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Novartis Research and Development

KJX839

Clinical Trial Protocol CKJX839A1US02 / NCT04929249

# A randomized, multicenter, open-label trial comparing the effectiveness of an "inclisiran first" implementation strategy to usual care on LDL cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease and elevated LDL-C (≥70 mg/dL) despite receiving maximally tolerated statin therapy (VICTORION-INITIATE)

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# Table of contents

## List of tables



## List of figures

## List of abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ACE | Angiotensin Converting Enzyme |
| AE | Adverse Event |
| AHA | American Heart Association |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| ApoB | Apolipoprotein B |
| ARB | Angiotensin II Receptor Blockers |
| ASCVD | Atherosclerotic Cardiovascular Disease |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| [redacted] | [redacted] |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CABG | Coronary Artery Bypass Grafting |
| CHD | Coronary Heart Disease |
| CMO&PS | Chief Medical Office and Patient Safety |
| [redacted] | [redacted] |
| COVID-19 | Coronavirus Disease 2019 |
| CPK | Creatinine Phosphokinase |
| CRA | Clinical Research Associate |
| CRF | Case Report/Record Form (paper or electronic) |
| CRO | Contract Research Organization |
| CT | Computerized Tomography |
| CTA | Computed Tomography Angiography |
| CV | Cardiovascular |
| CVD | Cardiovascular Disease |
| DIN | Drug Inducted Nephrotoxicity |
| dL | Decilitre |
| DNA | Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| eGFR | Estimated Glomerular Filtration Rate |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| eTMF | Electronic Trial Master File |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| g | Gram |

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|---|---|
| GalNAc | N-Acetylgalactosamine |
| GCP | Good Clinical Practice |
| GDMT | Guideline-Directed Medical Therapy |
| GGT | Gamma-Glutamyl Transferase |
| GLDH | Glutamate Dehydrogenase |
| GPP | Good Pharmaceopidemiology Practices |
| [redacted] | [redacted] |
| 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 |
| HRSA | Health Resources and Services Administration |
| NYHA | New York Heart Association |
| IUD | Intrauterine Device |
| 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 |
| 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] |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MDCT | Multidetector Computed Tomography |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram(s) |

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|---|---|
| MI | Myocardial Infarction |
| mL | Milliliter(s) |
| MMRM | Mixed-Effects Model Repeated Measures |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger Ribonucleic Acid |
| [redacted] | [redacted] |
| non-HDL-C | Non-High-Density Lipoprotein Cholesterol |
| NYHA | New York Heart Association |
| PAD | Peripheral Arterial Disease |
| PCI | Percutaneous Coronary Intervention |
| PCSK9 | Proprotein Convertase Subtilisin/Kexin Type 9 |
| PFS | Pre-filled Syringe |
| PI | Principal Investigator |
| [redacted] | [redacted] |
| PT | Prothrombin Time |
| QMS | Quality Management System |
| RISC | RNA-Induced Silencing Complex |
| RNA | Ribonucleic Acid |
| RNA-PCR | Reversed Transcription and Subsequent Polymerase Chain Reaction |
| RBC | Red Blood Cell(s) |
| RNAi | Ribonucleic Acid Interference |
| s.c. | Subcutaneous |
| SC | Steering Committee |
| SAE | Serious Adverse Event |
| sCR | Serum Creatinine |
| siRNAs | Small Interfering Ribonucleic Acids |
| SMQ | Standardized MedDRA Query |
| SOP | Standard Operating Procedures |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TBL | Total Bilirubin |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| µL | Microliter |
| U/L | Units per Litre |
| ULN | Upper Limit of Normal |
| US | United States |
| VLDL-C | Very-Low-Density Lipoprotein Cholesterol |
| WBC | White Blood Cell(s) |
| WHO | World Health Organization |
| WoC | Withdrawal of Consent |

# Glossary of terms

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| 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 |
| [redacted] | |
| 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 |
| 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. |
| 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. |

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| Investigational drug/ treatment | The drug whose properties are being tested in the study |
| Maximally tolerated statin therapy | Maximally tolerated statin therapy in accordance with the 2018 ACC/AHA guidelines |
| 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 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. |
| [redacted] | |
| 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 |

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| 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 video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial. |
| Treatment arm/group | A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. |
| Treatment of interest | The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment. |
| Variable (or endpoint) | The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event. |
| Withdrawal of study consent (WoC) | 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 02

## 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 #15 has been modified. Similarly, the study design has been modified to reflect the same. Protocol Summary and Section 5 reflects "50" US sites.

## 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."
- Protocol Summary and Section 5: Reflects a change of "40" sites to "50" US sites.
- Section 5.2 Exclusion #15: Added "Treatment with monoclonal antibodies directed towards PCSK9 or inclisiran within 90 days of screening."

# Amendment 01

## Amendment rationale

The purpose of the clinical study amendment is to update the protocol in order to be aligned with other inclisiran Phase III studies with respect to the documentation of statin intolerance, cardiovascular medical history, assessment of injection site reactions and definition of hyperglycemia-related events. 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
- Section 3 added language 'if and when inclisiran becomes commercially available' and changed to 'approximately' 40 sites
- Figure 3-1 removed 'Baseline' from Visit 1
- Section 6.5.1 revised dose modification text
- Section 6.5.2 removed 'not applicable'
- Section 6.5.2.1 added 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
  - [redacted]
  - 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 ASCVD Medical History
  - added Statin Intolerance Medical History
  - added 'Prior' to concomitant medications
  - added Surgical/Medical procedures
  - added Injection Site Reaction Assessment
  - added footer to Prior/Concomitant Medications
  - [redacted]
- Section 8.2 removed 'date of birth'
- Section 8.4.1.3 removed lactate
- Section 8.4.4 added Injection site reactions and Hyperglycemia-related event information
- Section 8.5.2 added batch testing of Lp(a), added analysis of proteins, and clarified analysis *during the study* 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 text for unexplained increases in transaminases or total bilirubin, as well as instructions on follow-up, as this is now captured in Sections 6.5.2.1, Appendix 2 and in the remainder of the paragraph

## 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

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| **Protocol number** | KJX839A1US02 |
| **Full Title** | A randomized, multicenter, open-label trial comparing the effectiveness of an "inclisiran first" implementation strategy to usual care on LDL cholesterol (LDL-C) in patients with atherosclerotic cardiovascular disease and elevated LDL-C (≥70 mg/dL) despite receiving maximally tolerated statin therapy (VICTORION-INITIATE) |
| **Brief title** | A randomized study to evaluate the effect of an "inclisiran first" implementation strategy compared to usual care in patients with atherosclerotic cardiovascular disease and elevated LDL-C despite receiving maximally tolerated statin therapy (VICTORION-INITIATE) |
| **Sponsor and Clinical Phase** | Novartis Phase IIIb |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | The purpose of this study is to assess the effectiveness of an "inclisiran first" implementation strategy (addition of inclisiran to maximally tolerated statin therapy immediately upon failure to achieve acceptable LDL-C with maximally tolerated statin therapy alone) compared to usual care in an ASCVD population, [redacted]. The rationale of the study is as follows:<br>• Phase III trials demonstrated the efficacy of inclisiran compared to placebo. Evaluation of inclisiran compared to usual care, which may include other non-statin LDL-C lowering therapies, may be a more clinically relevant comparison.<br>• Guidelines recommend a stepwise algorithm for LDL-C lowering, where ezetimibe and PCSK9 inhibiting monoclonal antibodies are sequentially added if patients fail to reach acceptable LDL-C levels. Addition of inclisiran earlier in the algorithm (i.e., immediately after statins) could increase the proportion of patients reaching acceptable LDL-C with fewer therapies.<br>• [redacted]. |
| **Primary Objective(s)** | • To assess the effect on LDL-C of an "inclisiran-first" implementation strategy compared to usual care at Day 330 in participants with ASCVD and an LDL-C ≥70 mg/dL despite maximally tolerated statin therapy<br>• To assess the non-inferiority of an "inclisiran first" implementation strategy compared to usual care on discontinuation of background statin therapy at Day 330 |
| **Secondary Objectives** | • To assess the absolute change in LDL-C of an "inclisiran first" implementation strategy compared to usual care at Day 330, as well as average of percent and absolute changes in LDL-C levels to each post-baseline visit<br>• To assess the proportion of participants reaching pre-specified LDL-C targets among those receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 |

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| | • To assess plasma lipids, lipoproteins and triglycerides in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330<br>• To assess changes in and adherence to background lipid-lowering therapy in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330<br>• To assess visit-to-visit LDL-C variability from Day 90 until Day 330<br>• To assess overall safety and tolerability of inclisiran |
| **Study design** | The study design will be a randomized, two-arm, parallel-group, open-label, multicenter, clinical trial comparing an "inclisiran first" implementation strategy to usual care in approximately 444 participants (1:1 randomization) with established ASCVD and elevated LDL-C (or non-HDL-C) despite treatment with maximally tolerated statin therapy. |
| **Study population** | The study will include male and female participants ≥18 years of age with a history of ASCVD (coronary heart disease, ischemic cerebrovascular disease or peripheral arterial disease) who have elevated LDL-C (≥70 mg/dL) or non-HDL-C (≥100 mg/dL) despite being treated with maximally tolerated statin therapy. A total of approximately 444 participants will be randomized to the “inclisiran first” implementation strategy or usual care in a 1:1 ratio at approximately 50 US sites. |
| **Key Inclusion criteria** | Participants eligible for inclusion in this study must meet **all** of the following criteria:<br>1. Signed informed consent must be obtained prior to participation in the study<br>2. Males and females ≥18 years of age<br>3. History of ASCVD, documented by hospital records, claims data and/or prior laboratory/imaging assessments<br>a. Coronary heart disease (CHD):<br>• Prior myocardial infarction<br>• Prior coronary revascularization (PCI or CABG)<br>• Angiographic or CT-imaging (e.g., MDCT/CTA) evidence of coronary atherosclerosis (>70% stenosis in at least one major epicardial coronary artery)<br>b. Cerebrovascular disease:<br>• Prior ischemic stroke confirmed by a brain imaging study, CT orMRI; thought not to be caused by atrial fibrillation, valvular heartdisease or mural thrombus<br>• Carotid artery stenosis >70% on prior angiography or ultrasound<br>• History of prior percutaneous or surgical carotid arteryrevascularization<br>c. Peripheral arterial disease (PAD):<br>• Prior documentation of a resting ankle-brachial index ≤0.85<br>• History of prior percutaneous or surgical revascularization of aniliac, femoral, or popliteal artery or aortic aneurysm<br>• Prior non-traumatic amputation of a lower extremity due toperipheral artery disease<br>4. Serum LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL<br>5. Fasting triglyceride <5.65 mmol/L (<500 mg/dL) at screening |

