Official Title: Two Part (Double-blind Inclisiran Versus Placebo [Year 1] Followed by Open-label Inclisiran [Year 2]) Randomized Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Inclisiran in Adolescents (12 to Less Than 18 Years) With Homozygous Familial Hypercholesterolemia and Elevated LDL-cholesterol (ORION-13)

NCT Number: NCT04659863

Document Date: Clinical Study Protocol (Amendment 2): 17-Feb-2023

NOVARTIS

Novartis Research and Development

KJX839/inclisiran

Clinical Trial Protocol CKJX839C12302

Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-13)

Document type:	Amended Protocol Version
EUDRACT number:	2020-002755-38
Version number:	02 (Clean)
Clinical Trial Phase:	III
Release date:	17-Feb-2023 (Content Final)

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

List of tables

List of figures

List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse Drug Reaction
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BfArM	Federal Institute for Drugs and Medical Devices
BMI	Body Mass Index
BUN	Blood urea nitrogen
C(P)K	Creatine (phospho)kinase
CFR	Code of Federal Regulation
CHD	Coronary heart disease
[redacted]	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTFG	Clinical Trials Facilitation and Coordination Group
CTT	Clinical trial team
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
DILI	Drug induced liver injury
DIN	Drug-induced nephrotoxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
ERCP	Endoscopic retrograde cholangiopancreatography
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FH	Familial Hypercholesterolemia
FPG	Fasting plasma glucose
GalNAc	N-Acteylgalactosamine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol

HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR(s)	Injection site reaction(s)
IUD	Intrauterine device
IUS	Intrauterine system
kg	Kilogram(s)
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
[redacted]	[redacted]
LFT(s)	Liver function test(s)
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein (a)
MCV	Mean corpuscular volume
mg	milligram(s)
MI	Myocardial infarction
mL	milliliter(s)
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
mRNA(s)	Messenger ribonucleic acid(s)
PCR	Protein-creatinine ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PT/INR	Prothrombin Time / International Normalized Ratio
RBC	Red blood cell(s)
RISC(s)	Ribonucleic acid (RNA)-induced silencing complex(es)
RNA	Ribonucleic acid
s.c.	Subcutaneous
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
sCr	Serum creatinine
SD	Standard deviation
siRNA(s)	Small interfering ribonucleic acid(s)

SoC	Standard of Care
SOP(s)	Standard Operating Procedure(s)
SUSAR(s)	Suspected Unexpected Serious Adverse Reaction(s)
TBV	Total blood volume
TEAE	Treatment emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low density lipoprotein cholesterol
WBC	White blood cell(s)

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria
Control drug	Any study drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal validity, and/or evaluate comparative effects of the investigational drug
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; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
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.
Investigational drug/ treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
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 number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent	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 2 (17-Feb-2023)

Amendment rationale

[redacted]

In addition [redacted] several small clarifications/corrections/additions are included in this protocol amendment:

- A small inaccuracy in a unit conversion for LDL-C is fixed.

[redacted]

[redacted]

Changes to the protocol

The revisions made to the protocol are listed in the Table below.

Section	Description of change
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Other small clarifications/corrections/additions	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Section 15 References	A new reference associated with the current amendment is added.

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

Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs)

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

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

The changes herein do not affect the Informed Consent.

Summary of previous amendments

Amendment 1 (01-Oct-2020)

Amendment rationale

[redacted]

This amendment is issued before the original protocol was sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities, i.e. before any participants were screened or randomized.

Changes to the protocol

The revisions made to the protocol are listed below.

[redacted]

[redacted]

Protocol summary

Protocol number	CKJX839C12302
Full Title	Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-13)
Brief title	A multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia
Sponsor and Clinical Phase	Novartis / Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This is a pivotal phase III study designed to evaluate safety, tolerability, and efficacy of inclisiran in adolescents with homozygous familial hypercholesterolemia (HoFH) and elevated low density lipoprotein cholesterol (LDL-C). The use of inclisiran for the treatment of HoFH in adolescent patients who require additional lipid lowering will be investigated in order to obtain needed pediatric information on inclisiran.
Primary Objective(s)	The primary objective of the study is to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C
Secondary Objectives	Evaluate the effect of inclisiran compared to placebo on reducing LDL-C [time-adjusted percent change] over Year 1 Evaluate the effect of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and proprotein convertase subtilisin/kexin type 9 (PCSK9) over time Evaluate the safety and tolerability of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HoFH
Study design	Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study
Study population	Adolescents (age 12 to <18 years) with HoFH; approximately 12 participants; males and females
Key Inclusion criteria	• HoFH diagnosed by genetic confirmation • Fasting LDL-C >130 mg/dL (3.4 mmol/L) at screening • On maximally tolerated dose of statin (investigator's discretion) with or without other lipid-lowering therapy (e.g. ezetimibe). Maximum tolerated dose of statin is defined as the maximum dose of statin that, at the investigator's discretion, can be taken on a regular basis without adverse events that would lead to a reduction in statin dose • Participants on lipid-lowering therapies (such as statin and/or e.g. ezetimibe) should be on a stable dose for ≥ 30 days before screening with no planned medication or dose changes during study participation • Participants on a documented regimen of LDL-apheresis will be allowed to continue the apheresis during the study, if needed. The apheresis schedule is not allowed to change during the double-blind period of the trial and must permit that an apheresis coincides with each study visit • Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m2 at screening
Key Exclusion criteria	• Documented evidence of a null (negative) mutation in both LDLR alleles • Previous treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9 • History of poor response to therapy with any monoclonal antibody directed towards PCSK9

