LDL-C) by 50% or more in patients with stable established atherosclerotic cardiovascular disease (ASCVD) who are treated with maximally tolerated statin therapy (Ray et al 2020). It is not known, however, if participants who have had a recent acute coronary syndrome (ACS) would have similar effects on LDL-C, with respect to the use of inclisiran, since these patients were excluded from participation in the Phase III registration trials.

The purpose of this trial is to assess the LDL-C lowering effects of aggressive LDL-C management with inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS and have an LDL-C ≥70 mg/dL while receiving statin therapy.

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

1.1.1 Atherosclerotic cardiovascular disease (ASCVD)

Patients who have experienced an ASCVD event, including patients with coronary heart disease (CHD), are at a higher risk of having another cardiovascular (CV) event (Grundy et al 2019). Lowering of low density lipoprotein cholesterol (LDL-C) is one of the most important treatment strategies to help prevent a recurrent CV event (Baigent et al 2010). CHD patients, including those who experienced an ACS, should receive long-term intensive lipid lowering therapy starting with a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) as reductions in LDL-C have demonstrated significant reductions in CV morbidity and mortality both in patients with stable ASCVD and in those with a recent ACS (Mills et al 2011; Cannon et al 2004; Collins et al 2016).

The most recent treatment guidelines by the American Heart Association and the American College of Cardiology now recommend initiating a high intensity statin (atorvastatin (40 mg) or rosuvastatin (20 mg)) as early as possible (1-4 days) after the diagnosis of ACS has been made with a goal of achieving at least 50% reduction in LDL-C (Grundy et al 2019). In those same patients whose LDL-C remains ≥70 mg/dL, use of other non-statin therapies are recommended for additional reductions in LDL-C.

A more aggressive reduction in LDL-C in ACS patients was associated with further reductions in CV morbidity and mortality but data is limited when evaluating the efficacy of various lipid lowering therapies when added to statin therapy (Wilson et al 2019). Aggressive LDL-C targets are not easy to achieve in patients following an ACS with statin therapy alone (Rosenblit 2019; Koskinas et al 2019). The risk of recurrent CV events is lower in patients receiving more intensive LDL-C lowering with the addition of non-statin therapies (e.g., ezetimibe and PCSK9-inhibition) in patients already on maximally tolerated statin therapy but requires a structured step-wise approach to achieve target goals (Cannon et al 2015; Sabatine et al 2017; Schwartz et al 2018). Reasons for poor LDL-C

control rates in ACS patients can be attributed to multiple factors including: the inability to titrate statins to higher doses due to tolerability issues at higher doses, lack of a therapeutic target or goal to achieve for LDL-C with no regular assessment of LDL-C levels, and poor adherence to lipid lowering therapy (Lambert-Kerzner et al 2015; Anderson et al 2018). Employing a guideline directed medical therapy plan in ACS patients with a LDL-C goal of <70 mg/dL can be achieved. However, it requires the use of high-intensity statins at maximally tolerated doses and the use of add-on non-statin therapies (Cannon et al 2017).

1.1.2 Mechanism of RNA Interference

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering ribonucleic acids (siRNAs). Typically, synthetic siRNAs are 19-base to 25-base pair double-stranded oligonucleotides in a staggered duplex with a two- to four-nucleotide overhang at one or both of the 3' ends. Such siRNAs can be designed to target an endogenous messenger RNA (mRNA) transcript of a given gene. When introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-Induced Silencing Complex (RISC). This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the target mRNA and the suppression of the target protein encoded by the mRNA (Elbashir et al 2001).

Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration (Soutschek et al 2004), various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo, in animal models (including in rodents and nonhuman primates) and humans employs intravenous delivery of siRNA in lipid nanoparticle (LNP) formulations (Soutschek et al 2004; Morrissey et al 2005; Geisbert et al 2006; Zimmermann et al 2006; Coelho et al 2020; Tabernero et al 2013). Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to an N-acetylgalactosamine (GalNAc) carbohydrate ligand (Ashwell and Morell 1974). Conjugation of a triantennary GalNAc ligand to a siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and down regulation of hepatic proteins.

1.1.3 Inclisiran

Inclisiran is a chemically synthesized, subcutaneously administered, double-stranded siRNA, conjugated on the sense strand with triantennary GalNAc to facilitate uptake specifically by hepatocytes. In hepatocytes, inclisiran utilizes the RNAi mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation (Nishikido and Ray 2018). Inclisiran was approved by the FDA on December 22nd, 2021, approved under the name Leqvio and is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical ASCVD who require additional lowering of LDL-C. (reference USPI).

1.1.4 Non clinical studies

Inclisiran was specifically designed with molecular and biochemical characteristics to minimize untoward side effects which are reflected by the absence of dose limiting toxicities in preclinical models. For example, GalNAc ligands were added to the RNA strands in order to target inclisiran to receptors on hepatocytes, thereby greatly reducing uptake by heterologous tissue with tissue distribution being primarily localized in the liver (Nishikido and Ray 2018). In addition, once inclisiran is inside the cell, there is a low likelihood of off-target binding because inclisiran is sequestered within RISC and guided to its complementary mRNA sequence.

Inclisiran was well tolerated in all non-clinical studies (Ray et al 2020). The most common findings were related to the expected pharmacological effects of inclisiran on lipid profiles and histopathological findings of vacuolation in hepatocytes of rats and lymph node macrophages of monkeys and the presence of basophilic granules in hepatocytes of monkeys and kidneys of rats. These microscopic findings are not considered adverse effects because they are not associated with changes in clinical pathology parameters. Liver function enzymes were only minimally to mildly increased, and were reversible following treatment-free periods, and there were no changes in urinalysis or urine chemistry parameters.

1.1.5 Clinical Studies

Inclisiran lowers LDL-C for sustained periods while only requiring twice yearly injections resulting in effective reductions in LDL-C (50% or more) in stable ASCVD patients in as soon as 3 months after the first injection. In the double-blind, placebo-controlled, multicenter Phase III ORION trials, involving 3,655 patients (about half of which received inclisiran, n=1,833), after the initial administration of inclisiran, LDL-C levels were quickly reduced with more than 65% of patients (placebo controlled) reaching an LDL-C <70 mg/dL when used on top of a maximally tolerated statin (Ray et al 2020). Adverse events in the Phase III trials were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran than with placebo; such reactions were generally mild, and none were severe or persistent. The phase III studies with inclisiran, however, were performed in stable ASCVD patients and did not include those who had a recent ACS event.

1.2 Purpose

Given the importance of achieving LDL-C targets in ACS patients and the unique LDL-C lowering properties of inclisiran a study is needed to better assess the effects of having inclisiran part of the care management pathway in participants who have a recent ACS (in-patient/out-patient) within 5 weeks of screening. Implementation of a systematic LDL-C management pathway including treatment with inclisiran in patients who have experienced an ACS and have an LDL-C ≥70 mg/dL despite being on statin therapy could increase the proportion of patients who reach acceptable LDL-C levels and thereby lower their risk of recurrent ischemic events.

The Phase III trials with inclisiran provided high-quality evidence supporting the efficacy and safety/tolerability of inclisiran, however, the highly controlled conditions under which these double-blind, placebo-controlled registration trials were conducted limit their ability to reflect the complexity and diversity of actual clinical practice. For example, adherence to lipid lowering medication that rely on patient self-administration, including statins, in clinical trials

is often higher than in real-world clinical practice, in part due to the better monitoring of the patient. In addition, in order to meet the inclusion criteria of the inclisiran Phase III trials, participants needed to be on stable lipid-lowering therapy without plans to switch therapy during the follow-up period, while switches in lipid lowering therapy (statin and non-statin) therapy are common in routine clinical practice.

In summary, the purpose of this study is to assess the effect on LDL-C of implementation of an LDL-C management care pathway that includes initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS with LDL-C ≥70 mg/dL despite receiving statin therapy compared to usual care without inclisiran.