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| | 6. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology<br><br>7. Participants should be on maximally tolerated statin therapy, as determined by the investigator, with no immediate plans to modify lipid lowering therapies. Statin intolerant patients are eligible if they had documented side effects on at least 2 different statins, including one at the lowest standard dose<br><br>8. 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 |
| **Key Exclusion criteria** | Participants meeting any of the following criteria are not eligible for inclusion in this study.<br><br>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<br><br>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<br><br>3. New York Heart Association (NYHA) class III or IV heart failure or last known left ventricular ejection fraction <30%<br><br>4. Significant cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation at the time of screening<br><br>5. Major adverse cardiovascular event within 6 months prior to randomization<br><br>6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite antihypertensive therapy<br><br>7. Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years<br><br>8. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the two years prior to randomization<br><br>9. 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:<br>a. 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<br>b. 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<br>c. Male sterilization (at least 6 m prior to screening). For female participants in the study, the vasectomized male partner should be the sole partner for that participant |

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| | d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)<br>e. 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)<br><br>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.<br><br>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.<br>10. Known history of alcohol and/or drug abuse within the last 5 years (occasional casual users of illicit drugs in the opinion of the investigators are not excluded)<br><br>11. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.<br><br>12. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes<br><br>13. Planned use of other investigational products or devices during the course of the study<br><br>14. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:<br>a. Participants who are unable to communicate or to cooperate with the investigator<br>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)<br>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 – including potential participants who indicate that their participation is contingent on receiving inclisiran)<br>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<br>e. Persons directly involved in the conduct of the study<br><br>15. Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9, or with inclisiran or ezetimibe.<br><br>16. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or alanine aminotransferase (ALT) elevation >3x |

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| | 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 |
| **Study treatment** | Inclisiran (KJX839), 284 mg, 1.5 ml Liquid in a single-use prefilled syringe (PFS) for s.c. administration<br>Usual care per treating physician |
| **Treatment of interest** | An "inclisiran first" implementation strategy (addition of inclisiran to maximally tolerated statin therapy immediately upon failure to reach acceptable LDL-C levels with maximally tolerated statin therapy alone) compared to usual care (per treating physician). |
| **Efficacy assessments** | The primary efficacy assessments will be LDL-C and discontinuation of statin therapy. Other efficacy assessments will include measurement of Apo B, Lp(a), non-HDL-C, VLDL-C, total cholesterol, triglycerides, and HDL-C. |
| **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. |
| [redacted] | |
| **Data analysis** | The primary efficacy variables are the following:<br>1. Percent change from baseline in LDL-C<br>2. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no)<br>The primary analysis time point for both primary efficacy variables is at Day 330.<br>Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit, baseline, [redacted] 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 effect at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ("inclisiran first" implementation strategy – usual care) is less than 0, statistical significance in favor of "inclisiran first" implementation strategy is shown.<br>For primary efficacy variable 2, a one-sided 98.75% confidence interval for treatment difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinued statin therapy at Day 330 will be computed using the normal approximation to the binomial distribution. Non-inferiority of the "inclisiran first" implementation strategy to usual care will be declared if the upper limit of the confidence interval does not exceed the non-inferiority margin of 15%.<br>The secondary efficacy variables are the following:<br>1. Absolute change from baseline in LDL-C |

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| | 2. Average percent change from baseline in LDL-C levels to each post-baseline visit<br><br>3. Average absolute change from baseline in LDL-C levels to each post-baseline visit<br><br>4. Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)<br><br>5. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)<br><br>6. Achieving LDL-C < 70 mg/dL (yes, no)<br><br>7. Achieving LDL-C < 55 mg/dL (yes, no)<br><br>8. Percent change from baseline in apoB<br><br>9. Absolute change from baseline in apoB<br><br>10. Percent change from baseline in non-HDL-C<br><br>11. Absolute change from baseline in non-HDL-C<br><br>12. Percent change from baseline in VLDL-C<br><br>13. Absolute change from baseline in VLDL-C<br><br>14. Percent change from baseline in total cholesterol<br><br>15. Absolute change from baseline in total cholesterol<br><br>16. Percent change from baseline in Lp(a)<br><br>17. Absolute change from baseline in Lp(a)<br><br>18. Percent change from baseline in HDL-C<br><br>19. Absolute change from baseline in HDL-C<br><br>20. Percent change from baseline in triglycerides<br><br>21. Absolute change from baseline in triglycerides<br><br>22. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)<br><br>23. Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies prescribed divided by total number of study days)<br><br>Analyses of secondary efficacy variables 1 and 8 - 21 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).<br><br>Secondary efficacy variable 2, 3, and 23 will be analyzed using a linear model with treatment, baseline LDL-C, and [redacted] as explanatory variables.<br><br>Secondary efficacy variables 4 - 7 will be analyzed at each time point using a logistic regression model with treatment, baseline LDL-C, [redacted] as explanatory variables.<br><br>Secondary efficacy variable 22 will be analyzed at each time point using a proportional odds model with treatment, baseline LDL-C, and [redacted] as explanatory variables. |

| | |
|---|---|
| | Visit-to-visit LDL-C variability from Day 90 until Day 330 will be reported, using various measures of variability (standard deviation, coefficient of variation). |
| **Key words** | Hyperlipidemia, 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 (s.c.) 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 established atherosclerotic cardiovascular disease (ASCVD) who are treated with maximally tolerated statin therapy compared to placebo in randomized, double-blind, placebo-controlled trials (Ray et al 2020).

This protocol describes a trial to evaluate the effectiveness of an "inclisiran-first" implementation strategy (i.e., initiation of inclisiran immediately after failing to reach acceptable LDL-C levels with maximally tolerated statin therapy alone, before addition of ezetimibe) compared to usual care without inclisiran in a population with ASCVD [redacted]. This study will be conducted in compliance with Good Clinical Practices (GCP) and Good Pharmaceopidemiology Practices (GPP), including the Declaration of Helsinki and all applicable regulatory requirements.

### 1.1.1 Atherosclerotic cardiovascular disease (ASCVD)

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in approximately 18 million deaths annually (Roth et al 2017). Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated LDL-C is a major risk factor for the development of CVD (Grundy et al 2019). Lowering LDL-C has been shown to reduce the risk of CHD and strokes and the clinical risk reduction is linearly proportional to the absolute LDL-C reduction without an apparent threshold below which further lowering yields no further benefit (Giugliano et al 2017; Baigent et al 2010). Moreover, large trials combined with evidence from studies of people with genetically-determined lower LDL-C have confirmed the safety of exposure to low levels of LDL-C over long periods of time (Cohen et al 2006; Giugliano et al 2017).

Approximately 30 million people in the United States are treated with lipid lowering therapies, predominantly statins, to lower LDL-C and the associated risk of ASCVD (Wong et al 2016). The 2018 American College of Cardiology (ACC) / American Heart Association (AHA) cholesterol guidelines recommend a step-wise algorithm for LDL-C lowering in patients with established ASCVD (Grundy et al 2019). Briefly, all ASCVD patients should be treated with high intensity statin therapy. If LDL-C remains 70 mg/dL or higher, ezetimibe can be considered. If LDL-C remains 70 mg/dL or higher despite treatment with statins and ezetimibe, addition of a PCSK9 inhibiting monoclonal antibody can be considered in very high risk patients (Grundy et al 2019). The position of PCSK9 inhibiting monoclonal antibodies after ezetimibe is partially due to the high price of those therapies as well as the inconvenience of frequent parenteral administration (Grundy et al 2019). Nonetheless, ezetimibe lowers LDL-C by only approximately 20% and therefore many patients may still have elevated LDL-C despite statin-ezetimibe combination therapy, while many more patients would be able to reach acceptable LDL-C levels if more potent LDL-C lowering therapies would be initiated before ezetimibe. This would also reduce the problem of polypharmacy.

Additional contributing factors responsible for the fact that only a minority of patients with ASCVD have LDL-C levels <70 mg/dL include suboptimal guideline implementation, inability to tolerate statins at sufficiently high doses, poor adherence to therapies, and system barriers such as high cost of therapy (Wong et al 2016; Lowenstern et al 2018; Fitchett et al 2015;Mann et al 2010; Poluzzi et al 2008; Cannon et al 2020).

These and other factors are responsible for the fact that the trend in the United States (US) of lower CV morbidity and mortality observed between 1980 and 2010 has stalled. In fact recent data show an increase in CV mortality (Virani et al 2020).

### 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 a N-acetylgalactosamine (GalNAc) carbohydrate ligand (Ashwell and Morell 1974). Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and down regulation of hepatic proteins.

### 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 (Khvorova 2017). 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. Inclisiran is now approved by the trade name as LEQVIO by FDA for commercial use.