	• Treatment with mipomersen or lomitapide (within 5 months of screening) • Active liver disease or unexplained, confirmed alanine aminotransferase (ALT), aspartate aminotransferase (AST) elevation >3x ULN, or total bilirubin elevation >2x ULN (except patients with Gilbert's syndrome) • Pregnant or nursing females • Heterozygous familial hypercholesterolemia (HeFH) • Recent and/or planned use of other investigational medicinal products or devices • Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome • Major adverse cardiovascular events within 1 month prior to randomization
Study treatment	Part 1 (Year 1): • Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) in 1.5 mL solution • Placebo Part 2 (Year 2): • Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) in 1.5 mL solution * Inclisiran is also referred to as KJX839.
Treatment of interest	The randomized treatment (the investigational treatment inclisiran or the control treatment placebo) as add-on to optimal standard of care lipid-lowering therapy for HoFH. The type and dose of the concomitant lipid-lowering therapy for HoFH must remain stable during Part 1 (Year 1) of the study.
Efficacy assessments	The primary efficacy assessment will be LDL-C Other efficacy assessments will include: • Apolipoprotein B (Apo B), lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo A1), PCSK9
Key safety assessments	Adverse event (AE) monitoring, vital signs, laboratory parameters (blood and urine), anti-drug antibodies (ADA) measurement, growth, pubertal development
Other assessments	[redacted]
Data analysis	The analysis for the primary objective will evaluate differences between participants treated with inclisiran and placebo in percentage change from baseline to the Day 330 visit in LDL-C using summary statistics. Secondary efficacy endpoints will also be evaluated using summary statistics. No formal hypothesis testing is planned. Safety analyses will include summaries of the incidence of AEs, laboratory parameters, ADA measurements, vital signs, and maturation.
Key words	Homozygous familial hypercholesterolemia (HoFH), LDL-cholesterol (LDL-C), adolescents, pediatric, small interfering ribonucleic acid (siRNA)

1 Introduction

1.1 Background

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually (WHO 2017). Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated low density lipoprotein cholesterol (LDL-C) is a major risk factor for the development of CVD (Grundy et al 2004, Go et al 2014). Lowering LDL-C has been shown to reduce the risk of death or heart attack and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005, Giugliano et al 2017).

Millions of people worldwide are treated with lipid-lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death, nonfatal myocardial infarction (MI) and nonfatal stroke or associated events (Casula et al 2012). Despite the availability of statins alone or in combination with other lipid-lowering medications, with current therapies for the management of elevated LDL-C, many at-risk patients do not reach LDL-C goals (Jones et al 2012, Jameson et al 2014, Barkas et al 2015, Fitzgerald et al 2017). This is particularly true in patients with pre-existing CHD and/or diabetes or a history of familial hypercholesterolemia (FH), who are at the highest risk and require the most intensive management (Davidson et al 2005).

FH is a genetic disorder that causes high levels of LDL-C in the blood and is characterized by premature cardiovascular (CV) disease. It is caused by mutations in genes encoding proteins which regulate low density lipoprotein receptor (LDLR)-mediated clearance of LDL-C, including (in decreasing order of prevalence) LDLR, apolipoprotein B (Apo B), and proprotein convertase subtilisin/kexin type 9 (PCSK9) (Santos et al 2016). There are two clinical manifestations depending on the presence of one or two affected alleles in these genes. The milder heterozygous form (heterozygous familial hypercholesterolemia [HeFH]) results from a single affected allele. The more severe homozygous form (homozygous familial hypercholesterolemia [HoFH]) results from biallelic pathogenic variants in one of these genes, or one pathogenic variant in each of two different genes (Santos et al 2016).

Recent studies suggest that FH is more common than previously projected, with 1/160,000 to 1 in 300,000 estimated to have HoFH and 1/200 to 1 in 250 people (instead of the historical 1/500) to have HeFH (Najam and Ray 2015, Wiegman et al 2015). There are an estimated 34 million people with FH worldwide, but the majority remain undiagnosed (~90%) and current treatment is often suboptimal (Wilemon et al 2020).

Patients with HoFH have an extremely high risk of CVD. They often have LDL-C levels ranging between 3- to 6-fold higher than normal (> 13 mmol/L (500 mg/dL)) (Nordestgaard et al 2013, Wiegman et al 2015), and, if untreated, many will manifest coronary or other CV disease in childhood or adolescence (Wiegman et al 2015). The severity of the HoFH phenotype depends on the residual LDLR activity; HoFH patients who are LDLR-negative (<2% activity) have higher LDL-C levels and poorer clinical prognosis, and also tend to present earlier than LDLR-defective patients (2-25% residual activity) (Bertolini et al 2013, Kolansky et al 2008, Moorjani et al 1993, Varghese 2014). Children with HoFH primarily present with dermatological manifestations such as tendon xanthomas and interdigital

xanthomas. Ocular manifestations include xanthelasma and corneal arcus (Varghese 2014). Most individuals with HoFH experience severe atherosclerotic vascular disease by their mid twenties and aortic stenosis is common (Youngblom et al 2016).

As the degree and duration of exposure to elevated LDL-C levels increases the atherosclerotic burden, early treatment of FH to lower LDL-C levels is vital (Varghese 2014) and lipid-lowering therapy is therefore recommended to be started as early as possible in HoFH (Cuchel et al 2014). In accordance with recommendations from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, a LDL-C target of ≤130 mg/dL is recommended in children/adolescents (Expert Panel 2011). Lifestyle intervention and maximal statin therapy are the mainstays of treatment in HoFH, often in combination with ezetimibe and other lipid-modifying therapy (Cuchel et al 2014, Wiegman et al 2015). Even at the highest doses of the most efficacious statins, however, only modest reductions in LDL-C plasma levels of 10-25% are observed in most patients with HoFH. Where available, low density lipoprotein (LDL)-apheresis is regarded an important adjunctive treatment for HoFH, however, it is recognized that its use, including the age for initiation and frequency of treatment, represent a compromise between access to centers, the severity of the disease, affordability, and the patient's choice (Cuchel et al 2014).