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 assess the effect on LDL-C of implementation of an LDL-C management care pathway that includes initiation of inclisiran in participants with a recent hospitalization (in-patient/out-patient) for an ACS with LDL-C ≥70 mg/dL despite receiving statin therapy compared to usual care without inclisiran at Day 330	• Percent change from baseline in LDL-C • Achieving LDL-C < 70 mg/dL (yes, no)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess (1) the absolute change from baseline in LDL-C level by visit, and (2) average of percent and absolute changes from baseline in LDL-C levels to each post-baseline visit, in the inclisiran + usual care group compared to usual care group at Day 330	• Absolute change from baseline in LDL-C • Average percent change from baseline in LDL-C levels to each post-baseline visit • Average absolute change from baseline in LDL-C levels to each post-baseline visit
• To assess the proportion of participants reaching pre-specified LDL-C targets in the inclisiran + usual care group compared to usual care group at Day 330	• Achieving ≥ 50% reduction from baseline in LDL-C (yes, no) • Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline) • Achieving LDL-C < 55 mg/dL (yes, no)
• To assess plasma lipoproteins and triglycerides in the inclisiran + usual care group compared to usual care group at Day 330	• Percent change and absolute change from baseline in apoB • Percent change and absolute change from baseline in VLDL

Objective(s)	Endpoint(s)
	• Percent change and absolute change from baseline in non-HDL-C • Percent change and absolute change from baseline in total cholesterol • Percent change and absolute change from baseline in Lp(a) • Percent change and absolute change from baseline in HDL-C • Percent change and absolute change from baseline in triglycerides
• To assess changes in and adherence to background lipid-lowering therapy in the inclisiran + usual care group compared to usual care group at Day 330	• Intensity of lipid lowering therapy (decrease in dose, no change in dose, increase in dose) • Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days) • Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)
• To assess overall safety and tolerability of inclisiran	• Adverse events
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	
• To assess major adverse cardiovascular events (MACE) (investigator determination) in the inclisiran + usual care group compared to usual care group at Day 330	• Cardiovascular death (yes, no) • Non-fatal MI (yes, no) • Resuscitated cardiac arrest (yes, no) • Non-fatal ischemic stroke (yes, no) • Composite MACE (cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke) (yes, no)
[redacted]	

2.1 Primary estimands

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

The primary clinical question of interest in this study is to evaluate the effect on LDL-C of implementation of an LDL-C management care pathway with inclisiran versus usual care in participants who are discharged after an ACS on statin therapy or have documented statin intolerance and do not have their LDL-C at the target level. The justification for the primary estimand is that it will evaluate the LDL-C lowering effect of inclisiran on both the percent change in LDL-C and the achievement of the target LDL-C (<70 mg/dL) compared to a usual care of implementation pathway in participants following a recent ACS, including potential changes in concomitant therapy. Further details can be found in Section 12.

Primary estimand 1: The primary analysis of primary efficacy variable 1 (percent change from baseline in LDL-C) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
-
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Least-squares mean difference between inclisiran + usual care group and usual care group

Primary estimand 2: The primary analysis of primary efficacy variable 2 (achieving LDL-C < 70 mg/dL) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Achieving LDL-C < 70 mg/dL (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Odds ratio of inclisiran + usual care to usual care for achieving LDL-C < 70 mg/dL

2.2 Secondary estimands

Not applicable.

3 Study design

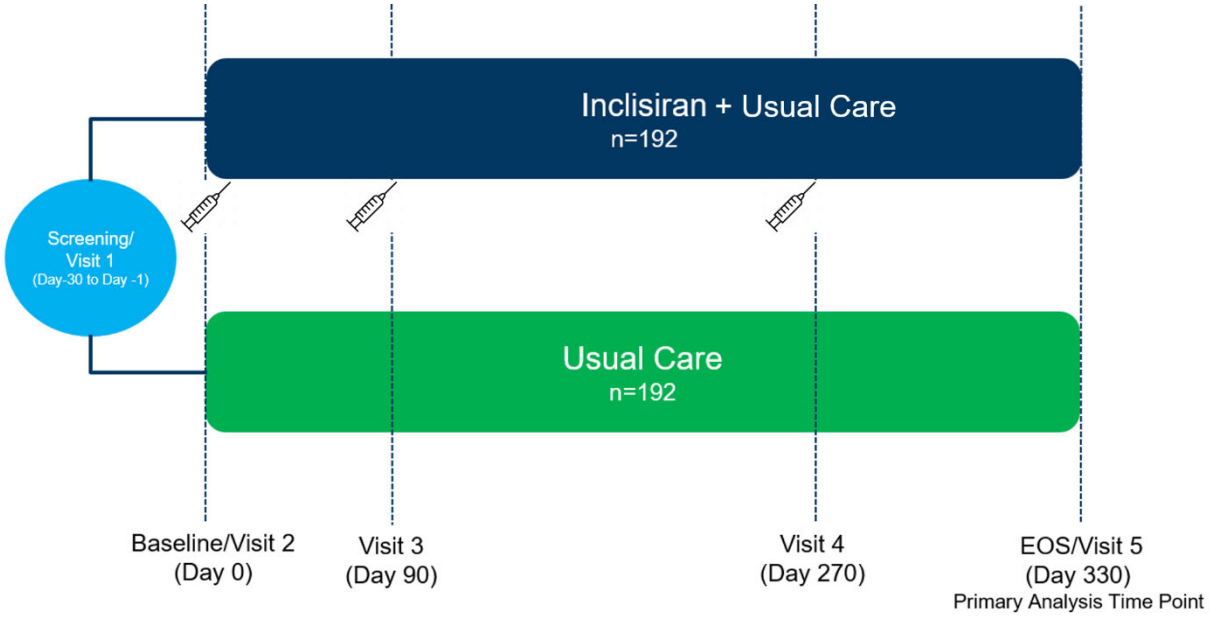
This is a randomized, parallel-group, open-label, multicenter study comparing an LDL-C management strategy including inclisiran plus usual care with usual care A total of approximately 384 participants will be randomized 1:1 to aggressive LDL-C management with inclisiran plus usual care (intervention arm) and usual care (control arm). Identification of participants will take place during hospitalization or in the weeks following discharge with screening soon thereafter. Screening of participants must take place within 5 weeks after discharge.

Potential participants who are discharged after an ACS on statin therapy (which is considered routine care) or have documented statin intolerance will be screened and receive an LDL-C test

within 5 weeks post-discharge (to allow for the realization of the full effect of statin therapy). After the LDL-C test, participants with an LDL-C ≥70 mg/dL are eligible for the trial as long as they meet all other inclusion criteria. Participants will be randomized to inclisiran + usual care or usual care. All participants will be maintained on statin therapy during inclisiran treatment, but concomitant lipid-lowering therapy and LDL-C assessments will be at the discretion of the treating (primary) physician, mimicking real-world clinical decision-making and enabling the evaluation of inclisiran compared to usual care in patients with a recent ACS. Usual care may therefore include addition of ezetimibe, PCSK9-inhibiting monoclonal antibodies and/or commercially available inclisiran (Note: participants treated with inclisiran should not be treated with PCSK9-inhibiting monoclonal antibodies). After randomization, the treating physician will not have access to LDL-C values obtained as part of the study but will be able to perform LDL-C assessments at their discretion, to mimic usual care. The rationale of not providing the treating physician the LDL-C values obtained as part of the study is that those results might influence decisions made by him/her and could therefore undermine "usual care". Commercially available inclisiran may be used for appropriate patients in the usual care arm at the sole discretion of the treating physician, without any influence from the PI. LDL-C measurement and assessment of lipid lowering medications at each visit will be performed to assess adherence to background statin therapy.

The collection of data from trial sites through eCRFs may also be complemented with EHR data and claims data (e.g., lipid measurements and concomitant medications), if available. While study visits will be preferentially performed in-person at the study sites, phone or virtual home-visits are an acceptable alternative if in-person visits are not permitted or impractical (e.g., due to a public health emergency). Site or home health nursing service may be used to assist with blood draws and/or study medication administration if required at these visits. Informed consent forms will be available in English and Spanish.

Figure 3-1 Study Design



Remote procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1 Assessment schedule performed at a remote location.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site or 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. Any off-site healthcare professionals utilized during the trial must be agreed with Novartis before use. In addition to procedures performed by the off-site healthcare professional, the on-site staff will perform certain procedures remotely using tele-visits.