### 1.1.4 Nonclinical 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 (Ray et al 2020). 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. This is highlighted by tissue distribution studies in rats showing that compared to liver, inclisiran exposure in other tissues was 36- to 1076-fold lower than liver.

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 which is highly conserved across diverse ethnic and geographical populations (Ray et al 2020). The specificity of the active antisense strand of inclisiran was determined by performing a comprehensive search against the human transcriptome using an exhaustive "brute-force" algorithm implemented in the python script 'BruteForce.py'. The search revealed 20 possible off-target transcripts, two of which are not normally expressed in liver cells. The other 18 transcripts were subsequently assayed in an in vitro study to experimentally assess their response to inclisiran. The 18 gene transcripts were transfected into liver cells along with inclisiran and expression analysis indicated a ≥45-fold difference between the "on target" suppression of PCSK9 and the suppression of any of the "off-target" transcripts.

Inclisiran was well tolerated in all animal studies. 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 the double-blind, placebo-controlled, multicenter Phase III ORION trials, involving 3,655 participants (about half of whom received inclisiran, n=1,833), after the initial administration of inclisiran, LDL-C levels were quickly reduced with more than 75% of patients 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.

## 1.2 Purpose

Phase III trials with inclisiran have provided high-quality evidence supporting the efficacy, safety and tolerability of inclisiran compared to placebo on top of maximally tolerated statin therapy with or without ezetimibe. The clinical value of systematic implementation of an "**inclisiran first**" strategy (addition of inclisiran to maximally tolerated statin therapy

immediately after failing to reach acceptable LDL-C levels with maximally tolerated statin therapy alone, before addition of ezetimibe) compared to usual care has not been demonstrated.

It has been recognized that trials that are designed to test the efficacy of new interventions may not reflect the complexity and diversity of real-world clinical practice and may therefore not adequately inform practice (Koren et al 2004; Ford and Norrie 2016). Specific to inclisiran:

- The Phase III trials did not evaluate implementation of inclisiran at a specific position in the treatment algorithm, but rather studied the addition of inclisiran to maximally tolerated statin therapy with or without ezetimibe. As such, there currently is no direct evidence supporting the implementation of inclisiran immediately after a patient has been shown not to reach acceptable LDL-C levels on statins alone (but before initiation of ezetimibe). This strategy, however, may be particularly beneficial, as more patients would be expected to reach acceptable LDL-C levels using a statin-inclisiran combination than if they were using a statin-ezetimibe combination.
- Inclisiran was compared to placebo rather than usual care in the Phase III trials and changes in background lipid lowering therapy were not allowed. As such, there currently is no evidence on the implementation of inclisiran compared to usual care, which may include other non-statin LDL-C lowering therapies, while this comparison is the most relevant one for physicians and healthcare decision makers.
- "System barriers" such as extensive prior authorization requirements have been cited as barriers to optimization of LDL-C management (Cannon et al 2020). As such, proposed solutions to address undertreatment of hypercholesterolemia include addressing access and prior authorization barriers. However, there is no evidence to date that systematic implementation of non-statin LDL-C lowering therapies without such barriers would improve LDL-C management. This evidence would be clinically relevant for physicians and healthcare decision makers.
- [redacted]
- Since changes in background lipid-lowering therapy were not allowed in the Phase III trials, it was not possible to study discontinuation of statin therapy. Observational data have revealed that the proportion of patients taking a statin decreased after initiation of PCSK9 inhibitors (Rymer et al 2020). It will be important to assess whether inclisiran initiation leads to an increased propensity to discontinue statin therapy.
- In the Phase III inclisiran trials, patients and physicians were blinded to LDL-C levels during the trial, whereas in clinical practice LDL-C is measured to gauge adequacy of and adherence to therapy and make treatment decisions.
- The trial will enable the collection of additional safety data, especially in patients treated with maximally tolerated statin therapy before ezetimibe and in diverse populations.

Hence, the purpose of this trial is to evaluate the effectiveness of an "inclisiran first" implementation strategy compared to usual care in patients with ASCVD on LDL-C reduction and statin discontinuation at one year.

# 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 an "inclisiran-first" implementation strategy compared to usual care at Day 330 in participants with ASCVD and an LDL-C ≥70 mg/dL despite maximally tolerated statin therapy | • Percent change from baseline in LDL-C |
| • To assess the non-inferiority of an "inclisiran first" implementation strategy compared to usual care on discontinuation of background statin therapy at Day 330 | • Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (yes, no) |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To assess the absolute change in LDL-C of an "inclisiran first" implementation strategy compared to usual care at Day 330, as well as average of percent and absolute changes in LDL-C levels to each post-baseline visit | • Absolute change from baseline in LDL-C<br>• Average percent change from baseline in LDL-C levels to each post-baseline visit<br>• Average absolute change from baseline in LDL-C to each post-baseline visit |
| • To assess the proportion of participants reaching pre-specified LDL-C targets among those receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 | • Achieving ≥ 50% reduction from baseline in LDL-C (yes, no)<br>• Achieving LDL-C < 100 mg/dL (among the subset of participants with LDL-C >100 mg/dL at baseline) (yes, no)<br>• Achieving LDL-C < 70 mg/dL (yes, no)<br>• Achieving LDL-C < 55 mg/dL (yes, no) |
| • To assess plasma lipids, lipoproteins and triglycerides in participants receiving an "inclisiran first" implementation strategy compared to usual care at Day 330 | • Percent change and absolute change from baseline in apoB<br>• Percent change and absolute change from baseline in non-HDL-C<br>• Percent change and absolute change from baseline in VLDL-C<br>• Percent change and absolute change from baseline in total cholesterol<br>• Percent change and absolute change from baseline in Lp(a)<br>• Percent change and absolute change from baseline in HDL-C<br>• Percent change and absolute change from baseline in triglycerides |
| • To assess changes in and adherence to background lipid-lowering therapy in participants receiving an "inclisiran first" | • Intensity of lipid lowering therapy (decrease in dose, no change in dose, increase in dose) |

| Objective(s) | Endpoint(s) |
|---|---|
| implementation strategy compared to usual care at Day 330 | • Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies divided by total number of study days) |
| • To assess visit-to-visit LDL-C variability from Day 90 until Day 330 | • LDL-C measures of variability (standard deviation, coefficient of variation) |
| • To assess overall safety and tolerability of inclisiran | • Adverse events |

## 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 is:

What is the effectiveness of an "inclisiran first" implementation strategy compared to usual care in patients who have not reached their LDL-target despite treatment with a maximally tolerated statin? Inclisiran will be added to maximally tolerated statin therapy and will be compared to usual care. Eligible participants will have established ASCVD and elevated LDL-C despite being treated with maximally tolerated statin therapy and should not be on ezetimibe or PCSK9 inhibiting monoclonal antibodies. Although at baseline there should be no plans to modify

background lipid-lowering therapy, the participants' treating physicians are recommended to treat patients in accordance with the 2018 ACC/AHA cholesterol guideline (Grundy et al 2019).

The justification for the primary estimands is that these will capture both the effects of the inclisiran and the effect of changes in, adherence to, and discontinuation of additional medications, mirroring the conditions in clinical practice. 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 first" implementation strategy 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 first" implementation strategy and usual care

Primary estimand 2: The primary analysis of primary efficacy variable 2 (discontinuation of statin therapy) to address the primary objective will be based on the following estimand:

- Population: Defined through appropriate inclusion/exclusion criteria to reflect the targeted population and if a participant was not statin intolerant at the beginning of the trial
- Variable: Discontinuation of statin therapy (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: "Inclisiran first" implementation strategy 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 first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy

## 2.2 Secondary estimands

Not applicable.

# 3 Study design

The study design will be a randomized, two-arm, parallel-group, open-label, multicenter, clinical trial. Approximately 444 participants will be randomized 1:1 to "inclisiran first" implementation strategy or to usual care. Eligible participants have established ASCVD and elevated LDL-C (or non-HDL-C) despite treatment with maximally tolerated statin therapy (but without ezetimibe) Figure 3-1. The unit of randomization will be the participant, and the sample size calculation is described in Section 12.8.

To minimize selection bias and increase generalizability of the results, potential study sites and potentially eligible participants will be identified using electronic data sets (EHR, claims and/or laboratory data). The goal in selecting study sites is to ensure a representative sample of sites in terms of geography, patient population, and lipid management practices. For example, the inclusion of specialized lipid clinics in the trial would lead to more intensive treatment than is typical and would therefore reduce the generalizability of the results. [redacted] ll participants who meet the eligibility criteria are to be invited using a standardized invite (please refer to the paragraph on the rationale for this method of recruitment in Section 4.1). There are no restrictions on the specialty of the treating physician or investigator because prior data shows that there are no differences in appropriate LDL-C lowering therapy based on guidelines between different specialties (Cassagnol et al 2020).

Participants in both groups will remain on maximally tolerated statin therapy, unless they are statin-intolerant at baseline. In the usual care group, treating physicians are recommended to treat patients in accordance with the 2018 ACC/AHA guidelines (Grundy et al 2019). Treatment decisions will be at the discretion of the treating physician (including commercial prescription of inclisiran). In the strategy group post-randomization, but addition of other non-statin LDL-C lowering therapies (e.g., ezetimibe or bempedoic acid) is allowed to reach acceptable LDL-C levels. This "inclisiran first" implementation strategy group, inclisiran will be administered initially at randomization, 90 days later and six months thereafter. PCSK9-inhibiting monoclonal antibodies are not to be used in the “inclisiran first” implementation could be the case, for example, if a patient has an LDL-C ≥70 mg/dL despite treatment with a maximally tolerated statin and inclisiran.