Despite recent advances, current treatment options are still limited for children with HoFH, and the known limitations of contemporary therapies are particularly relevant among children with FH who are at the highest risk of future CV events, and thus require the most intensive and aggressive management of hypercholesterolemia (Stone et al 2014). Thus, there remains a clear unmet medical need for treatments that will lower LDL-C, especially in pediatric populations.

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

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

Small interfering ribonucleic acids (siRNAs) selectively and catalytically silence the translation of their complimentary target messenger ribonucleic acids (mRNAs) in a sequence specific manner through the formation of effector ribonucleic acid (RNA)-induced silencing complexes (RISCs), utilizing a highly specific endogenous mechanism for regulating gene expression (Ray et al 2019). Inclisiran is a chemically modified double-stranded small interfering RNA, conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RISC and directs catalytic breakdown of mRNA for PCSK9. This inhibits translation of PCSK9 protein. Reduced intrahepatic PCSK9 increases LDLR recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation (Fitzgerald et al 2017).

In the ORION clinical development program, 3660 participants with atherosclerotic CV disease (ASCVD), ASCVD risk equivalent, and/or HeFH were studied in three confirmatory 18-months phase III studies comparing inclisiran versus placebo adjunctive to maximally tolerated statin therapy, and an additional 681 participants were treated in phase I and phase II studies. In the phase III studies, treatment with inclisiran sodium 300 mg given by subcutaneous (s.c.) injection on Day 1, Day 90, and every 6 months thereafter, resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 48% to 52%, with time-adjusted average reductions of 44% to 54% sustained over 18 months (Raal et al 2020, Ray et al 2020). The efficacy of inclisiran was consistent across phase I, phase II and phase III studies, with no differences across a broad range of subpopulations.

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

Based on the established benefit-risk profile in adults, inclisiran may improve the treatment of children/adolescents with HoFH, with a low injection burden given the only twice yearly dosing.

Study CKJX839C12302 (ORION-13) is planned to investigate inclisiran in adolescents aged 12 to <18 years of age with HoFH.

1.2 Purpose

Study CKJX839C12302 (ORION-13) is a pivotal phase III study designed to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (aged 12 to <18 years) with HoFH and LDL-C >130 mg/dL (3.4 mmol/L). The use of inclisiran (as an adjunct to stable, optimal background lipid-lowering therapy) for the treatment of HoFH in adolescent patients who require additional lipid-lowering will be investigated in order to obtain needed pediatric information on inclisiran. The follow-up period (Part 2/Year 2) serves to collect longer-term data on inclisiran and also allows access of study participants to a potentially effective treatment.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective is to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C	• Percentage change in LDL-C from baseline to Day 330 (Year 1) See Section 2.1 for primary estimand
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the effect of inclisiran compared to placebo on reducing LDL-C [time-adjusted percent change] over Year 1	• Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1)
• Evaluate the effect of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and PCSK9 over time	• Percent change and absolute change in LDL-C, Apo B, lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo A1) and PCSK9 from baseline to each assessment time up to Day 720 (Year 2)
• Evaluate the safety and tolerability of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HoFH	• Incidence, severity and relationship to study drug of treatment-emergent adverse events (AEs) and serious adverse events (SAEs); vital signs; laboratory parameters; anti-drug antibodies (ADA) measurement; growth (height, weight, body mass index (BMI)); pubertal development (steroid hormones and Tanner staging)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of the test treatment versus placebo on change in LDL-C after 330 days of treatment in adolescents with HoFH who are on stable, optimal standard of care (SoC) lipid-lowering therapy, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid-lowering therapy.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of changes in additional medication(s) used for HoFH, if they occur, as would be the case in clinical practice.

The primary estimand is described by the following attributes:

1. Population: Adolescents with the HoFH condition of interest and elevated LDL-C on stable optimal SoC lipid-lowering therapy. Further details about the population are provided in Section 5.
2. Endpoint: Percentage change in LDL-C from baseline to Day 330 (Year 1).
3. Treatment of interest: The randomized treatment (the investigational treatment inclisiran or the control treatment placebo) as add-on to optimal SoC lipid-lowering therapy for HoFH. The type and dose of the concomitant lipid-lowering therapy for HoFH must remain stable during Part 1 (Year 1) of the study. Further details about the investigational treatment and control treatment are provided in Section 6.

The summary measure: difference between treatments in mean percentage change at Day 330.

2.2 Secondary estimands

Not applicable.

3 Study design

This study is a two-part (double-blind, placebo-controlled / open-label) multicenter study in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C (>130 mg/dL / 3.4 mmol/L) on stable, individualized, optimal SoC background lipid-lowering therapy (including maximally tolerated statin treatment).

The overall study duration is 748 days (excluding a safety follow-up call 30 days after the end of study (EOS) visit).

Following an approximately 4 weeks screening/run-in period, the study has two sequential parts (Figure 3-1).

- **Part 1 (Year 1):** 12 months double-blind, parallel group period in which participants will be randomized to receive either inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) s.c. or placebo (given at Days 1, 90 and 270).
- **Part 2 (Year 2):** 12 months single arm, open-label follow-up period with all participants receiving inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) s.c. Participants randomized to placebo in Part 1 will receive inclisiran starting on Day 360 ("Switch" Day 360). Participants randomized to inclisiran in Part 1 will receive placebo on Day 360. This dose of inclisiran/placebo on Day 360 will remain blinded in order to maintain the blind

for Part 1 of the study. All participants will receive subsequent doses of open-label inclisiran on Days 450 and 630.

* Inclisiran is also referred to as KJX839.

Informed consent will be obtained before initiation of any study-specific procedures (see Section 5.1 and Section 7 for details). Participants who meet the inclusion/exclusion criteria will be required to maintain their current lipid-lowering treatment unchanged for Part 1 (Year 1) of the study (including the screening/run-in period). Investigators must ensure that each participant receives individualized, optimal SoC lipid-modifying treatment [including maximally tolerated statin treatment (investigator's discretion) with or without other lipid-lowering therapy (e.g. ezetimibe)], and that this treatment was stable for ≥ 30 days before screening. Maximum tolerated dose of statin is defined as the maximum dose of statin that, at the investigator's discretion, can be taken on a regular basis without AEs that would lead to a reduction in statin dose. Intolerance to statin must be documented.