4 Rationale

4.1 Rationale for study design

Following an ACS, patients are at increased risk of recurrent ischemic events. Lowering LDL-C reduces the risk of recurrent events in patients with ASCVD, with a magnitude of clinical benefit that is proportional to the reduction in LDL-C levels. In view of the high risk of recurrent events in patients with a recent ACS, early initiation of aggressive lipid-lowering therapy, including non-statin therapies, is particularly beneficial.

Clinical care pathways for patients with a recent ACS, as endorsed by clinical treatment guidelines, include discharge on high-intensity statin therapy and follow-up with LDL-C measurement four to twelve weeks post-discharge, and consideration of non-statin therapies (e.g., ezetimibe and/or a PCSK9 inhibiting monoclonal antibody) if a patient has a less-than 50% reduction in LDL-C or an LDL-C ≥70 mg/dL. Despite these treatment options only a minority of patients who are eligible actually receive non-statin therapies in current clinical practice and as a result, most patients will not reach their target LDL-C level. The poor management of blood cholesterol is partly a consequence of clinical inertia and partly a consequence of limitations of currently available non-statin therapies (i.e., ezetimibe has a limited LDL-C lowering effect and PCSK9 inhibiting monoclonal antibodies require patient self-administration by injection every 2 to 4 weeks). The one-year study duration of this trial will enable comparison of LDL-C lowering strategies in participants following an ACS using inclisiran compared to usual care.

Additional important considerations of the study design include:

- **Recruitment:** Potentially eligible participants, recently hospitalized for an ACS (in-patient/out-patient), will be identified by the primary investigator and be invited to contact the research site for screening and inclusion. Eligible participants will need to consent to having health records made available as part of the collection of medical and pharmacy claims in order to assess healthcare resource utilization during the study.

- **Responsibilities of principal investigator:** Study visits will be done by the principal investigator while routine care is performed by the participant's own treating physician. As a consequence, the treating physician will not see participants more frequently due to trial participation and will not be aware of the laboratory assessments performed in the context of the study (routine or usual care laboratory tests and changes in therapy are at their discretion).
- **Open label:** The study will be performed as an open-label study to mimic decision making in usual care, following from the primary objective of the study. For example, if the study would have been performed as a double-blind placebo-controlled study, it would not be possible to study the effect of inclisiran treatment on statin discontinuation as participants and investigators would not be aware of treatment allocation.
- **Duration of study period:** The study is designed as a one-year trial with a total of three inclisiran doses. The Phase III trials of inclisiran had a follow-up duration of 18 months. In the Phase II trial (ORION-1), it was shown that the second dose at Day 90 lowers LDL-C to a slightly greater level then after the initial administration (Ray et al 2017). Based on these trials, the maximum reduction in LDL-C is achieved approximately 4 to 5 months after initiation of therapy. Prior studies have shown that approximately one-third of patients discontinue statin therapy in the three years following initiation of therapy (Khunti et al 2018). A follow-up duration of one year enables: 1) observation of the steady-state LDL-C lowering effect of inclisiran, 2) observation of a meaningful difference in statin discontinuations, should such a difference exist, and 3) observation of potential differences in variables that likely require longer-term treatment of inclisiran to become apparent, such as patient reported outcomes.

Implementation of a systematic LDL-C management pathway including treatment with inclisiran in participants who have experienced an ACS and have an LDL-C ≥70 mg/dL, despite receiving statin therapy, could increase the proportion of participants who reach acceptable LDL-C levels and thereby lower the risk of recurrent ischemic events in these participants. Inclisiran has not been previously evaluated in patients with a recent ACS. In this context, we aim to assess the LDL-C lowering effects of aggressive LDL-C management with inclisiran in patients with a previous hospitalization for an ACS.

4.1.1 Rationale for choice of background therapy

Participants are required to be receiving statin therapy, or have documentation of statin intolerance, at the time of identification and screening (~2-5 wks following an ACS) without plans to adjust lipid lowering therapy at that point in time. Adjustments in lipid-lowering therapy other than inclisiran during the study will occur at the discretion of the treating (primary) health care practitioner in both treatment groups, mimicking real-world clinical decision-making. Inclisiran will not be excluded from the usual care group post-approval – it is assumed based on historical and anticipated product uptake shortly after launch that potential inclisiran treatment in the usual care group will be minimal and thus will not significantly interfere with the study. Participants receiving inclisiran during the trial should not be simultaneously treated with a PCSK9 inhibiting monoclonal antibody.

4.2 Rationale for dose/regimen and duration of treatment

Previous studies have shown that a 300 mg dose of inclisiran sodium is well tolerated and provides maximum efficacy (i.e., doses higher than 300 mg did not provide additional efficacy in LDL-C lowering). The 300 mg dose of inclisiran will be administered on Day 0, Day 90 and Day 270, consistent with the dose and dosing regimen that was studied in the Phase III trials. Modelling and simulation have demonstrated that the 300 mg dose of inclisiran results in sustained reductions in LDL-C (Ray et al 2017). A treatment duration of one year will be sufficient to assess changes in LDL-C due to inclisiran and changes in concomitant lipid-lowering therapy.

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

After all participants complete their baseline visit, the demographic and baseline characteristics may be summarized to help design new studies.

4.5 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and stopping rules.

Participants taking part in this clinical study will receive statin therapy and/or other LDL-C lowering therapies as considered necessary by their treating physician and consistent with standard of care. Reduction of LDL-C has been associated with reduced CV risk both by epidemiology and in controlled clinical trials. Modification of concomitant therapy is at the discretion of the participants' treating physician. Additionally, study assessments and frequent visits will provide close monitoring of participants' conditions and may provide information that may benefit post-ACS patients in the future.

Support for the planned administration of inclisiran to participants with elevated LDL-C is provided by the following:

- Inclisiran has been studied in a Phase III program for the patient population eligible for this study.
- Injection site reaction is the only adverse event known to be attributed to inclisiran treatment. To date, all injection site reactions were localized, predominantly mild or occasionally moderate, transient, and resolved without sequelae.
- The potential for immunogenicity of inclisiran was shown to be low.
- Reduction of LDL-C has been associated with reduced CV risk both by epidemiology and in controlled clinical trials.

[redacted]

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

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

This study will include male or female participants ≥18 years of age with a recent hospitalization (in-patient/out-patient) for an ACS (within 5 weeks) and elevated LDL-C (≥70 mg/dL) despite being treated with statin therapy by their health care practitioner. We plan to randomize approximately 384 participants at up to approximately 130 US sites.

5.1 Inclusion criteria

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

1. Males and females ≥18 years of age
2. Recent ACS (in-patient/out-patient) within 5 weeks of screening, defined as:
   Ischemic symptoms with unstable pattern, occurring at rest or minimal exertion within 24 hours of an unscheduled hospital admission or emergency department visit, due to presumed or proven obstructive coronary disease AND at least one of the following:
   a. Elevated cardiac biomarkers (cardiac troponin (cTn) or the MB fraction of creatinine kinase (CKMB)) with at least one value above the 99th percentile of the upper reference limit (URL) or defined by the local laboratory MI diagnosis cut-off values OR
   b. Resting ECG changes consistent with ischemia or infarction AND additional evidence of obstructive coronary disease
3. Serum LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
4. Fasting triglycerides <4.52 mmol/L (<400 mg/dL) at screening
5. Calculated glomerular filtration rate >20 mL/min by estimated glomerular filtration rate (eGFR)
6. Participants must be willing and able to give informed consent before initiation of any study related procedures and willing to comply with all required study procedures
7. Participants are required to be on statin therapy, or have documented statin intolerance, as determined by the investigator, following hospitalization (in-patient/outpatient) for an ACS. Statin intolerant patients are eligible if they had intolerable side effects on at least 2 different statins, including one at the lowest standard dose.

5.2 Exclusion criteria

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

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the participant at significant risk (according to investigator's [or delegate] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class IIIb or IV heart failure or last known left ventricular ejection fraction <25%.
4. Significant cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation at the time of screening.
5. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization (assessed at screening visit) despite antihypertensive therapy.
6. Recurrent acute coronary syndrome event within 2 weeks prior to randomization.
7. Coronary angiography and revascularization procedure (PCI or CABG surgery) performed within 2 weeks prior to the randomization visit or planned after randomization.
8. Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years.
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or 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.

11. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
    a. Approved vaccines or vaccines used under Emergency Use Authorization should not be considered part of this exclusion criteria. Patients can receive COVID vaccines during inclisiran trials.
    b. While use of COVID anti-viral therapies approved for use under Emergency Use Authorization would need to adhere to the washout period outlined above, prior to screening, they would not be considered as criteria for trial termination/discontinuation.
12. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
13. Planned use of other investigational products or devices during the course of the study.
14. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    a. Participants who are unable to communicate or to cooperate with the investigator.
    b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency).
    c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
    d. Have any medical or surgical condition, which in the opinion of the investigator would put the participant at increased risk from participating in the study.
    e. Persons directly involved in the conduct of the study.
15. Treatment with monoclonal antibodies directed towards PCSK9 or inclisiran within 90 days of screening.
16. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or (ii) alanine aminotransferase (ALT) elevation >3x ULN, aspartate aminotransferase (AST) elevation >3x ULN, or total bilirubin elevation >2x ULN (except

patients with Gilbert's syndrome) at screening confirmed by a repeat measurement at least one week apart.

6 Treatment

6.1 Study treatment

All eligible participants will be randomized to receive either inclisiran + usual care or usual care (standard of care per treating physician). The following study treatment will be provided: Inclisiran (KJX839), 284 mg, 1.5 ml Liquid in a single-use prefilled syringe (PFS) for s.c. administration.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Inclisiran, KJX839 284 mg 1.5 ml	PFS, Liquid for injection	s.c.	Inclisiran sodium 300 mg / 1.5 ml (equivalent to 284 mg of inclisiran)	Sponsor (local)

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Participants will be assigned at Visit 2/Baseline to one of two treatment groups (inclisiran + usual care and usual care) in a ratio of 1:1 to require approximately 384 participants (192 participants per treatment group) to be randomized.

6.1.4 Treatment duration

The planned duration of treatment is 330 days from randomization. Participants may be discontinued from treatment at any time due to adverse events, disease progression and/or at the discretion of the investigator or the participant.

6.2 Other treatment(s)

Not applicable

6.2.1 Concomitant therapy

All prior cardiovascular medications (e.g., antiplatelets (aspirin, thienopyridines), non-vitamin K oral anticoagulants (NOACs), beta-blockers, ACE-inhibitors or ARBs, other antihypertensives, antidiabetics, and lipid lowering therapies) administered before the

participant is enrolled in the study but still receiving must be recorded in the appropriate Case Report Forms, or where applicable, sourced from the EHR and mapped into the clinical study.

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

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Not applicable

6.2.2 Prohibited medication

The treatments displayed in the table below are not allowed to be used simultaneously with inclisiran in the treatment arm. No modifications of therapy is required or recommended in the usual care arm.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action to be taken
Alirocumab (Praluent)	Participants randomized to inclisiran: monoclonal antibodies directed against PCSK9 are prohibited for the full duration of the study	Discontinue PCSK9 inhibitor
Evolocumab (Repatha)	Participants randomized to inclisiran: monoclonal antibodies directed against PCSK9 are prohibited for the full duration of the study	Discontinue PCSK9 inhibitor

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

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

6.3.2 Treatment assignment, randomization

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 system provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to the package containing the investigational drug(s).

At Visit 2/Baseline, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the two treatment groups in 1:1 ratio (inclisiran + usual care vs usual care). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment group and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization scheme for participants will be reviewed and approved by a member of the Novartis Biometrics group.

6.4 Treatment blinding

This is an open-label study and study treatment is not blinded, thus treatments will be known to participants, investigator staff, including persons performing the study assessments.

6.5 Dose escalation and dose modification

Dose interruptions for the investigational study medication (inclisiran) are not permitted.

If a planned dose is missed by less than 3 months, administer inclisiran and maintain dosing according to the participant's original schedule. If a planned dose is missed by more than 3 months, start a new dosing schedule - administer inclisiran initially, again at 3 months, and followed by dosing, thereafter, every 6 months.

Dose interruptions must be recorded on the inclisiran Dose Administration case report form for the investigational study drug.

6.5.1 Dose modifications

Study drug administration of inclisiran [inclisiran (KJX839), 284 mg liquid in PFS, 1.5 ml] should be temporarily interrupted or permanently discontinued in participants with:

1. Intolerable AEs, or if the investigator believes that continuing dosing will be detrimental to the participant's mental or physical health. This includes severe or serious reactions at the injection site and any anaphylactic type reactions.
2. Liver laboratory values meeting the study drug interruption criteria listed in Table 16-4 and Table 16-5.

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

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

The dose interruptions must be recorded on an appropriate eCRF.

6.5.2 Follow-up for toxicities

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

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

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

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

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

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

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

Perform relevant examinations (Ultrasound or Magnetic resonance imaging (MRI), Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis). Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT

can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (https://livertox.nih.gov/rucam.html).

Table 6-3 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver function test (LFT) abnormalities.

Table 6-3 Guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities

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

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

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Compliance will be ensured by the investigator and/or study personnel at each dosing visit. This information should be captured in the source document at each visit. Study drug (inclisiran) accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of study drug exposure will be calculated based upon the dates recorded in the eCRF.

6.7 Preparation and dispensation

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

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

As per Section 4.6, during a Public Health emergency that limits or prevents on-site study visits, a home health nurse is permitted to administer the study medication at a participant's home (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible. The dispatch of study medication from the site to the participant’s home remains under the accountability of the Investigator.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

Medication labels will include storage conditions for the study treatment but no information about the participant except for the medication number.

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

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

6.7.2 Instruction for prescribing and taking study treatment

Packaging and Labeling

Investigational product [Inclisiran (KJX839), 284 mg Liquid PFS, 1.5 ml] will be provided by the sponsor. Medication labels will comply with regulatory requirements. The storage conditions will be described on the medication label.

The container closure system for the prefilled syringe consists of a Type I glass syringe with a stainless steel 27G 1/2" staked needle covered by a removable rigid needle shield and Flurotech covered bromobutyl plunger.

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Inclisiran (KJX839), 284 mg Liquid in PFS, 1.5 mL	Inclisiran sodium 300 mg/1.5 mL (equivalent to 284 mg inclisiran), s.c. use	Initially, 90 days later, 180 days after the second dose

Participants will be administered a single SC injection of 300 mg Inclisiran sodium for injection at predefined time points as described in the Schedule of Assessments (Table 8-1). Investigational product injection will be administered by qualified clinical study site staff under the supervision of the investigator or designee. The site of injection is the abdomen, arm or thigh. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

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

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 understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered

appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - [redacted]
  - As applicable, the consent will include language for the use of de-identification and tokenization technology that will allow for the acquisition and linkage of the participant to their health care data that exists in pharmacy and medical administrative claims databases
- As applicable, 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.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all 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 (+/- 7 days). Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment should continue to attend the remaining study visits as indicated in the Assessment Schedule (Table 8-1).

Participants who discontinue from study or withdraw their consent should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

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

- Participants need to fast for at least 8 hours for all visits (measurement of lipids/lipoproteins and blood glucose requires participants to be fasting). If the participant has not fasted, the collection of laboratory evaluations must be rescheduled.
- Blood donation will not be allowed at any time during the study

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.

As per Section 4.6, during a Public Health emergency 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.

If a public health emergency limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Virtual visits [e.g., phone calls, video visits (preferred)] or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of a public health emergency until it is safe for the participant to visit the site again.