The sponsor will not provide access to therapies other than inclisiran (only for patients randomized to the “inclisiran first” implementation strategy group). In both groups, laboratory assessments (including LDL-C) will be performed at screening, Day 0, Day 90, Day 180, Day 270 and Day 330. The results of the laboratory assessments performed as part of the trial will be available tothe participants' physicians in both study groups. Hence, to minimize reporting bias, participants in the "inclisiran first" implementation group and participants in the usual care group will havean equivalent number of study visits, and an equivalent number of blood draws (including LDL-C tests).

The study will identify approximately 50 sites for participation. Each site will have a principal investigator (PI) who is responsible for study visits, while all aspects of the participants' routine care will remain the responsibility of the participants' own treating physician in both groups. While it is expected that most patients will have a treating physician who is distinct from the PI, a PI who wishes to include his or her own patients in the trial would have to be (temporarily) transition routine care to a separate physician. This will reduce the effect that trial participation might have on treatment decisions if the PI and treating physician were the same individual (e.g., more aggressive treatment due to more frequent touchpoints).

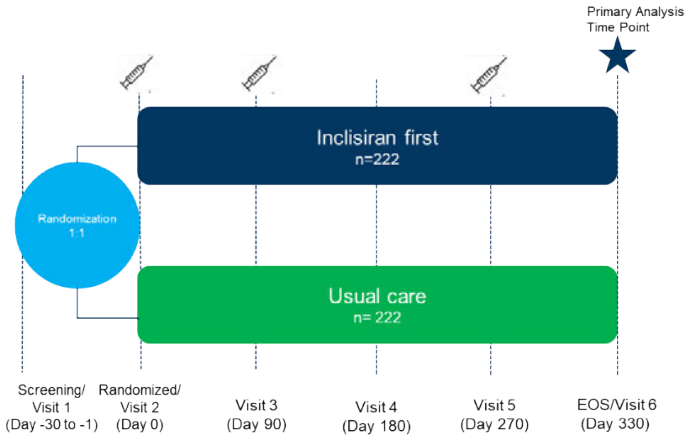
Since inclisiran is commercially available in the US as of late-2021, utilization of it in the usual care group at the sole discretion of the treating physician will not be encouraged, but will also not be prohibited to avoid withholding of appropriate care. If treatment with a PCSK9-inhibiting monoclonal antibody was initiated and a patient would have to be transitioned to inclisiran, the PCSK9- inhibiting monoclonal antibody should be discontinued.

The collection of data from trial sites through eCRFs will be complemented with EHR data and claims data (e.g., lipid measurements and concomitant medications).

Participants randomized to “inclisiran first” implementation strategy group will receive inclisiran at Day 0, Day 90 and Day 270, consistent with the dosing regimen studied in the Phase III trials.

While study visits will be preferentially performed in-person at the study sites, phone or virtual visits are an acceptable alternative if in-person visits are not permitted or impractical 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.

The remote procedures will be offered at certain sites as determined by Novartis based on national and local regulations.

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

Participants with established ASCVD are at increased risk of (recurrent) ischemic events. Lowering LDL-C reduces the risk of CV events in patients with ASCVD, with a magnitude of clinical benefit that is proportional to the reduction in LDL-C levels (Giugliano et al 2017). In view of the high risk of (recurrent) events in patients with established ASCVD and the fact that the majority of patients with established ASCVD have elevated LDL-C despite the availability of highly effective treatment options, addition of better or less frequently administered non-statin therapies could be beneficial.

This trial will compare an "inclisiran first" implementation strategy to usual care. The Phase III trials, which were designed to test the efficacy and safety of inclisiran, compared inclisiran to placebo. Neither changes in background lipid-lowering therapy, nor LDL-C tests, were allowed in those trials. Given the availability of non-statin LDL-C lowering therapies other than inclisiran and the fact that LDL-C tests are performed in routine care to assess adherence and to guide therapeutic management, a comparison with usual care which may include other non-statin therapies is more clinically relevant for clinicians and healthcare decision makers.

Clinical treatment guidelines recommend addition of non-statin LDL-C lowering therapies in patients with ASCVD and LDL-C ≥70 mg/dL despite maximally tolerated statin therapy (Grundy et al 2019). Non-statin therapies that are currently included in the 2018 ACC/AHA cholesterol guidelines include ezetimibe and PCSK9-inhibiting monoclonal antibodies. In large part due to the high costs and inconvenience of administration of PCSK9 inhibiting monoclonal antibodies, the guidelines recommend initial use of ezetimibe and addition of PCSK9 inhibiting monoclonal antibodies only in *very high risk* patients who fail to reach acceptable LDL-C levels

despite being treated with a combination of high intensity statin therapy and ezetimibe (Grundy et al 2019). Nonetheless, many patients still fail to reach acceptable LDL-C levels while being treated with a statin-ezetimibe combination due to the fact that ezetimibe lowers LDL-C by only ~20%. Therefore, addition of a more potent therapy without the disadvantagesof PCSK9 inhibiting monoclonal antibodies, such as inclisiran, might be a valuable alternativeto ezetimibe in patients with elevated LDL-C despite maximally tolerated statin therapy - i.e., an "inclisiran first" implementation strategy. Important considerations of the study design include:

**Recruitment:** Potentially eligible participants will be pre-screened using EHR, claims and/or laboratory databases. This will maximize the representativeness of the sample because it will reduce selection bias that occurs when investigators identify all participants by convenience sampling. Moreover, centrally identifying potential study sites and participants using EHR, claims and/or laboratory data will allow us to ensure that the study sites are representative while excluding sites that manage lipids more aggressively than is typical (for example specialized lipid clinics). Eligible participantswill need to consent to having health records made available as part of the collection ofmedical and pharmacy claims. [redacted]

**Responsibilities of principal investigator / routine care physician:** Study visits will be done by the PI while routine care is performed by the participant's own treating physician. Communication and coordination between the PI and treating physician is allowed. However, PIs are asked to refrain from influencing treatment decisions that areusually made by the treating physician to maximize external generalizability (i.e., the influence of study participation on routine care should be as limited as possible). The PIand treating physician can be from the same practice.

**Open-label:** The study will be performed as an open-label study to mimic routine caredecision-making, following from the primary objective of the study. For example, if thestudy would have been performed as a double-blind placebo-controlled study, it wouldnot 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 (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 slightly more than after a single administration (Ray et al 2017). Based on thesetrials, the maximum reduction in LDL-C is achieved approximately 4 to 5 months afterinitiation 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) assessment of variables that likely require longer-term treatment to observe meaningful treatment differences, such as patient reported outcomes.

**Choice of non-inferiority margin for discontinuation of statin therapy:** The samplesize of the trial, as described in Section 12.8.1, is partially based on the co-primary efficacy variable of discontinuation of statin therapy. The non-inferiority margin of 0.15in the proportion of participants who discontinue statin therapy by Day 330 was chosento reflect a clinically meaningful difference in statin discontinuation rates between the groups, while considering statin discontinuation rates described in other studies (Khunti et al 2018).

### 4.1.1 Rationale for choice of background therapy

Participants are required to be on maximally tolerated statin therapy at the time of identification and screening without plans to adjust lipid lowering therapy at that point in time.

Other than inclisiran in the inclisiran arm, therapies will not be made available by the sponsor. The trial could be criticized if patients in the usual care arm could not receive non-statin therapies because of insurance issues. To address the bias that may arise due to differences in access to therapies, randomization will be stratified by [redacted] as described in Section 6.3.2 of the protocol, and various statistical methods will adjust for [redacted] at baseline (yes, no). Importantly, valuable insights can be gathered from studying the implementation of an "inclisiran first" implementation strategy versus usual care without providing access to therapies:

- It increases the external validity of the trial
- It enables the study of implementation of an effective LDL-C lowering therapy in the absence of access barriers
- It enables examination of implementation of inclisiran in [redacted]

Inclisiran will not be excluded from the comparator group post-approval to avoid withholding of an approved therapy if deemed necessary by the treating physician, although the use of inclisiran in the comparator group is discouraged. Inclisiran will not be provided by the sponsor to participants in the comparator group. It is assumed based on historical and anticipated product uptake shortly after launch that potential inclisiran treatment in the comparator 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 since simultaneous use has not been evaluated in registration trials.

## 4.2 Rationale for dose/regimen and duration of treatment

In the Phase III clinical program, inclisiran was studied at one fixed dose [(inclisiran (KJX839), 284 mg liquid in prefilled syringe (PFS), 1.5 ml inclisiran sodium 300 mg. This dose will be administered on Day 0, Day 90 and Day 270, consistent with the dosing regimen that was studied in the Phase III trials. 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 maximally-tolerated statin therapy with or without other LDL-C lowering therapies. 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 – participants will not be withheld appropriate care. The study may also provide information that may benefit ASCVD 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 that included the population eligible for this study.
- Inclisiran was considered to be generally well-tolerated in Phase III trials (Ray et al 2017). Injection site reactions were more frequent in inclisiran-treated participants than in participants receiving placebo, but were localized, predominantly mild or occasionally moderate, transient, and resolved without sequelae.
- The potential for immunogenicity of inclisiran was shown to be low (Landmesser et al 2020).
- Reduction of LDL-C has been associated with reduced CV risk both by epidemiology and in controlled clinical trials (Grundy et al 2019).

An expanded risk-benefit summary is provided in the Inclisiran Investigator's Brochure (IB).

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

The study will include male and female participants ≥18 years of age with a history of ASCVD (coronary heart disease, ischemic cerebrovascular disease or peripheral arterial disease) who have elevated LDL-C (≥70 mg/dL) or non-HDL-C (≥100 mg/dL) despite being treated with maximally tolerated statin therapy. A total of approximately 444 participants will be randomized to the "inclisiran first" implementation strategy or usual care in a 1:1 ratio at approximately 50 US sites.