Approximately 12 participants who meet the inclusion/exclusion criteria will be randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg s.c. or placebo on Day 1 (baseline). A second and third dose of inclisiran or placebo will be given on Day 90 and Day 270, respectively. The primary endpoint will be measured at Day 330.

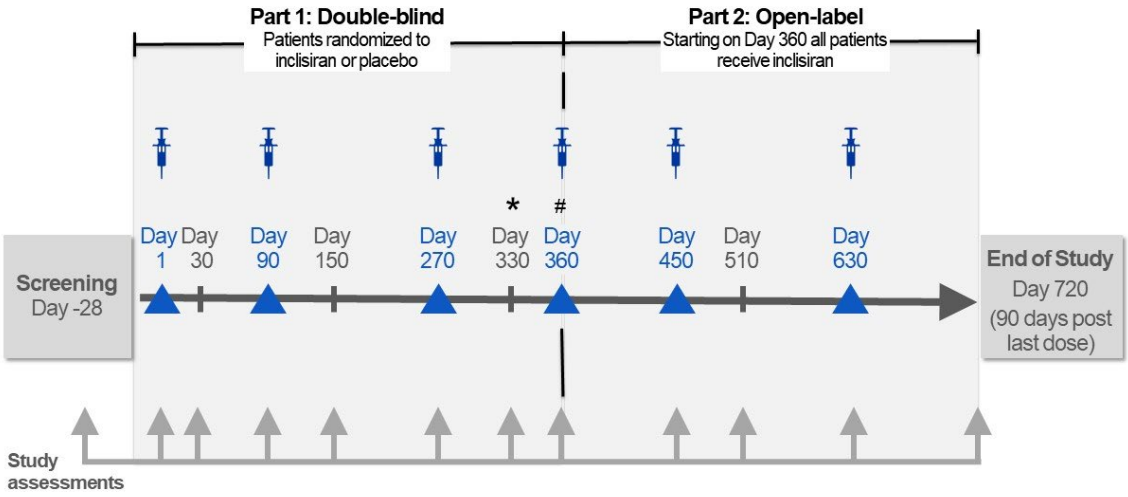
Participants initially randomized to placebo will transition to inclisiran starting on Day 360 and the study will then change to an open-label, single arm follow-up period of inclisiran sodium 300 mg s.c. (Part 2). In order to maintain the blind for Part 1 of the study, on the "switch" day (Day 360), participants randomized to placebo in Part 1 will receive blinded inclisiran, while participants randomized to inclisiran in Part 1 will receive blinded placebo. All participants will receive subsequent doses of open-label inclisiran on Day 450 and Day 630.

The EOS visit will be on Day 720. In addition, a safety follow-up call will be conducted 30 days after the last study visit or 90 days after the last administration of study drug, whatever is longer.

Inclisiran and placebo will be administered exclusively by a health care provider at the study site. Participants will be observed in the clinic for at least 4 hours post injection on Day 1 and Day 360 (i.e. first dosing of inclisiran) and for at least 30 minutes post injection for all other dosing visits before being discharged.

Participants on a documented regimen of LDL-apheresis will be allowed to continue their same regimen during the study, if needed. The apheresis schedule is not allowed to change during Part 1 (Year 1) of the study (including the screening/run-in period). The apheresis schedule must also allow that an apheresis coincides with each study visit. Study drug is to be administered the same day, after completion of apheresis (the next scheduled apheresis should not occur within 72 hours after an administration of study drug). Blood samples for LDL-C (and other laboratory assessments of efficacy and safety) must be obtained immediately before the scheduled apheresis treatment at each applicable study visit (including screening and baseline (Day 1)).

Figure 3-1 Study Design



* Primary endpoint assessed at Day 330. # "Switch Day": Participants randomized to placebo in Part 1 will start to receive inclisiran on Day 360. Participants randomized to inclisiran in Part 1 will receive placebo on Day 360 only to maintain the blind for Part 1.

4 Rationale

4.1 Rationale for study design

Part 1 of the study (Year 1) has a randomized, parallel group, placebo-controlled design to provide evidence for the efficacy, safety, and tolerability of inclisiran in adolescents with HoFH. This study design is the most appropriate trial design to answer the clinical questions of interest on the use of inclisiran in this pediatric patient population.

The open-label single-arm design for Part 2 of the study (Year 2) is appropriate to obtain additional long-term data, with a maximum number of participants exposed to the investigational drug.

A screening/run-in period of approximately 4 weeks is used to ensure the entry criteria are met (allowing test results to be received) and to ensure stabilization of individualized, optimal SoC background lipid-lowering therapy prior to randomization.

An unequal 2:1 randomization was chosen in agreement with regulatory authorities. This unequal randomization allows to maximize exposure to the active investigational drug and to enhance collection of corresponding efficacy/safety information in the pediatric study population.

4.1.1 Rationale for choice of background therapy

It is required that all participants receive individualized, optimal SoC lipid-lowering treatment for HoFH at study entry, which must remain unchanged for Part 1 (Year 1) of the study (including the screening/run-in period). Optimal SoC for adolescents with HoFH comprises maximally tolerated statin treatment with or without additional lipid-lowering treatment (e.g. ezetimibe), in accordance with international/local practice and treatment guidelines as well as regulatory authorities. No specific background medication is required during the conduct of the study; any statin and other lipid-lowering therapies approved for use in this population may be used (unless specifically prohibited per protocol; see Section 5.2 and Section 6.2.2 for details). LDL-apheresis is also allowed as adjunctive treatment per protocol in line with current practice and guidelines.