Unscheduled Visits

Participants may be seen at any time for an unscheduled visit, e.g., if they experience deterioration or AEs that in the opinion of the Investigator/qualified site staff requires closer monitoring. The assessment(s) performed at an unscheduled visit must include at a minimum: an assessment of concomitant medications, vital signs, and an AE/SAE assessment. Any additional assessments performed are at the Investigator/qualified site staff's discretion.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment[1]**				**Unplanned**
Visit Name	**Visit 1**	**Baseline/Visit 2**	**Visit 3**	**Visit 4**	**EOS/Visit 5**	**Unscheduled Visit**
Days	**-30 to -1**	**0**	**90**	**270**	**330**	**-**
Informed Consent	X					
Inclusion / Exclusion criteria	X	X				
Physical Examination	S		S	S	S	
Demography	X					
Medical History	X					
ACS Medical History	X					
Statin Intolerance Medical History	X					
Height and Weight[2]	X	X	X	X	X	
Pulse Rate	X	X	X	X	X	X
Blood Pressure	X	X	X	X	X	X
Prior/Concomitant medications[3]	X	X	X	X	X	X
Surgical / Medical procedures	X	X	X	X	X	X
Urinalysis		X			X	
Pregnancy and assessments of fertility[4]	X	X	X	X	X	
Hematology	X	X			X	
Full Clinical Chemistry		X				
Limited Chemical Chemistry	X		X	X	X	
Hepatitis Markers	X					
Lipids and lipoproteins[5]	X	X	X	X	X	
Coagulation	X	X				
Biomarker-Lipoprotein(a)		X	X	X	X	

Period	Screening	Treatment[1]				Unplanned
Visit Name	Visit 1	Baseline/Visit 2	Visit 3	Visit 4	EOS/Visit 5	Unscheduled Visit
Days	-30 to -1	0	90	270	330	-
Electrocardiogram (ECG)	X					
Randomization		X				
Inclisiran Dose Administration		X	X	X		
IRT Transaction	X	X	X	X	X	
Injection Site Reaction Assessment		X	X	X	X	
Clinical Outcome Assessment(s)		X	X	X	X	
[redacted]						
Adverse Events	X	X	X	X	X	X
[redacted]						

[X]Assessment to be recorded in the clinical database or received electronically from a vendor
[S]Assessment to be recorded in the source documentation only
[1]Due to a Public Health Emergency, if participant is unable to attend in-person visit, phone or virtual visit is an acceptable alternative. At home visits by site staff or a nursing service may be used to assist with blood draws and/or study medication administration if required at this visit.
[2]Height only to be performed at Visits 1 and 2
[3] 30 days prior to randomization
[4]All female participants of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (central lab). A urine pregnancy test will be conducted at the local site for remaining visits.
[5]LDL-C, apolipoprotein B, VLDL, non-HDL-C, total cholesterol, triglycerides, and HDL-C. In addition, samples will be collected for biobanking at Visits 2-5.
[redacted]

8.1 Screening

A participant's eligibility for the study will be assessed during the 30 day screening period (Day -30 to Day -1). Screening is flexible in duration based on the time required for participants to be evaluated for eligibility. It is permissible to re-screen a participant if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. It is permissible to re-screen a participant if he/she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. If the re-screen is approved, a new participant number will be allocated to the participant and he/she will need to re-perform all Visit 1 procedures. A participant may be re-screened once. The participant must provide new written informed consent before they are re-screened.

The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen failure 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 Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants include age, sex, race, ethnicity, and source of patient referral. Any relevant medical history including surgical/medical procedures, protocol solicited medical history, and/or current medical conditions before obtaining informed consent will be recorded in the Medical History eCRF. A detailed medical history (including cardiovascular and other conditions relevant to the study population to be enrolled) and current medical conditions present, including the presentation and management of index MI event will also be recorded. Where possible, diagnoses and not symptoms, will be recorded. All medications and relevant medical histories will be recorded on the corresponding eCRFs.

8.3 Efficacy

The primary efficacy variables are the following:

1. Percent change from baseline in LDL-C
2. Achieving LDL-C < 70 mg/dL (yes, no)

The secondary efficacy variables are the following:

1. Absolute change from baseline in LDL-C
2. Average percent change from baseline in LDL-C levels to each post-baseline visit
3. Average absolute change from baseline in LDL-C levels to each post-baseline visit
4. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)
5. Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)
6. Achieving LDL-C < 55 mg/dL (yes, no)
7. Percent change from baseline in apoB
8. Absolute change from baseline in apoB
9. Percent change from baseline in VLDL
10. Absolute change from baseline in VLDL
11. Percent change from baseline in non-HDL-C
12. Absolute change from baseline in non-HDL-C
13. Percent change from baseline in total cholesterol
14. Absolute change from baseline in total cholesterol
15. Percent change from baseline in Lp(a)
16. Absolute change from baseline in Lp(a)
17. Percent change from baseline in HDL-C
18. Absolute change from baseline in HDL-C
19. Percent change from baseline in triglycerides
20. Absolute change from baseline in triglycerides
21. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)
22. Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days)
23. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)

The exploratory efficacy variables are the following:

8. Cardiovascular death (yes, no)

9. Non-fatal MI (yes, no)
10. Resuscitated cardiac arrest (yes, no)
11. Non-fatal ischemic stroke (yes, no)
12. Composite MACE (cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke) (yes, no)

[redacted]

8.3.1 LDL-cholesterol

The primary efficacy assessment will be LDL-C, from which the two primary efficacy variables (percent change from baseline in LDL-C; achieving LDL-C < 70 mg/dL [yes, no]) are derived. Samples for LDL-C will be collected at screening and on visits 1, 2, 3, 4 and 5 (Table 8-1).

After randomization, the treating physician will not have access to LDL-C values obtained as part of the study.

8.3.2 Other lipoprotein measures

Other efficacy assessments will include measurement of Apolipoprotein B, Lp(a), VLDL, non-HDL-C, total cholesterol, triglycerides, HDL-C, discontinuation of statin therapy and changes in other background lipid lowering therapies. Samples for these additional efficacy biomarkers will be collected at Visits 1, 2, 3, 4 and 5 (Table 8-1). Assessment of lipid lowering medications will be collected at each of these visits and will be complemented, when possible, by any additional information obtained from EHR and claims data to verify adherence to background therapy.

8.3.3 Appropriateness of efficacy assessments

The assessment of LDL-C and other lipoproteins are standard in both clinical practice and in trials evaluating the efficacy of lipid-modifying therapies in patients following a recent ACS with an elevated LDL-C (Grundy et al 2019). LDL-C reduction, which is an effect of the mechanism of action of inclisiran, is a well-defined biomarker that is routinely assessed in clinical trials and is the primary efficacy variable of the study. Laboratory and other assessments related to the secondary and exploratory objectives are in line with the expected efficacy of inclisiran. Utilization of other lipid lowering therapies, including, but not limited to, statins, is another important component to LDL-C efficacy and assessment of their use, including adherence, will be collected to further evaluate the effectiveness of inclisiran in this study. [redacted]

8.4 Safety

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

As per Section 4.6, during a Public Health emergency that limits or prevents on-site study visits regular phone or virtual calls should occur for safety monitoring and discussion of the participant´s health status until the participant can again visit the site. If a participant cannot visit the site to have pregnancy tests done, a home urine pregnancy test kit may be used. Participants can perform the urine pregnancy test at home at the time of the scheduled visit and report the result to the site, or a communication process should be established with the participant so that the site is informed of the pregnancy test results. If a visit by site staff or home nursing staff is arranged, 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.

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

For details on AE collection and reporting, refer to AE section. Please consult the Investigator's Brochure for the specific (non-routine) safety assessments.

Table 8-2 Safety Assessment

Assessment	Specification
Physical	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. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from visit 3 except where a complete physical examination is required (see above). 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 CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Vital signs	Vital signs include 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 a validated device, e.g. standard sphygmomanometer or an automated BP device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

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

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

In case of abnormal dipstick urinalysis results, microscopy and other assessments (e.g. serum albumin and serum total protein) will be performed at the local laboratory and the abnormality recorded as an AE.

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

Clinically notable laboratory findings are defined in Section 16.1

Local laboratory assessments may be performed on an as-needed basis for unscheduled visits. Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator on the source document and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the patient's AE eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

As per Section 4.6, during a Public Health emergency that limits or prevents on-site study visits, if a visit by site staff/home nursing staff is arranged, specimen samples should be collected during the visit and processed and handled in line with the study laboratory manual.