## 5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Males and females ≥18 years of age
3. History of ASCVD, documented by hospital records, claims data and/or prior laboratory/imaging assessments
   a. Coronary heart disease (CHD):
      - Prior myocardial infarction
      - Prior coronary revascularization (PCI or CABG)
      - Angiographic or CT-imaging (e.g., MDCT/CTA) evidence of coronary atherosclerosis (>70% stenosis in at least one major epicardial coronary artery)
   b. Cerebrovascular disease:
      - Prior ischemic stroke confirmed by a brain imaging study – CT or MRI; thought not to be caused by atrial fibrillation, valvular heart disease or mural thrombus
      - Carotid artery stenosis >70% on prior angiography or ultrasound
      - History of prior percutaneous or surgical carotid artery revascularization
   c. Peripheral arterial disease (PAD):
      - Prior documentation of a resting ankle-brachial index ≤0.85
      - History of prior percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery or aortic aneurysm
      - Prior non-traumatic amputation of a lower extremity due to peripheral artery disease
4. Serum LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
5. Fasting triglyceride <5.65 mmol/L (<500 mg/dL) at screening

6. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology
7. Participants should be on maximally tolerated statin therapy, as determined by the investigator, with no immediate plans to modify lipid lowering therapies. Statin intolerant patients are eligible if they had documented side effects on at least 2 different statins, including one at the lowest standard dose
8. 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

## 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 eitherinterfere 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 clinicalstudy results
3. New York Heart Association (NYHA) class III or IV heart failure or last known left ventricular ejection fraction <30%
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. Major adverse cardiovascular event within 6 months prior to randomization
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic bloodpressure >110 mmHg prior to randomization despite antihypertensive therapy
7. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 2 years
8. History of malignancy that required surgery (excluding local and wide-local excision),radiation therapy and/or systemic therapy during the two years prior to randomization
9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing ofinvestigational drug. Basic contraception methods include:
    a. 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
    b. 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
    c. Male sterilization (at least 6 m prior to screening). For female participants in the study, the vasectomized male partner should be the sole partner for that participant

d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
e. 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)
f. In case of use of oral contraception, women should have been stable on the same pill for aminimum 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 leastsix 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.

10. Known history of alcohol and/or drug abuse within the last 5 years (occasional casual users of illicit drugs in the opinion of the investigators are not excluded)
11. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
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 – including potential participants who indicate that their participation is contingent on receiving inclisiran)
    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. Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9, or with inclisiran or ezetimibe.

16. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or 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 leastone week apart.

# 6 Treatment

## 6.1 Study treatment

Inclisiran (KJX839), 284 mg, 1.5 ml liquid in a single-use PFS for s.c. administration.

Usual care per treating physician

### 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<br>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 the following 2 treatment groups ("inclisiran first" implementation strategy vs usual care) in a ratio of 1:1 using a randomization process to enroll approximately 444 participants (222 participants per treatment group).

### 6.1.4 Treatment duration

The planned duration of treatment is 330 days from date of randomization. Participants may be discontinued from treatment at any time due to adverse events, disease progression and/or treatment is discontinued 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 (i.e. aspirin, thienopyridines), anticoagulants, 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 electronic 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 electronic Case Report Forms, or where applicable, sourced from the EHR and mapped into the clinical study database.

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 below table are not allowed to be used simultaneously with inclisiran in the active arm but may be prescribed independently via the treating physician's discretion 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

All participants derived from the EHR database will receive an invitation from their treating physician to be involved in a clinical trial and to have an in-person screening visit at the investigator site. Each potential participant who agrees to participation will be 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.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

### 6.3.2 Treatment assignment, randomization

At visit 2, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the two treatment groups in 1:1 ratio ("inclisiran first" implementation strategy or 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 numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. 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).

Randomization will be stratified by [redacted]. The stratification ensures balanced allocation of participants to treatment groups within the [redacted] strata.

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

## 6.4 Treatment blinding

Not applicable.

## 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 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 phosphokinase (CPK) values >5 x ULN confirmed by repeat test when the CPK 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]

[redacted]

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 CPK.

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 canbe 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.

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 (inclisiran) 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 study medication label. No study medications will be provided for usual care group.

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

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 in PFS, 1.5M 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 s.c. 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 included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - 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 who took study treatment

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 the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible (+/- 7 days). Missed or rescheduled visits should not lead to automatic discontinuation. 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.

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.

## Table 8-1 Assessment Schedule

| **Epoch** | **Screening** | **Treatment**[1] | | | | |
|---|---|---|---|---|---|---|
| **Visit Name** | **Visit 1** | **Baseline/Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **EOS/Visit 6** |
| **Days** | **-30 to -1** | **0** | **90** | **180** | **270** | **330** |
| Inclusion / Exclusion Criteria | X | X | | | | |
| Informed Consent | X | | | | | |
| Medical History | X | | | | | |
| ASCVD Medical History | X | | | | | |
| Statin Intolerance Medical History | X | | | | | |
| Demography | X | | | | | |
| Pregnancy and Assessments of Fertility[2] | X | X | X | X | X | X |
| | | | | | | |
| Height and Weight[3] | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X |
| Physical Examination[4] | S | | S | S | S | S |
| Electrocardiogram (ECG) | X | | | | | |
| Full Clinical Chemistry | | X | | | | X |
| Limited Clinical Chemistry | X | | X | X | X | |
| Hepatitis Markers | X | | | | | |
| Hematology | X | X | | X | | X |
| Coagulation | X | X | | | | X |
| Urinalysis | | X | | | | X |
| Lipids and Lipoproteins[5] | X | X | X | X | X | X |
| | | | | | | |
| Randomization | | X | | | | |
| IRT Transaction | X | X | X | X | X | X |
| Inclisiran Dose Administration | | X | X | | X | |

| **Epoch** | **Screening** | **Treatment**[1] | | | | |
|---|---|---|---|---|---|---|
| **Visit Name** | **Visit 1** | **Baseline/Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **EOS/Visit 6** |
| **Days** | **-30 to -1** | **0** | **90** | **180** | **270** | **330** |
| Adverse Events | X | X | X | X | X | X |
| Injection Site Reaction Assessment | | X | X | X | X | X |
| Prior/Concomitant Medications[7] | X | X | X | X | X | X |
| Surgical/Medical Procedures | X | X | X | X | X | X |
| [redacted] | | | | | | |
| HealthiVibe Trial Feedback Questionnaire[9] | | X | | X | | X |

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] 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 in the local laboratory for remaining visits.
[3] Height only to be performed at Visits 1 and 2
[4] Visits 3, 4 and 5 will be a limited/focused physical examination.
[5] LDL-C, apolipoprotein B, Lp(a), non-HDL-C, VLDL-C, total cholesterol, triglycerides, and HDL-C. [redacted]
[redacted]
[7] 30 days prior to randomization
[redacted]
[9] Questionnaire is optional for trial participants.

## 8.1 Screening

A participant who enters screening but is determined not to be eligible 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. Participants must provide new written informed consent before they are re-screened.

### 8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate 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). The IRT must be notified within 2 days of the screen fail.

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

## 8.2 Participant demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity, type of insurance, household income and highest completed education. Relevant medical history/current medical condition data includes data collected up to the point in which informed consent is signed. 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. Discontinuation of statin therapy (i.e., no statin script ≥ 30 days before the end-of-study visit) (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 ≥ 50% reduction from baseline in LDL-C (yes, no)
5. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)

6. Achieving LDL-C < 70 mg/dL (yes/no)
7. Achieving LDL-C < 55 mg/dL (yes, no)
8. Percent change from baseline in apoB
9. Absolute change from baseline in apoB
10. Percent change from baseline in non-HDL-C
11. Absolute change from baseline in non-HDL-C
12. Percent change from baseline in VLDL-C
13. Absolute change from baseline in VLDL-C
14. Percent change from baseline in total cholesterol
15. Absolute change from baseline in total cholesterol
16. Percent change from baseline in Lp(a)
17. Absolute change from baseline in Lp(a)
18. Percent change from baseline in HDL-C
19. Absolute change from baseline in HDL-C
20. Percent change from baseline in triglycerides
21. Absolute change from baseline in triglycerides
22. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)
23. Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies prescribed divided by total number of study days)

### 8.3.1 Primary efficacy assessments

The primary efficacy assessments will be LDL-C and discontinuation of statin therapy. Samples for LDL-C will be collected at screening (Visit 1) and on visit days 2, 3, 4, 5 and 6 (Table 8-1).

### 8.3.2 Other efficacy assessments

Other efficacy assessments will include measurement of Apolipoprotein B, Lp(a), non-HDL-C, VLDL-C, total cholesterol, triglycerides, and HDL-C. Samples for these additional efficacy biomarkers will be collected at Visits 1, 2, 3, 4, 5 and 6 (Table 8-1).

### 8.3.3 Appropriateness of efficacy assessments

The assessment of lipids and lipoproteins is standard in both clinical practice and in trials evaluating the efficacy of lipid-modifying therapies (Grundy et al 2019). Utilization of other therapies (including, but not limited to, statin discontinuation, adherence to therapies and changes in therapy) are frequently used variables to evaluate the effectiveness of therapies in clinical studies. The patient-reported outcomes instruments used in this study are validated instruments that have been previously used in clinical trials.

## 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 examination | A complete physical examination will be performed at Visits 1 and 6. It 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 examinations. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Visits 3, 4 and 5 physical exams will be a limited/focused examination.<br>Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. |
| Vital signs | Vital signs will be assessed at Visits 1, 2, 3, 4, 5 and 6. This will include blood pressure and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non- dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the participant for all vital signs assessments and where possible, the same person doing the assessment. |
| Height and weight | Height in centimeters if possible will be measured at Visits 1 and 2. Body weight to the nearest 0.1 kg without shoes, will be measured at Visits 1, 2, 3, 4, 5 and 6. |

### 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 (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.

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.