4.2 Rationale for dose/regimen and duration of treatment

The established dose regimen for inclisiran for adults is 300 mg s.c. on Day 1, Day 90 and every 6 months thereafter. Based on nonclinical and clinical data, including phase I, II and III clinical studies as well as pharmacodynamic (PD) modeling in adult participants, the same dose and dose regimen will also be used in the present study in adolescents.

In adult participants, maximum reductions in LDL-C and PCSK9 levels with inclisiran were achieved with single s.c. doses of 300 mg inclisiran sodium, with no additional meaningful benefit observed at higher doses. Three large pivotal phase III studies in adult participants with ASCVD, ASCVD risk equivalents, and/or HeFH demonstrated that the dose regimen used in the present study (300 mg inclisiran sodium s.c. on Day 1, Day 90 and every 6 months thereafter) resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 48% to 52%, with time-adjusted average reductions of 44% to 54% sustained over 18 months. This dose and regimen also showed good tolerability of inclisiran, with a safety profile similar to placebo, except for a higher incidence of AEs at the injection site with inclisiran. No patient populations were identified that required an inclisiran dose adjustment. Doses up to 900 mg (3-fold therapeutic dose) were studied which was safe and well tolerated in healthy adult subjects.

Adult data has shown that the plasma PK of inclisiran does not predict PD effects. Inclisiran is rapidly cleared from plasma in 24 to 48 hours depending on the dose level, yet because of its site and mechanism of action, its LDL-C lowering effect is measurable for more than 6 months even after a single dose, the basis of the 6-monthly dosing interval. Inclisiran is delivered to hepatocytes due to its conjugated structure with GalNAc and stored intracellularly in RISC complexes, where target protein suppression occurs for months, resulting in the disconnect between plasma PK and PD effects. In view of this time dissociation between PK and PD data, a plasma concentration vs. PD effect relationship cannot be established. From phase I study data, only a weak relationship was observed between inclisiran C_{max} and minimum LDL-C levels, due to the indirect processes involved between s.c. administration of inclisiran and reduction of LDL-C in the bloodstream. Additionally, after multiple administrations in the phase I study, inclisiran plasma exposure ratios were close to one, indicating no PK accumulation. A modelling and simulation analysis based on phase II study (ORION-1) data in adults suggest that the PD effect of inclisiran neither strengthens nor attenuates over time after repeated administrations up to 2 years of treatment.

In general, dosing and PK in adolescents are similar to those in adults (Momper et al 2013). Pharmacokinetics of inclisiran is expected to be similar in adolescents and adults as inclisiran is metabolized by exonuclease and endonuclease activity, with urinary excretion contributing to plasma elimination. Hence, the 300 mg dose, which has been shown to be efficacious, safe and well tolerated in adult phase III studies, as mentioned above, has been chosen as the dose for this study.

[redacted]

The rationale for the approximately 1 year duration of the placebo-controlled Part 1 of the study is that it allows a reasonable number of 3 injections per participant (given the twice yearly dosing regimen) and is supported by the treatment effect observed in the phase III clinical trials (up to 18 months). The duration is also suitable to assess the longer-term efficacy as well as safety and tolerability, including safety areas of special interest. The additional approximately 1-year duration of the uncontrolled Part 2 of the study is suitable to collect meaningful additional long-term data on inclisiran.

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

Part 1 of the study (which includes assessment of the primary (Efficacy) endpoint) is placebo-controlled, which is a standard design in drug development to assess efficacy and safety, and ensures that differences in outcome will be a reliable/realistic measure of the treatment effect of inclisiran. The use of placebo as a comparator is justified since all enrolled participants will be treated with individualized, optimal SoC (including maximum tolerated statin ± other lipid-lowering treatment, e.g. ezetimibe) prior to the addition of study treatment.

Part 2 (1 year Safety follow-up) does not have a comparator arm; all patients will receive inclisiran, which represents a common and appropriate design to enable the collection of additional long-term safety data for the investigational drug for a maximum number of participants.

4.4 Purpose and timing of interim analyses/design adaptations

An independent Data Monitoring Committee (DMC) will review safety data regularly during the study. A recommendation may be taken to stop or amend the study at any of these reviews. Further details are provided in Section 10.2.4 and Section 12.7.

[redacted]

[redacted]

4.5 Risks and benefits

It is widely recognized that LDL-C plays a major role in the initiation and progression of ASCVD, including in HoFH, and accumulated exposure of elevated LDL-C is causally related to the development of ASCVD. As the degree and duration of exposure to elevated LDL-C levels increases the atherosclerotic burden, early treatment of HoFH is vital. Published expert guidelines recommend a LDL-C target of ≤130 mg/dL in children/adolescents. Current treatment options to achieve these targets are still limited for children with FH and the well-known limitations of contemporary therapies are particularly relevant among pediatric patients with FH. Furthermore, even at the highest doses of the most efficacious statins, only modest reductions in LDL-C plasma levels of 10%-25% are observed in most patients with HoFH.

In adult studies in participants with ASCVD, ASCVD risk equivalents, and/or HeFH, inclisiran given on Day 1, Day 90 and every 6 month thereafter lowered LDL-C by ~50% versus placebo in participants on maximally tolerated statin therapy ± other lipid-lowering therapies. The effect was persistent over time and reversible on stopping inclisiran.

In non-clinical toxicity studies, inclisiran was not carcinogenic or genotoxic, there was no effect on paternal performance, spermatogenesis, estrous cycle, and uterine or ovarian parameters and inclisiran did not show evidence of embryolethality, fetotoxicity, or teratogenicity. In addition, there were no effects of inclisiran on the development of the F1 generation, including survival, growth, physical and reflexological development, behavior, and reproductive performance. The safety profile of inclisiran in clinical studies was generally comparable to placebo. The only Adverse drug reaction (ADR) identified in clinical studies was a higher incidence of TEAEs at the injection site with inclisiran (preferred terms of injection site erythema, injection site hypersensitivity, injection site pruritus, injection site rash, and injection site reaction). However, all TEAEs at the injection site were localized, were predominantly mild or occasionally moderate, transient, and resolved without sequelae. The impact of this side effect is further mitigated by the infrequent dosing regimen of inclisiran.