Table 8-3 Clinical Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelet count, White blood cell count with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other)
Chemistry	**Full serum chemistry:** Albumin, Alkaline phosphatase (ALP), ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, inorganic Phosphate, Chloride, Sodium, Potassium, Creatinine, estimated Glomerular Filtration Rate (eGFR), Creatine kinase (CK), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin (TBL), Total Cholesterol, LDL-C (direct), VLDL, HDL-C. Apolipoprotein B, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Hemoglobin A1C, Glucose (fasting) and glycated hemoglobin (HbA1C) **Limited serum chemistry** (ONLY): AST, ALT, ALP, GGT, TBL, CK, creatinine, eGFR, fasting glucose and HbA1C
Coagulation	Prothrombin Time (PT), International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Red Blood Cells/Erythrocytes, Glucose, Ketones, White Blood Cells/Leukocytes, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel (only performed in the event of abnormalities) (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR (polymerase chain reaction) (screening visit)
Additional tests	Lipoprotein(a) (Lp(a)) [redacted]
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Visit 1. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study, participant number and date and kept in the source documents at the study site.

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

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test (hCG) performed at Visit 1 (central lab). In addition, these participants will have a urine pregnancy test conducted at the local site for Visits 2, 3, 4 and 5. If any of these tests are positive at Visits 1 and 2, the participant should not be enrolled in the trial. If a participant should become pregnant during the trial, the participant may remain in the trial for follow-up visits but cannot continue to receive inclisiran injections if randomized to the inclisiran arm.

During a Public Health emergency that limits or prevents on-site study visits, a urine home pregnancy test kit may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. If a visit by site staff/home nursing staff is arranged, it is important that participants perform the urine pregnancy test first, and only if the test result is negative, proceed with the administration of the study treatment.

8.4.4 Other safety evaluations

Injection site reactions

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

Anaphylactic reactions

Potential anaphylactic reactions should be assessed by Sampson criteria in Section 16.4 (Appendix 4).

Hyperglycemia-related events

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

'New onset of diabetes' should be reported as AE on the eCRF in participants with no medical history of diabetes when:

- HbA1c becomes ≥6.5% and/or
- Two consecutive values of FPG are ≥126 mg/dL (7.0 mmol/L)
- If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will need to be collected

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

- HbA1c increases from baseline >0.5%

- New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for the evaluation of recent ACS patients with ASCVD and elevated LDL-C and take into consideration the safety data obtained from previous clinical studies with inclisiran.

8.5 Additional assessments

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

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Outcome Assessments refer to the assessment (investigator determination) of major adverse cardiovascular events (MACE) during the trial (incidences of cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke).

[redacted]

8.5.3 Biomarkers

Blood samples for assessment of lipoprotein(a) (Lp(a)) will be collected at baseline and at all study visits as indicated in Table 8-1 (Assessment Schedule). [redacted] All results from Lp(a) measurements should be blinded for participants, investigator staff, and persons per assessments. If permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents the following option to the participant: Additional blood samples will be collected at four time points (see Table 8-1) and biobanked to allow analysis of other biomarkers and proteins related to cardio-metabolic disease or study drug mechanism during or after study close.

[redacted]

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant only applies to those in the inclisiran treatment group and occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of inclisiran can be initiated by either the participant or the investigator.

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

Study treatment of inclisiran must be discontinued under the following circumstances

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Any severe suspected drug related AE at the investigator's discretion

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

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

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

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

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Study treatment for participants in the inclisiran + usual care treatment group must be discontinued with no more inclisiran injections planned. In both the inclisiran + usual care and the usual care group no further assessments are to be conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination, include the following:

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

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

9.2 Study completion and post-study treatment

At the study completion/end of study visit, including participants who are prematurely withdrawn from the study, the referring or primary physician will continue to provide ongoing medical care. When the participant has completed all scheduled study assessments, the investigator must call the IRT to record the participant completion in the IRT.

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator or, in the event of an early study termination decision, the date of that decision (e.g., each participant will be required to complete the study in its entirety and thereafter there will be no further study treatments provided (i.e., no further inclisiran injections will be conducted).

For study participants who have successfully completed the study, further guidance will be provided separately concerning continuation of treatment and access to investigational drug. This guidance will be provided to sites prior to the completion visit of the first patient

(first patient last visit). For study participants who terminate prior to the end of the study or who withdraw from treatment, continuing treatment should be managed by the investigator and/or referring or primary physician

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

The occurrence of adverse events 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.

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

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

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

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

6. Its outcome *(i.e., recovery status or whether it was fatal)*

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

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

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

Once an adverse event 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).

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of reference ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory abnormalities are included in Section 16.1 (Appendix 1).

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity

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

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

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event 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 within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a

different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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 any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

Please refer to Appendix 2 (Section 16-2) for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-4 and Table 16-5. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

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

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

10.2.2 Renal safety monitoring

To ensure participant safety and enhance reliability in determining the nephrotoxicity potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events has to be followed. Every renal laboratory trigger or renal event as defined in Table 16-6 in Appendix 3 (Section 16.3) should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-7 in Appendix 3 (Section 16.3).

10.2.3 Steering Committee

A Steering Committee (SC) for this study will be established comprising medical experts and/or clinical investigators participating in the trial and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will provide input to the clinical study protocol and potential amendments to the clinical study protocol. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules.

11 Data Collection and Database management

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimands of interest. If the estimands that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimands should be weighed against any complications and potential drawbacks of the collection.

11.1 Data collection

Electronic CRF Collection

Designated investigator staff will enter some or all of the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained in the use of the EDC system and data entry guidelines. Automatic validation program checks for data discrepancies in the eCRFs will be applied allowing 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 CRF) 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 all participant data for archiving at the investigational site.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis study team management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/UBC representative will review the protocol and data capture requirements (i.e., direct EHR data capture 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 conduct on-site or virtual monitoring visits 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. Video conferencing, electronic Trial Master File (eTMF) and remote source document review technologies will be utilized as needed to ensure that essential monitoring functions are supported when virtual monitoring visits are conducted. 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/UBC/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

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

The analysis will be performed at the end of the trial, after the data for all participants are available.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group. For discrete variables, frequency counts and percentages at each time point will be reported by treatment group.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all randomized participants. According to the intent-to-treat principle, participants will be analyzed according to the treatment group they have been assigned to during the randomization procedure.

The Per-Protocol Set is a subset of the Full Analysis Set in which participants are not treated with any inclisiran if they are randomized to the usual care treatment group or do not have any major protocol deviations (including deviations from inclusion/exclusion criteria) in either treatment group.

The Restricted Set 1 is a subset of the Full Analysis Set which includes only participants without changes in background lipid-lowering therapy.

The Restricted Set 2 is a subset of the Full Analysis Set which includes only participants who received three doses of inclisiran in the inclisiran + usual care group (i.e., excludes patients in the inclisiran + usual care group who missed one or more doses) and all participants in the usual care group (including participants who may have used commercially available inclisiran).

The Safety Set includes all participants who received study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the Full Analysis Set.

Relevant medical histories and current medical conditions at baseline (i.e., prior to first dose of study treatment) will be summarized by system organ class and preferred term, by treatment group for the Safety Set.

12.3 Treatments

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

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoints

The primary efficacy variables are the following:

1. Percent change from baseline in LDL-C
2. Achieving LDL-C < 70 mg/dL (yes, no)

The primary analysis time point for both primary efficacy variables is at Day 330.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis of primary efficacy variable 1 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Least-squares mean difference between inclisiran + usual care group and usual care group

The null hypothesis is that the mean percent change from baseline in LDL-C at Day 330 for inclisiran + usual care and usual care treatment groups are equal. The alternative hypothesis is that the mean percent change from baseline in LDL-C at Day 330 for inclisiran + usual care treatment group is not equal to that of the usual care treatment group.

Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction as explanatory variables. An unstructured working correlation matrix will be assumed for this model (Diggle et al 2002). Least-squares mean of each treatment group, least-squares mean treatment difference, two-sided 97.5% confidence interval for the treatment difference, and p-value based on the fitted MMRM will be reported for each applicable visit (day). If the p-value based on a two-sided test for treatment at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ([inclisiran + usual care] - usual care) is less than 0, statistical significance in favor of inclisiran + usual care is shown. All efforts will be made to follow up participants until the end of the study. Participants will be expected to follow the visit schedule and assessments even after discontinuation of study treatment. Data after participants discontinued study treatment will be used in the analysis ("retrieved dropout").