#### 8.4.1.1 Hematology

Blood draws for hematology will include:

Hemoglobin, hematocrit, erythrocytes, reticulocytes, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count with differential.

#### 8.4.1.2 Coagulation

Blood draws for coagulation will include:

Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT).

#### 8.4.1.3 Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments (Table 8-1). Analysis will vary based on visit day as follows:

- **Full serum chemistry**: AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate dehydrogenase, bicarbonate, uric acid, creatinine, urea (BUN), estimated glomerular filtration rate (eGFR), hsCRP, sodium, potassium, magnesium, calcium, inorganic phosphate, chloride, albumin, total protein, hsCRP, glucose (fasting), [redacted]
- **Limited serum chemistry**: ONLY: AST, ALT, ALP, GGT, TBL, CPK, creatinine, eGFR, fasting glucose, hsCRP and [redacted].

#### 8.4.1.4 Urinalysis

Urinalysis will be performed in accordance with the assessment schedule (Table 8-1) at the investigational site (a standardized dipstick test will be supplied by the Central Laboratory). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

The following parameters will be assessed: pH, specific gravity, presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin. Microscopic panel will be only performed in the event of abnormalities (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells).

#### 8.4.1.5 Hepatitis markers

Hepatitis markers will be evaluated at screening only, and will include HBV-DNA, HBsAg, HBsAb, HBcAb and HCV RNA-PCR. Testing will be performed in a test sequence recommended by the Centers for Disease Control and Prevention.

### 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 eCRF as either medical history and/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 in the local laboratory at visits 2, 3, 4, 5 and 6. If any of these tests are positive at Visits 1 and/or 2, the participant should not be enrolled in the trial. If a participant tests positive at Visits 3, 4 or 5, or should become pregnant during the trial, the participant may remain in the trial for follow-up visits, but cannot continue to receive inclisiran injections.

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

#### 8.4.4.1 Anaphylactic reactions

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

#### 8.4.4.2 Injection site reactions

Injection site reactions (ISRs) should be monitored at each visit from the randomization visit onwards and through additional contacts with the participant between visits as needed. ISRs 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.

#### 8.4.4.3 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:

[redacted]

- 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 ([redacted]) when:

[redacted]

- 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 patients with atherosclerotic cardiovascular disease and elevated LDL-C.

## 8.5 Additional assessments

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

[redacted]

[redacted]

#### 8.5.3.3 HealthiVibe Optional Trial Feedback Questionnaire

This study includes an optional questionnaire, the "Trial Feedback Questionnaire" for participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect, or adverse events, and, therefore is not considered as trial data.

# 9 Study discontinuation and completion

## 9.1 Discontinuation and completion

### 9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- 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 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 must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

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

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

### 9.1.3 Lost to follow-up

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

### 9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

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

## 9.2 Study completion and post-study treatment

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 no further study treatment will be made available to them).

For study participants who have successfully completed the study/treatment epoch, 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 treatment epoch or who withdraw from treatment, continuing treatment should be managed by the investigator and/or referring 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.

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 participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in 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, an associate from the Novartis Chief Medical Office and Patient Safety (CMO & PS) organization 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 eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

## 10.2 Additional Safety Monitoring

### 10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification and evaluation of liver events consistent with normal clinical practice and monitoring.

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 and evaluationof renal events consistent with normal clinical practice and monitoring. Every renal laboratory trigger or renal event as defined in Table 16-6 in Section 16.3 (Appendix 3) should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-7 (Section 16.3 (Appendix 3).

### 10.2.3 Steering Committee

The Steering Committee (SC) for this study will comprise of 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

## 11.1 Data collection

### Integrated Data Acquisition Approach

The study may utilize a de-identified integrated data acquisition approach entailing capture of data directly from available site EHR databases in addition to manual data entry by site personnel into an electronic CRF (eCRF) and integration of linked pharmacy claims data records.

### Direct EHR Data Capture

If this approach is utilized by your site, the data collection would extract source data from a participant's electronic medical record and map the data into the project database. When using an electronic source record as the original point of data capture, there would be no additional manual site data entry step for the selected data. These data can be mapped directly into the project database, reducing the need for sites to perform manual data entry in the eCRFfor required routine care study data elements that are captured as part of the participant's EHR. If it is not possible to acquire data directly from the EHR, or if source data is not integrated to the clinical database, data capture and data management will revert to eCRF.

This study may incorporate electronic technology to map EHR data into the clinical database consistent with Use of Electronic Health Record Data in Clinical Investigations – Guidance for Industry July 2018 as well as FDA guidance regarding electronic source and regulations related to the maintenance of adequate participant case histories (21 CFR 312.62 [b]). All electronic source documentation and data collected in this study will "meet the same fundamental elements of data quality (e.g. attributable, contemporaneous, original, and accurate) that are expected of "paper records" into a system that is fully validated and conforms to 21 CFR Part 11 requirements.

Virtual / remote source data review will take place in order to review the EHR data to confirm data accuracy and to ensure all study objectives are met when integrated into the clinical study database.

### 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.

### Linked Pharmacy & Medical Claims Data

Participants may be asked to consent to having health records made available as part of the collection of medical and pharmacy claims in order to assess concomitant medication and clinical outcomes. This data would be sourced from pharmacy & medical claims databases that have been de-identified and tokenized to match the participant in the study. This de-identified data would be mapped into the project database. Logic checks to confirm accurate linkage would be performed by the clinical monitoring and data management teams.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. All integrated data would be presented to the site in a 21 CFR Part 11 compliant system for review and clarification of accuracy and quality.

The investigator/designee is responsible for assuring that all data (whether entered into the eCRF or harvested from the EHR) 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.

## 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 and the Data Review Portal. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

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

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/[redacted] 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/[redacted]/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 eCRFs 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

# 12 Data analysis and statistical methods

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

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 first” implementation strategy group (i.e., excludes patients in the “inclisiran first” implementation strategy 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 at randomization.

## 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. Discontinuation of statin therapy (i.e., no statin use ≥ 30 days before the end-of-study visit) (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 first" implementation strategy 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 first" implementation strategy and usual care

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

Primary efficacy variable 1 will be analyzed using mixed-effects model repeated measures (MMRM) with treatment, visit, baseline, [redacted], 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 effect at Day 330 is < 0.025 and the corresponding least squares mean treatment difference ("inclisiran first" implementation strategy – usual care) is less than 0, statistical significance in favor of "inclisiran first" implementation strategy is shown. All efforts will be made to follow up participants until the end of the study. Participants will be expected to followthe 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 and if a participant was not statin intolerant at the beginning of the trial
- Variable: Discontinuation of statin therapy (yes, no) [The primary analysis time point is at Day 330.]
- Treatment: "Inclisiran first" implementation strategy 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 first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy

The null hypothesis is that the difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy at Day 330 is at least 0.15 (non-inferiority margin). The alternative hypothesis is that the difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinue statin therapy at Day 330 is less than 0.15.

For primary efficacy variable 2, a one-sided 98.75% confidence interval for treatment difference ("inclisiran first" implementation strategy – usual care) in the proportion of participants who discontinued statin therapy at Day 330 will be computed using the normal approximation to the binomial distribution. Non-inferiority of the "inclisiran first" implementation strategy to usual care will be declared if the upper limit of the confidence interval does not exceed the non-inferiority margin of 0.15.

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 events 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 for whom it cannot be ascertained that they are on statin therapy at the end of study will be assumed to have discontinued statin therapy.

### 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 first" implementation strategy 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 first" implementation strategy 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 van Elteren test, adjusting for [redacted] (Stokes et al 2012). The probability of observing the same or a more favorable response with "inclisiran first" implementation strategy relative to usual care will be estimated using nonparametric methods, and the associated 97.5% confidence interval will also be reported (Chen and Kianifard 2000).

### 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 first" implementation strategy 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 first" implementation strategy and usual care

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 ≥ 50% reduction from baseline in LDL-C (yes, no)
5. Achieving LDL-C < 100 mg/dL (yes, no) (among the subset of participants with LDL-C ≥ 100 mg/dL at baseline)
6. Achieving LDL-C < 70 mg/dL (yes, no)
7. Achieving LDL-C < 55 mg/dL (yes, no)
8. Percent change from baseline in apoB
9. Absolute change from baseline in apoB
10. Percent change from baseline in non-HDL-C
11. Absolute change from baseline in non-HDL-C
12. Percent change from baseline in VLDL-C
13. Absolute change from baseline in VLDL-C
14. Percent change from baseline in total cholesterol
15. Absolute change from baseline in total cholesterol
16. Percent change from baseline in Lp(a)

17. Absolute change from baseline in Lp(a)
18. Percent change from baseline in HDL-C
19. Absolute change from baseline in HDL-C
20. Percent change from baseline in triglycerides
21. Absolute change from baseline in triglycerides
22. Intensity of lipid-lowering therapy (decrease in dose, no change in dose, increase in dose)
23. Proportion of days covered (total number of days on either statin, ezetimibe, bempedoic acid or PCSK9 inhibiting monoclonal antibody therapies prescribed divided by total number of study days)

Analyses of secondary efficacy variables 1 and 8 - 21 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 variable 2, 3, and 23 will be analyzed using a linear model with treatment, baseline LDL-C, and [redacted] 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 - 7 will be analyzed at each post-baseline visit using a logistic regression model with treatment, baseline LDL-C, and [redacted] as explanatory variables (Stokes et al 2012). The odds ratio, 95% confidence intervals 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 22 will be analyzed at each post-baseline visit using a proportional odds model with treatment, baseline LDL-C, and [redacted] 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.

Visit-to-visit LDL-C variability from Day 90 until Day 330 will be reported, using various measures of variability (standard deviation, coefficient of variation) (Bangalore et al 2015).