In general, the risk of participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring of safety parameters, as well as periodic review of the safety data by an independent DMC. Participants will also be observed in the clinic for at least 4 hours post injection on Day 1 and Day 360 (i.e. first dosing of inclisiran) and for at least 30 minutes post injection for all other dosing visits before being discharged.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy 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.

The benefit a participant might have by participating in the study is the close monitoring of their condition and close adherence to SoC lipid-lowering treatment.

5 Study Population

The study population consists of adolescents (12 to <18 years) with a genetic diagnosis of HoFH and LDL-C >130 mg/dL (3.4 mmol/L) on optimal SoC lipid-lowering therapy.

Approximately 12 participants meeting the eligibility criteria will be randomized.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained from the participant's parent(s)/legal representative(s) prior to the adolescent's participation in the study. A consent or assent may also be required for some participants depending on their age and local requirements. *An informed consent must be obtained from participants once they reach the local legal age of adulthood during the study.*
2. Male or female participants, ≥12 to <18 years of age at screening
3. HoFH diagnosed by genetic confirmation; see Section 16.1 (Appendix 1) for details
    - *Note: Participants with known null (negative) mutations in both LDLR alleles are not eligible (see Section 5.2 exclusion criteria #1)*
4. Fasting LDL-C >130 mg/dL (3.4 mmol/L) at the screening visit, measured at the central laboratory
5. On maximally tolerated dose of statin (investigator's discretion) with or without other lipid-lowering therapy (e.g. ezetimibe). Maximum tolerated dose of statin is defined as the maximum dose of statin that, at the investigator's discretion, can be taken on a regular basis without AEs that would lead to a reduction in statin dose
6. Participants on lipid-lowering therapies (such as statin and/or e.g. ezetimibe) should be on a stable dose for ≥ 30 days before screening with no planned medication or dose changes during study participation
7. Participants on a documented regimen of LDL-apheresis will be allowed to continue the apheresis during the study, if needed. The apheresis schedule is not allowed to change during the double-blind period of the trial and must permit that an apheresis coincides with each study visit
8. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 at screening
9. Willing to follow all study procedures including adherence to study visits, fasting blood draws, and compliance with study treatment regimens

5.2 Exclusion criteria

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

1. Documented evidence of a null (negative) mutation in both LDLR alleles
2. Previous treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9
3. History of poor response to therapy with any monoclonal antibody directed towards PCSK9 (e.g. <15% reduction in LDL-C)
4. Treatment with mipomersen or lomitapide (within 5 months of screening)

5. (i) Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or (ii) unexplained alanine aminotransferase (ALT), 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 1 week apart
6. Females who are pregnant or nursing, or who are of child-bearing potential, defined as all women physiologically capable of becoming pregnant (e.g. are menarchal) **unless** they agree to abstinence or, if sexually active, agree to the use of effective methods of contraception during dosing of study treatment. Female participants of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study. The effective contraception methods are:
    - Barrier method: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps). For UK sites only (if applicable): with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen
    - If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF)
    - Adolescent females who have not reached menarche are exempt from the above requirements; however, to be eligible for inclusion in the study, they must be willing to comply with the above requirements if they gain child-bearing potential during the study
7. 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's] judgment) if he/she participates in the clinical study
8. 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
9. Heterozygous FH
10. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    - Participants who are unable to communicate or to cooperate with the investigator
    - Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study)
    - Have any medical or surgical condition, which in the opinion of the investigator would put the participant at increased risk from participating in the study

- Persons directly involved in the conduct of the study

11. Treatment with other investigational medicinal products or devices within 30 days or five half-lives, whichever is longer
12. Planned use of other investigational products or devices during the course of the study
13. Hypersensitivity to any of the ingredients of inclisiran
14. Known history of alcohol and/or drug abuse
15. Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome
16. Major adverse cardiovascular events within 1 month prior to randomization
17. Severe concomitant non-cardiovascular disease that carries the risk of reducing life expectancy to less than 2 years
18. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the 3 years prior to randomization
19. Poorly controlled diabetes mellitus (i.e. hemoglobin A1c (HbA_{1c}) >10.0 %)
20. Previous participation in this study

6 Treatment

6.1 Study treatment

Participants will be randomized 2:1 to double-blind s.c. injections of inclisiran sodium 300 mg or placebo in Part 1 (Year 1) of the study, and subsequently all participants will receive open-label s.c. injections of inclisiran sodium 300 mg in Part 2 (Year 2) of the study.

Investigational and control drugs will not be dispensed to the participants but administered by qualified personnel at the study site.

6.1.1 Investigational and control drugs

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

Part 1 (Year 1) including "Switch" Day 360:

- Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution
- Placebo formulation to this active drug formulation

Placebo will be supplied as sterile normal saline (0.9% sodium chloride in water for injection). Placebo will be administered as a 1.5 mL s.c. injection to match the dose in the inclisiran arm.

The placebo pre-filled syringes will be blinded and look identical to the corresponding inclisiran pre-filled syringes.

Part 2 (Year 2):

- Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) in 1.5 mL solution	Solution for injection	Subcutaneous injection	Solution for injection in pre-filled syringe	Sponsor (global)
Placebo	Solution for injection	Subcutaneous injection	Solution for injection in pre-filled syringe	Sponsor (global)
* Inclisiran is also referred to as KJX839				

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Part 1 (Year 1):

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

- Inclisiran sodium 300 mg s.c.
- Corresponding placebo

Each participant will receive one injection of blinded inclisiran or placebo on Day 1, a second injection of blinded inclisiran or placebo on Day 90 and a subsequent injection of blinded inclisiran or placebo on Day 270 ("6 months dosing").