The primary analysis of primary efficacy variable 2 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Achieving LDL-C < 70 mg/dL (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Odds ratio of inclisiran + usual care to usual care for achieving LDL-C < 70 mg/dL

Let π_j denote the probability of achieving LDL-C < 70 mg/dL at Day 330 for treatment group j, j = 0, 1, where 0 corresponds to usual care and 1 corresponds to inclisiran + usual care. Accordingly, $\pi_j/(1 - \pi_j)$ is the odds for treatment group j, j = 0, 1.

The following null hypothesis (H_0) will be tested against the alternative hypotheses (H_A), corresponding to the comparison inclisiran + usual care versus usual care:

H_0: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] \leq 1$ versus H_A: $[\pi_1/(1 - \pi_1)]/[\pi_0/(1 - \pi_0)] > 1$

Primary efficacy variable 2 will be analyzed at each post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables (Stokes et al 2012). The odds ratio, two-sided 97.5% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. If the p-value based on a two-sided test for inclisiran + usual care versus usual care at Day 330 is < 0.025 and the corresponding odds ratio is greater than 1, statistical significance in favor of inclisiran + usual care is shown.

The primary analysis of both primary efficacy variables will be based on the Full Analysis Set.

12.4.3 Handling of intercurrent events of primary estimand

The remaining intercurrent event of the primary estimand for the two primary efficacy variables are the following: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.

12.4.4 Handling of missing values not related to intercurrent event

For the primary analysis of primary efficacy variable 1, the MMRM implicitly imputes missing data under a missing at random assumption.

For the primary analysis of primary efficacy variable 2, participants with missing LDL-C data will be assumed to have LDL-C ≥ 70 mg/dL (i.e., "non-responder").

12.4.5 Sensitivity analyses

The sensitivity analysis of primary efficacy variable 1 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Probability of observing the same or a more favorable response with inclisiran + usual care relative to usual care

For the above estimand, primary efficacy variable 1 will be analyzed at each time point for the Full Analysis Set using the Wilcoxon rank-sum test. The probability of observing the same or a more favorable response with inclisiran relative to usual care will be estimated using nonparametric methods, and the associated two-sided 97.5% confidence interval will also be reported (Chen and Kianifard 2000).

The sensitivity analysis of primary efficacy variable 2 to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Achieving LDL-C < 70 mg/dL (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care

- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. This intercurrent event will be ignored in the analysis, as the design of the trial allows for participants in the usual care group to potentially use inclisiran. 2. Discontinuation of study treatment. This intercurrent event will be ignored in the analysis.
- Summary measure: Treatment difference ([inclisiran + usual care] – usual care) in the proportion of participants who achieve LDL-C < 70 mg/dL

For the above estimand, primary efficacy variable 2 will be analyzed at each post-baseline visit for the Full Analysis Set using the two-sample z-test (normal approximation to the binomial distribution) to compare inclisiran + usual care versus usual care. If the treatment comparison p-value at Day 330 is < 0.025 and the proportion of participants who achieve LDL-C < 70 mg/dL is higher in inclisiran + usual care treatment group, statistical significance in favor of inclisiran + usual care is shown. A two-sided 97.5% confidence interval for the difference between inclisiran + usual care and usual care in the proportion of participants who achieve LDL-C < 70 mg/dL will be calculated, using the normal approximation to the binomial distribution.

12.4.6 Supplementary analysis

A supplementary analysis of primary efficacy variable 1 will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population
- Variable: Percent change from baseline in LDL-C [The primary analysis time point is at Day 330.]
- Treatment: Inclisiran + usual care or usual care
- Remaining intercurrent events: 1. Potential use of inclisiran by participants in the usual care group. 2. Discontinuation of study treatment. Data after the occurrence of either one of the above two intercurrent events will be excluded from the analysis (using MMRM).
- Summary measure: Least-squares mean difference between inclisiran + usual care group and usual care group

Subgroup analyses of the two primary efficacy variables will be performed by background lipid-lowering therapy at baseline. Other subgroups to be considered will be defined in the Statistical Analysis Plan.

12.4.7 Supportive analyses

The primary analysis of the two primary efficacy variables will be repeated for the Per-Protocol Set, Restricted Set 1, and Restricted Set 2.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy variables are the following:

1. Absolute change from baseline in LDL-C
2. Average percent change from baseline in LDL-C levels to each post-baseline visit
3. Average absolute change from baseline in LDL-C levels to each post-baseline visit
4. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)
5. Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)
6. Achieving LDL-C < 55 mg/dL (yes, no)
7. Percent change from baseline in apoB
8. Absolute change from baseline in apoB
9. Percent change from baseline in VLDL
10. Absolute change from baseline in VLDL
11. Percent change from baseline in non-HDL-C
12. Absolute change from baseline in non-HDL-C
13. Percent change from baseline in total cholesterol
14. Absolute change from baseline in total cholesterol
15. Percent change from baseline in Lp(a)
16. Absolute change from baseline in Lp(a)
17. Percent change from baseline in HDL-C
18. Absolute change from baseline in HDL-C
19. Percent change from baseline in triglycerides
20. Absolute change from baseline in triglycerides
21. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)
22. Proportion of days covered (total number of days on either statin, ezetimibe, or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days)
23. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)

Analyses of secondary efficacy variables 1 and 7 - 20 will be similar to the primary analysis of primary efficacy variable 1 (using MMRM, but with a two-sided 95% confidence interval for the treatment difference).

Secondary efficacy variables 2, 3, and 22 will be analyzed using a linear model with treatment and baseline LDL-C as explanatory variables. Least-squares mean of each treatment group, least-squares mean treatment difference, 95% confidence interval for the treatment difference, and p-value based on the fitted model will be reported.

Secondary efficacy variables 4 - 6 and 23 will be analyzed at each post-baseline visit using a logistic regression model with treatment and baseline LDL-C as explanatory variables (Stokes et al 2012). The odds ratio, 95% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. Missing data will be imputed using "non-responder" (i.e., "negative" outcome) imputation.

Secondary efficacy variable 21 will be analyzed at each post-baseline visit using a proportional odds model with treatment and baseline LDL-C as explanatory variables (Stokes et al 2012). The odds ratios, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported. Missing data will not be imputed.

Analyses of secondary efficacy variables will be based on the Full Analysis Set.

12.5.2 Safety endpoints

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

Adverse events

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

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

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

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

Vital signs

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time, and if reference ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5.3 Pharmacokinetics

Not applicable.

12.5.4 DNA

Not applicable.

12.5.5 Biomarkers

See Section 12.5.1.

12.5.6 PK/PD relationships

Not applicable.

[redacted]

12.6 Analysis of exploratory endpoints

The exploratory efficacy variables are the following:

[redacted]

8. Cardiovascular death (yes, no)
9. Non-fatal MI (yes, no)
10. Resuscitated cardiac arrest (yes, no)
11. Non-fatal ischemic stroke (yes, no)
12. Composite MACE (cardiovascular death, non-fatal MI, resuscitated cardiac arrest, or non-fatal ischemic stroke) (yes, no)

[redacted]

[redacted]

12.7 Interim analyses

After all participants complete their baseline visit, the demographic and baseline characteristics may be summarized to help design new studies. No analysis will be performed using post-baseline data. Thus, there is no need to adjust the level of significance for such interim analysis of baseline data.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size was calculated for the two primary efficacy variables with adjustment for multiple testing by using the Bonferroni procedure.

For primary efficacy variable 1, i.e., percent change from baseline in LDL-C, the standard deviation is assumed to be 40, partly based on the results from ORION-10 and ORION-11 clinical trials and considering that the standard deviation will likely be larger in this trial since changes in lipid-lowering therapy are allowed in both treatment groups. An expected mean treatment difference of 15 is assumed, which is smaller than the mean difference observed in the Phase III trials, to account for 1) potential lower utilization of background lipid-lowering therapy in the inclisiran + usual care treatment group compared to the usual care treatment group, and 2) the ability to add non-statin lipid lowering therapy, including commercially available inclisiran, in the usual care treatment group. A z-test, an allocation ratio of 1:1, and a two-sided significance level of 0.025 were also used in the calculation of sample size.