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]

[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 first" implementation group compared to the usual care group, and 2) the ability to add non-statin lipid lowering therapy (including participants who may have used commercially available inclisiran), in the usual care group. [redacted]

Table 12-1 considers total sample sizes for expected mean treatment differences of 15, 20, and 25 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 at Day 330 and a power of 0.90 were chosen to provide a total sample size of 354 participants.

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

| Mean treatment difference | Power = 0.85 | Power = 0.90 |
|---|---|---|

| | | |
|---|---|---|
| **15** | **306** | **354** |
| 20 | 172 | 200 |
| 25 | 112 | 128 |

For primary efficacy variable 2, i.e., discontinuation of statin therapy (yes, no), a [redacted] for a non-inferiority test of two proportions, an allocation ratio of 1:1, and a one-sided significance level of 0.0125 were used in the calculation of sample size. Table 12-2 considers total sample sizes for 0.20 and 0.25 as the true proportions of participants who discontinue statin therapy in each treatment group, and non-inferiority margins of 0.10 and 0.15 for the "inclisiran first" implementation group to be no worse than the usual care group (nQuery Version 8.4.1.0). From Table 12-2, a true proportion of 0.20 for participants who discontinue statin therapy in each treatment group by Day 330, a non-inferiority margin of 0.15, and a power of 0.90 were chosen to provide a total sample size of 354 participants.

**Table 12-2 Sample size calculations for statin therapy discontinuation**

| Proportion in usual care group | Non-inferiority margin | Power = 0.85 | Power = 0.90 |
|---|---|---|---|
| 0.20 | 0.10 | 688 | 796 |
| **0.20** | **0.15** | **306** | **354** |
| 0.25 | 0.10 | 806 | 932 |
| 0.25 | 0.15 | 360 | 414 |

Based on the sample size calculations in Table 12-1 and Table 12-2, a total sample size of 354 together with a loss to follow-up rate of 10% at Day 330 and a statin intolerance rate at baseline of 10% (i.e., a total of 20% due to loss to follow-up and statin intolerance at baseline) require approximately 444 participants (222 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.

# 15 References

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# 16 Appendices

## 16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

**Table 16-1 Clinically notable vital signs**

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

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

Notable laboratory values are defined in Table 16-2:

**Table 16-2 Clinically notable laboratory abnormalities for selected tests**

| Parameters | Criteria |
|---|---|
| **Hematology** | |
| Hemoglobin | ≤ 10 g/dL |
| Hematocrit | ≤ 0.8 × LLN |
| WBC (total) | ≤ 2.8 $\times 10^3$ / µL, ≥ 16 $\times 10^3$ / µL |
| Platelet count | ≤ 75 $\times 10^3$ / µL, ≥ 700 $\times 10^3$ / µL |
| [redacted] | [redacted] |
| **Clinical chemistry** | |
| Creatinine | > 2 mg/dL |
| CPK | > 1 and ≤ 3 × ULN |
| CPK | > 3 and ≤ 5 × ULN |
| CPK | > 5 and ≤ 10 × ULN |
| CPK | > 10 × ULN |
| ALT | > 1 and ≤ 3 × ULN |
| ALT | > 3 and ≤ 5 × ULN |
| ALT | > 5 × ULN |
| AST | > 1 and ≤ 3 × ULN |
| AST | > 3 and ≤ 5 × ULN |
| AST | > 5 × ULN |
| Total bilirubin | > 2 × ULN |
| ALP | > 2 × ULN |

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

**Table 16-3 Liver event and laboratory trigger definitions**

| | **Definition/ threshold** |
|---|---|
| Liver laboratory triggers<br>If ALT, AST and total bilirubin normal at baseline: | • ALT or AST > 5 × ULN<br>• ALP > 2 × ULN (in the absence of known bone pathology)<br>• Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)<br>• ALT or AST > 3 × ULN and INR > 1.5<br>• 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)<br>• Any clinical event of jaundice (or equivalent term)<br>• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>• 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:**<br>ALT or AST > 3 x ULN | Normal<br>For patients with Gilbert's syndrome: No change in baseline TBL | None | • **No change to study treatment**<br>• Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CPK, and GLDH in 48-72 hours.<br>• Follow-up for symptoms. |
| **If elevated at baseline:**<br>ALT or AST > 2 x baseline<br>or > 300 U/L (whichever occurs first) | | | |

<table>
<tr><th>ALT or AST</th><th>TBL</th><th>Liver Symptoms</th><th>Action</th></tr>
<tr><td>If normal at baseline:<br>ALT or AST > 5 x ULN for more than two weeks</td><td rowspan="2">Normal<br>For patients with Gilbert’s syndrome: No change in baseline TBL</td><td rowspan="2">None</td><td rowspan="8">• Interrupt study drug<br>1. Measure ALT, AST, ALP, GGT, TBL, direct and indirect bilirubin, PT/INR, albumin, CPK, and GLDH in 48-72 hours.<br>• Follow-up for symptoms.<br>• Initiate close monitoring and workup for competing etiologies.<br>• Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.</td></tr>
<tr><td>If elevated at baseline:<br>ALT or AST > 3 x baseline<br>or > 300 U/L (whichever occurs first) for more than two weeks</td></tr>
<tr><td>If normal at baseline:<br>ALT or AST > 8 x ULN</td><td>Normal</td><td>None</td></tr>
<tr><td colspan="3">ALT or AST increase with bilirubin increase:</td></tr>
<tr><td>If normal at baseline:<br>ALT or AST > 3 x ULN</td><td rowspan="2">TBL > 2 x ULN (or INR > 1.5)<br>For patients with Gilbert’s syndrome: Doubling of direct bilirubin</td><td rowspan="2">None</td></tr>
<tr><td>If elevated at baseline:<br>ALT or AST > 2 x baseline<br>or > 300 U/L (whichever occurs first)</td></tr>
<tr><td>If normal at baseline:<br>ALT or AST > 3 x ULN</td><td rowspan="2">Normal or elevated</td><td rowspan="2">Severe fatigue, nausea, vomiting, right upper quadrant pain</td></tr>
<tr><td>If elevated at baseline:<br>ALT or AST > 2 x baseline<br>or > 300 U/L (whichever occurs first)</td></tr>
</table>

**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<br>• 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<br>• Repeat LFT within 48-72 hours | Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total |

| Criteria | Actions required | Follow-up monitoring |
|---|---|---|
| | • Hospitalize if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF | bilirubin, Alb, PT/INR, ALP and GGT)<br>Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 10 x ULN | • Discontinue the study treatment immediately<br>• Hospitalize the participant<br>• Establish causality<br>• Record the AE and contributing factors(e.g. conmeds, med hx, lab) in the appropriate eCRF | ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) |
| Any AE potentially indicative of a liver toxicity* | • Consider study treatment interruption or discontinuation<br>• Hospitalization if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors(e.g., conmeds, med hx, lab) in the appropriate eCRF | 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 increase (sCR) 25 – 49% | Consider causes and possible interventions<br>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<br>Repeat assessment within 24-48h if possible<br>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected<br>Consider participant hospitalization and specialized treatment |
| New onset dipstick proteinuria ≥ 3+<br>OR<br>Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory) | Consider causes and possible interventions<br>Assess serum albumin & serum total protein<br>Repeat assessment to confirm<br>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected |
| New onset hematuria ≥ 3+ on urine dipstick | Repeat assessment to confirm<br>Distinguish hemoglobinuria from hematuria<br>Urine sediment microscopy<br>Assess sCr<br>Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation<br>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):<br>Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells<br>Blood pressure and body weight<br>Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid<br>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 –<br>• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr)<br>or<br>• 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.<br>• 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):

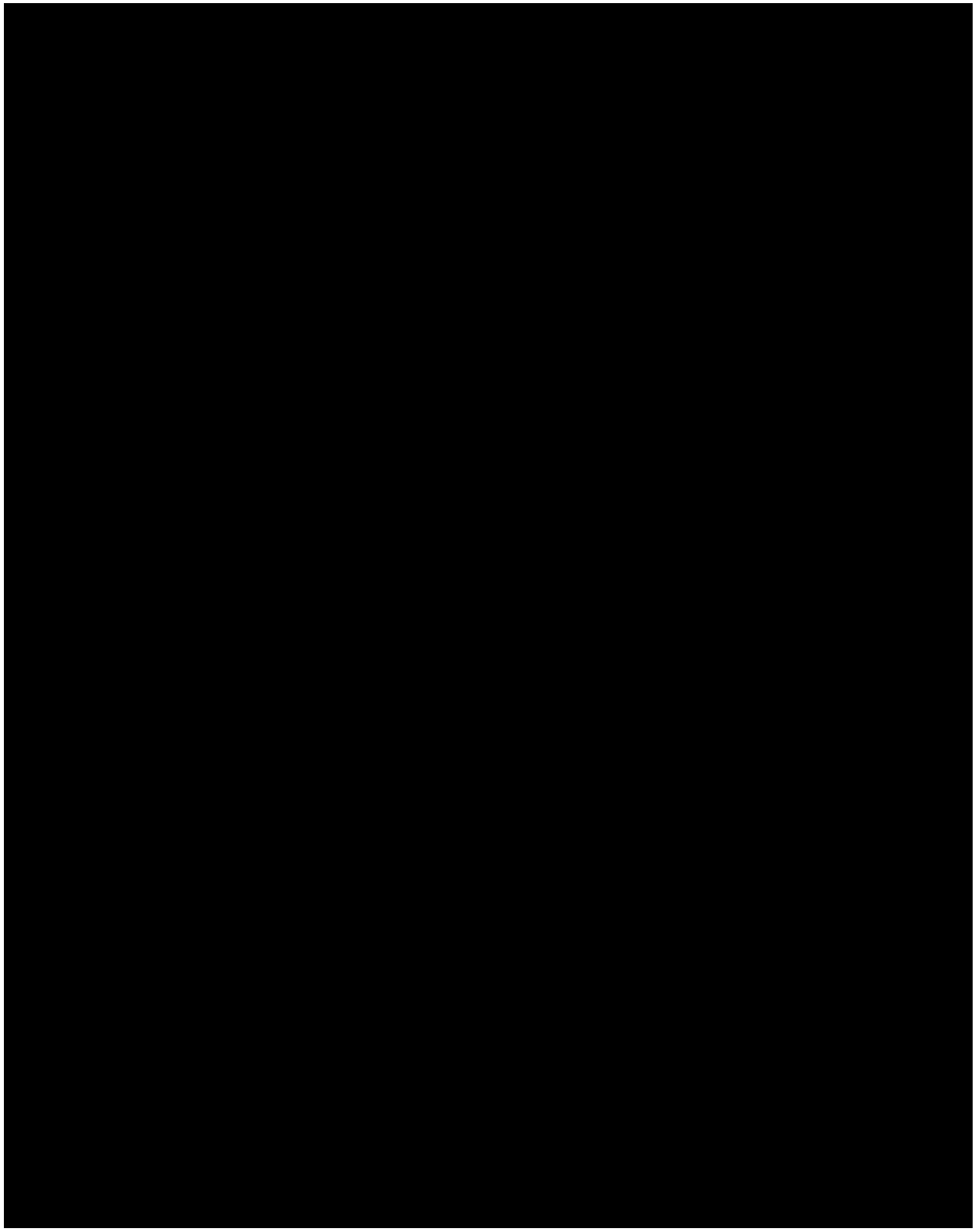
a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent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