Part 2 (Year 2):

Following a "Switch" Day (Day 360), all participants will receive the same active open-label inclisiran treatment:

- Inclisiran sodium 300 mg s.c.

Participants randomized to placebo in Part 1 will receive inclisiran sodium 300 mg s.c. starting on Day 360 ("Switch" Day 360). Participants randomized to inclisiran in Part 1 will receive placebo on Day 360. This dose of inclisiran/placebo on Day 360 will remain blinded in order to maintain the blind for Part 1 of the study.

All participants will receive subsequent doses of open-label inclisiran sodium 300 mg s.c. on Days 450 and 630.

6.1.4 Treatment duration

The expected duration of the participant's involvement in the study will be approximately 748 days, which includes a screening/run-in period (28 days) and subsequent treatment with study drug (1 year double-blind, placebo-controlled followed by 1 year open-label follow-up), with the EOS visit on Day 720 (Year 2). In addition, a safety follow-up call will be conducted 30 days after the last study visit or 90 days after the last administration of study drug, whatever is longer.

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

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access (see Section 9.2).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Concomitant lipid-lowering therapy

Investigational and control drug will be given in addition to stable, individualized, optimal SoC for HoFH patients, which includes maximally tolerated dose of statin (investigator's discretion) with or without other lipid-lowering therapy (e.g. ezetimibe). Maximum tolerated dose of statin is defined as the maximum dose of statin that, at the investigator's discretion, can be taken on a regular basis without AEs that would lead to a reduction in statin dose. Intolerance to statin must be documented as medical history attributed to the statin in question in the source documentation and on an appropriate Electronic Case Report Form (eCRF).

Participants are required to maintain their current lipid-lowering treatment unchanged for Part 1 (Year 1) of the study, including the screening/run-in period (i.e. no medication or dose changes; see also Section 6.2.2). Lipid-lowering medications taken by the participant from 3 months prior to randomization through the End of the Study must be recorded, including doses, on an appropriate eCRF.

Participants on a documented regimen of LDL-apheresis will be allowed to continue their same regimen during the study, if needed. The apheresis schedule is not allowed to change during Part 1 (Year 1) of the study (including the screening/run-in period). The apheresis schedule must also allow that an apheresis coincides with each study visit. Study drug is to be administered the same day, after completion of apheresis (the next scheduled apheresis should not occur within 72 hours after an administration of study drug). Blood samples for LDL-C (and other laboratory assessments of efficacy and safety) must be obtained immediately before the scheduled apheresis treatment at each applicable study visit (including screening and baseline (Day 1)). LDL-apheresis, which the participant receives from 2 months prior to randomization through the End of the Study, must be recorded on an appropriate eCRF.

Other concomitant therapy

All other medications, procedures and significant non-drug therapies used by the participant in the 3 months prior to randomization must be recorded on the appropriate eCRFs, independent of whether they will be continued during the study or not. Each concomitant drug must be individually assessed against all exclusion criteria.

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

If in doubt the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue study medication.

6.2.2 Prohibited medication

Participants need to be on stable background lipid-lowering therapy for Part 1 (Year 1) of the study (including the screening/run-in period), i.e. the type and dose of lipid-lowering therapy must not be altered during this time. Use of the treatments displayed in Part A of Table 6-2 below are therefore not allowed to be newly added at any time during Part 1 (Year 1) of the study, including the screening/run-in period.

In addition, use of the treatments displayed in Part B of Table 6-2 below are not allowed at any time during the entire study duration.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken with study treatment
PART A: Medications not allowed to be newly added during Part 1 (Year 1) of the study		
Medications* prescribed to lower LDL-C (e.g., statins, ezetimibe, niacin, colesevelam, bile acid absorption inhibitors, LDL-apheresis) **For monoclonal antibodies directed towards PCSK9, mipomersen and lomitapide, see Part B*	Part 1 (Year 1) of the study (including screening/run-in period)	None
Any medication taken for the purpose of lipid-lowering, including over-the-counter or herbal therapies	Part 1 (Year 1) of the study (including screening/run-in period)	None
PART B: Regular prohibited medications		
Monoclonal antibodies directed towards PCSK9	Full Study Duration	Discontinue study treatment
Mipomersen, lomitapide	Full Study Duration	Discontinue study treatment
Other investigational treatments	Full Study Duration	Discontinue study treatment

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her entire participation in the trial. 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 the participant's parent(s)/legal representative(s) / participant (if applicable) signing the ICF, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment blinding

Part 1 (Year 1)

Part 1 of the study is randomized, double-blind and placebo-controlled. Participants, investigator staff, persons performing the assessments, and the clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until at least database lock for all Part 1 (Year 1) data, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: the independent statistician and programmer who need to have access to prepare interim analysis reports for the DMC [redacted] These personnel will not be involved in any other trial activities. (2) The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, and appearance.

[redacted]

Any [redacted] anti-drug antibodies and results from lipid/lipoprotein/PCSK9 measurements after the first administration of study drug until the Day 360 visit should be blinded for participants, investigator staff, persons performing the assessments and the CTT.

[redacted]

Unblinding will occur in the case of participant emergencies and at the conclusion of the study. Unblinding of the CTT and other parties (as needed) will also occur after the Year 1 database lock, which is planned after all participants have completed the Day 360 visit.

Part 2 (Year 2)

Due to the single-arm, open-label design, treatment in Part 2 of the study will be open to participants, investigator staff, persons performing the assessments, and the CTT.

In order to maintain the blind for Part 1 of the study, on the "switch" day (Day 360), participants randomized to placebo in Part 1 will receive blinded inclisiran, while participants randomized to inclisiran in Part 1 will receive blinded placebo.

6.5 Dose escalation and dose modification

Dose adjustments of study treatment are not permitted.