Table 12-1 considers total sample sizes for expected mean treatment differences of 10, 15, and 20, and powers of 0.85 and 0.90 (nQuery Version 8.4.1.0). From Table 12-1, an expected mean treatment difference of 15 (based on means of 40 and 55 at Day 330 in the usual care and inclisiran + usual care treatment groups, respectively) and a power of 0.85 were chosen to provide a total sample size of 306 participants.

Table 12-1 Sample size calculations for percent change from baseline in LDL-C

Mean treatment difference	Power = 0.85	Power = 0.90
10	688	796
15	**306**	**354**
20	172	200

For primary efficacy variable 2, i.e., achieving LDL-C < 70 mg/dL (yes, no), a z-test, an allocation ratio of 1:1, and a two-sided significance level of 0.025 were used in the calculation of sample size. Table 12-2 considers total sample sizes for several expected proportions of participants who achieve LDL-C < 70 mg/dL at Day 330 in the usual care and inclisiran + usual care treatment groups, and powers of 0.85 and 0.90 (nQuery Version 8.4.1.0). From Table 12-2, the expected proportions of 0.55 and 0.75 in the usual care and inclisiran + usual care treatment groups, respectively, and a power of 0.85 were chosen to provide a total sample size of 242 participants.

Table 12-2 Sample size calculations for achieving LDL-C < 70 mg/dL

Proportion in usual care group	Proportion in inclisiran + usual care group	Power = 0.85	Power = 0.90
0.50	0.65	464	536
0.50	0.70	256	294
0.55	0.70	446	514
0.55	**0.75**	**242**	**278**

Based on the sample size calculations in Table 12-1 and Table 12-2, a total sample size of 306 together with a loss to follow-up rate of 20% at Day 330 require approximately 384 participants (192 participants per treatment group) to be randomized. This will also allow examination of subgroups with reasonable sample sizes.

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Table 16-1 Clinically notable vital signs

Vital sign	Notable abnormalities
Pulse (beats/min)	either ≥120 + increase ≥25* or > 130either ≤50 + decrease ≥30* or < 40
BP (mmHg)	[redacted]

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

Notable laboratory values are defined in Table 16-2:

Table 16-2 Clinically notable laboratory abnormalities for selected tests

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

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

Table 16-3 Liver event and laboratory trigger definitions

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

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

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

ALT or AST	**TBL**	**Liver Symptoms**	**Action**
ALT or AST increase without bilirubin increase:			
If normal at baseline: ALT or AST > 3 x ULN	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			

ALT or AST	TBL	Liver Symptoms	Action
If normal at baseline: ALT or AST > 5 x ULN for more than two weeks	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline: ALT or AST > 8 x ULN	Normal	None	
ALT or AST increase with bilirubin increase:			
If normal at baseline: ALT or AST > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT or AST > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-5 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Albumin, PT/INR, ALP and GGT)

Criteria	Actions required	Follow-up monitoring
	• Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Albumin, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

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

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

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

Table 16-6 Specific renal alert criteria and actions

Renal event	Actions
Confirmed serum creatinine (sCr) increase 25 – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase ≥ 50% [+] + **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m^2** [+]	Consider causes and possible interventions Repeat assessment within 24-48h if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Repeat assessment to confirm Distinguish hemoglobinuria from hematuria Urine sediment microscopy Assess sCr Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder

[+] Corresponds to KDIGO (Kidney Disease: Improving Global Outcomes) criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. (*Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity*.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-7 Renal event follow-up

Follow-up of renal events
Assess, document and record in appropriate eCRF(s): Urine dipstick and sediment microscopy evidence of drug-induced nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells Blood pressure and body weight Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the appropriate eCRF(s)
Monitor participant regularly (frequency at investigator's discretion) until – - Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or albumin-to-creatinine ratio (ACR) <300 mg/g Cr) or - Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. - Analysis of urine markers in samples collected over the course of the DIN event

ACR (Albumin-to-creatinine ratio), DIN (Drug-Induced Nephrotoxicity), PCR (Protein-creatinine ratio), MRI (Magnetic Resonance Imaging), sCR (serum creatinine)

16.4 Appendix 4: Sampson Criteria for Diagnosing Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., painful abdominal cramps, vomiting)

3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):

a. Adults: systolic blood pressure <90 mmHg or >30% decrease from that person's baseline

Source: Sampson et al 2005 *and* Sampson et al 2006

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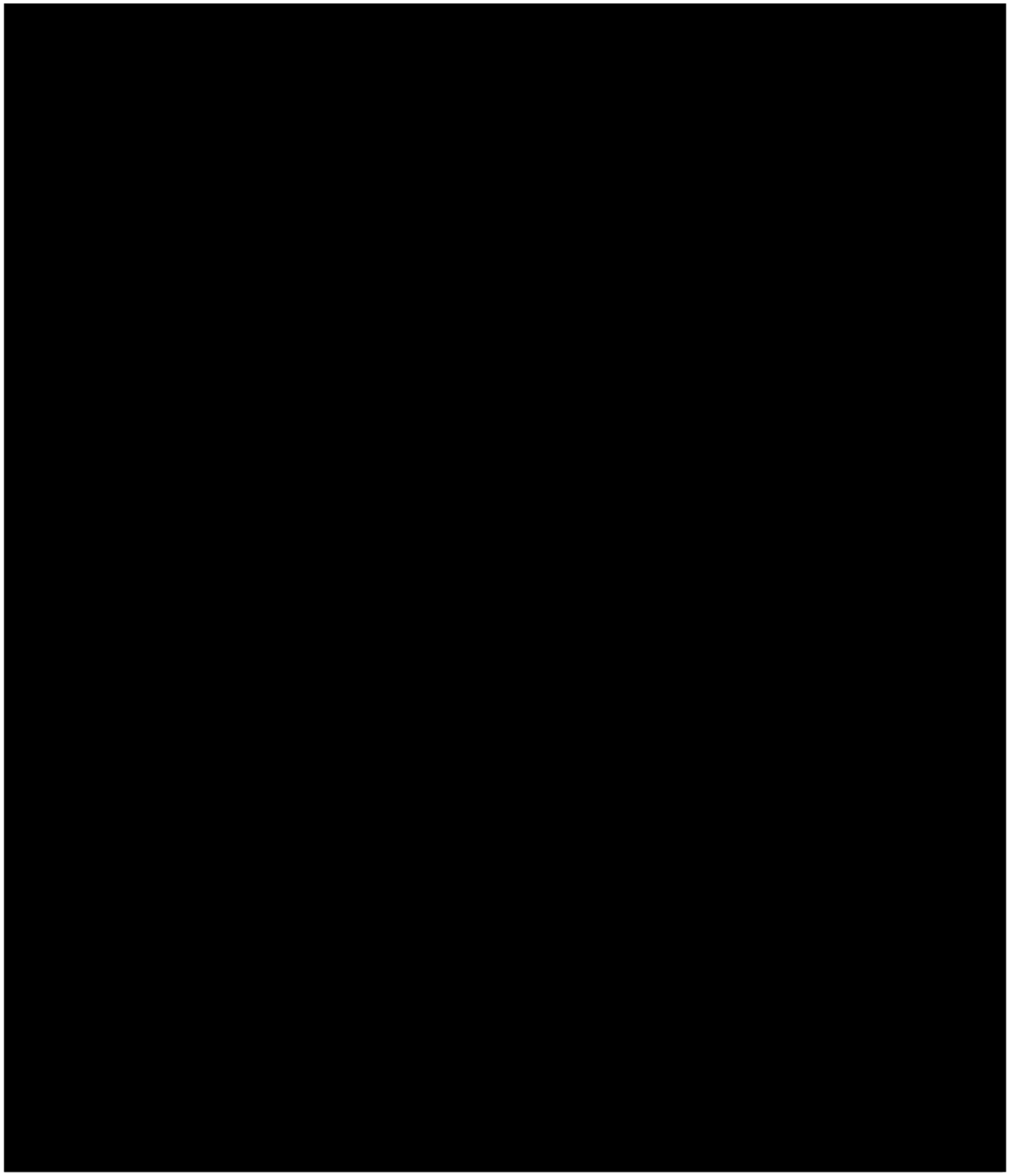
[redacted]



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