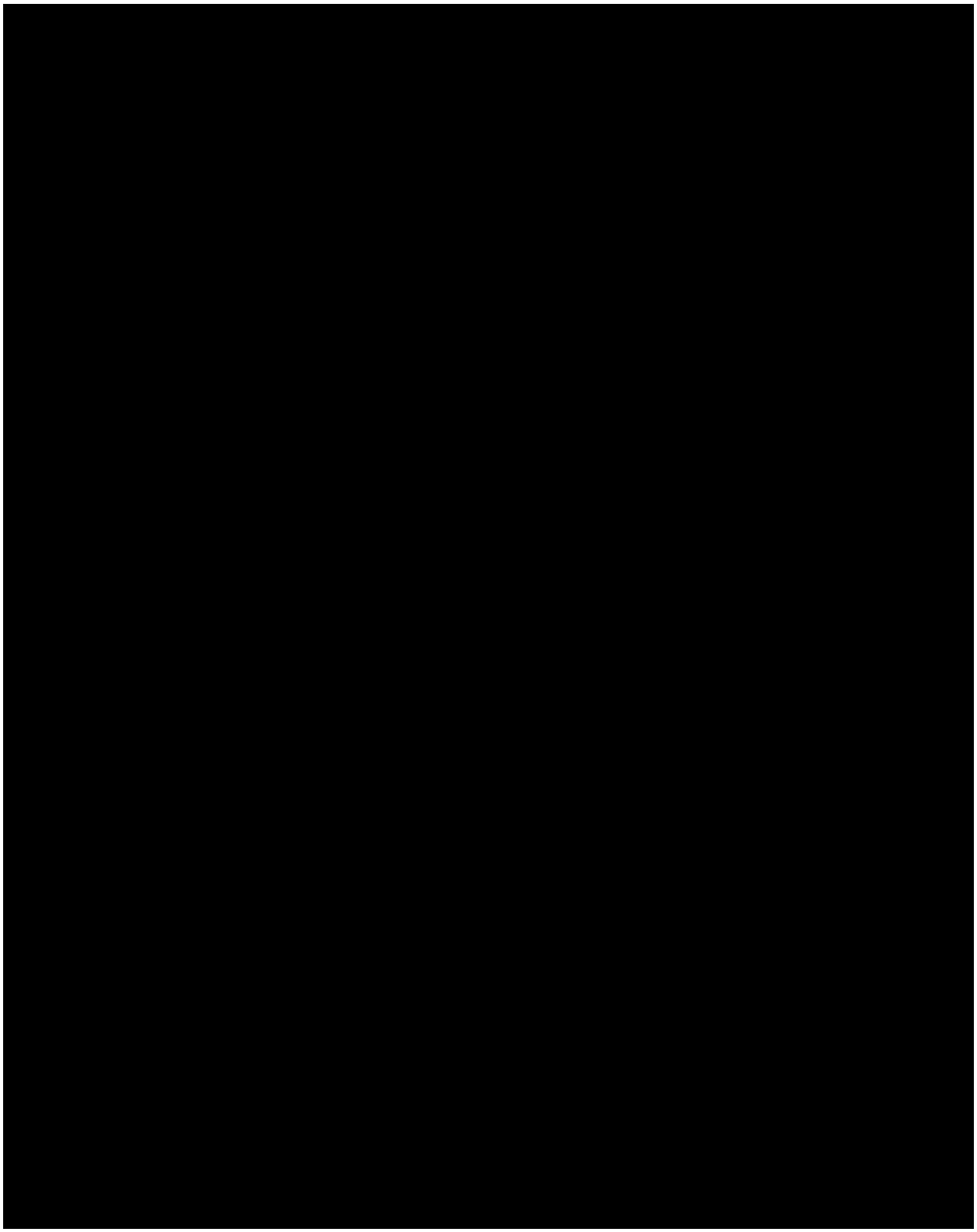
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):

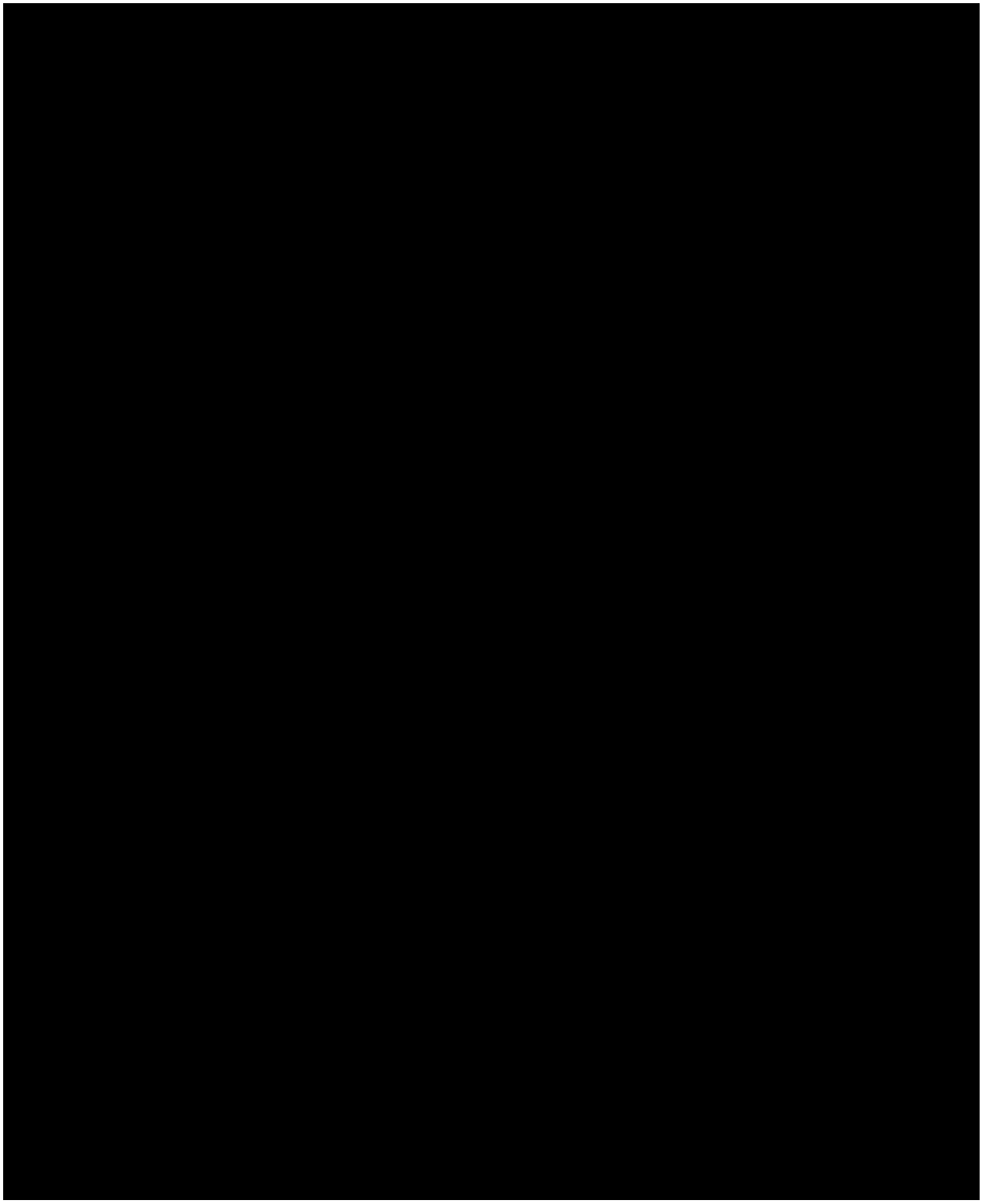
a. Infants and children: low systolic blood pressure (age specific) or > 30% decrease in systolic blood pressure*
b. Adults: systolic blood pressure <90 mmHg or >30% decrease from that person's baseline

*Low systolic blood pressure for children is age specific and defined as: <70 mmHg for age 1 month to 1 year; <70 mmHg + [2 x age] for age 1 to years; <90 mmHg for age 11 to 17 years

Source: (Sampson et al 2005) and (Sampson et al 2006)







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