6.5.1 Dose modifications

Dosing with study treatment should be temporarily interrupted as follows:

Part 1 (Year 1):

- If from the Day 150 visit onwards a participant's LDL-C is below 25 mg/dL (0.65 mmol/L) at the last visit prior to the time of the next scheduled dose, the IRT will assign blinded placebo to be administered at the next scheduled dosing visit independent of which treatment group the participant was randomized to; i.e. if the participant was treated with inclisiran, study treatment will be interrupted in a blinded fashion via the IRT.

Part 2 (Year 2):

- If from the Day 450 visit onwards a participant's LDL-C is below 25 mg/dL (0.65 mmol/L) at the last visit prior to the time of the next scheduled dose, the investigator should withhold the dose at the next scheduled dosing visit. This will be flagged accordingly by the central laboratory.
- These dose interruptions must be recorded on an appropriate eCRF.

Treatment discontinuation is mandatory for specific events listed in Section 9.1.1.

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

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

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

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

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 >2.0x 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.

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

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

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI

Disease	Assessment
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)	• Ceruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin
ANA (antinuclear antibody), ASMA (anti-smooth muscle antibody), CD (carbohydrate-deficient), CHF (chronic heart failure), CMV (cytomegalovirus), EBV (Epstein-Barr virus), ERCP (Endoscopic retrograde cholangiopancreatography), HAV (hepatitis A virus), HBc (hepatitis B core), HBsAG (HBV surface antigen), HBV (hepatitis B virus), HCV (hepatitis C virus), HEV (hepatitis E virus), HSV (herpes simplex virus), Ig (Immunoglobulin), MCV (mean corpuscular volume), MRI (Magnetic Resonance Imaging)	

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, thyroid stimulating hormone (TSH); CVD / ischemic hepatitis – ECG, prior hypotensive episodes; type 1 diabetes / glycogenic hepatitis).

In addition to the causes listed in Table 6-3, metabolic disorders should be excluded in children by measuring the following parameters: urinary ketones, ammonia, glucose, lactate, lactate:pyruvate ratio, alpha fetoprotein, arterial blood gas analysis.

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

[redacted]

6.6.2 Recommended treatment of adverse events

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

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

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

6.6.3 Emergency breaking of assigned treatment code

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

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

- protocol number
- name
- participant number

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

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

6.7 Preparation and dispensation

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

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

Investigator staff will identify the study medication kits to administer 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 using the medication kit, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by 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

Investigational and control drugs will not be dispensed to the participants. Study drug injections will be performed exclusively at the study site by qualified clinical study site staff under the supervision of the investigator or designee.

The site of injection is the abdomen, alternating sides for each injection. Injections should not be done into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

Participants will be administered one s.c. injection of study drug at pre-defined visits as specified in the Assessment Schedule (Table 8-1) and summarized below.

- **Part 1:** Each participant will receive one injection of blinded inclisiran or placebo on Day 1, a second injection of blinded inclisiran or placebo on Day 90 and a subsequent injection of blinded inclisiran or placebo on Day 270 ("6 months dosing").
- **Part 2:** Participants randomized to placebo in Part 1 will receive a single injection of blinded inclisiran on Day 360, while participants randomized to inclisiran in Part 1 will receive a single injection of blinded placebo on Day 360. All participants will receive subsequent doses of open-label inclisiran on Day 450 and Day 630.

Injections will be administered after all other study assessments have been completed for the visit. At the Randomization (Day 1) and Day 360 visits, vital signs (blood pressure and pulse) and ADA (Day 1 only) will be assessed a second time 4 hours after injection [redacted]

Participants must be observed in the clinic for at least 4 hours post injection on Day 1 and Day 360 (i.e. first dosing of inclisiran) and for at least 30 minutes post injection for all other dosing visits before being discharged.

Should a participant develop signs or symptoms of anaphylaxis when study drug is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as possible).

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

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

7 Informed consent procedures

Eligible participants may only be included in the study after the participant's parent(s)/legal representative(s) or the participant (if applicable) provides (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

In cases where the participant's parent(s)/legal representative(s) give consent, 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 should indicate assent by personally signing and dating the written informed consent document or a separate assent form (as per local requirements). An informed consent must be obtained from the participant once he/she reaches the local legal age of adulthood during the study.

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 and participant assent where applicable must be documented in the participant's source documents.

Novartis will provide to investigators in separate documents proposed ICF(s) and age appropriate assent form(s) that comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and are considered appropriate for this study. Any changes to the proposed consent/assent forms suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the informed consent and should be discussed with the participant's parent(s)/legal representative(s) and, to the extent possible, 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/assent and then must be discussed with the participant's parent(s)/legal representative(s) and, to the extent possible, the participant.

Women of child bearing potential and her parent(s)/legal representative(s) 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.

8 Visit schedule and assessments

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

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

Participants who prematurely and permanently discontinue from study treatment will continue to be followed up in the study according to the Assessment Schedule unless informed consent is withdrawn.

Participants who prematurely discontinue the study for any reason [e.g. if a participant's parent(s)/legal representative(s) / a participant (if applicable) decide to prematurely and permanently discontinue the participant from study treatment and decline further follow-up visits] should be scheduled for an EOS visit as soon as possible. At this final visit, AEs and concomitant medications should be recorded in the corresponding eCRFs.

Participants will have to comply with the following restrictions:

- Participants should have fasted for at least 8 hours for all visits for fasting lipids/lipoproteins/PCSK9 and glucose blood samples (if the participant has not fasted, the collection of laboratory evaluations must be rescheduled)
- Participants must refrain from unaccustomed strenuous physical exercise for 48 hours before the screening and any study visit until the follow-up has been completed
- Blood donation will not be allowed at any time during the study

If an extraordinary situation (like e.g. during the coronavirus disease (COVID)-19 pandemic) limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff / home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the extraordinary situation until it is safe for the participant to visit the site again. This also includes administration of study treatment by qualified study site personnel at a location other than the study site.

Table 8-1 Assessment Schedule

Period	**Screening[1]**	**Part 1 (Double-blind, placebo-controlled)**						**Part 2 (Open-label, single-arm)**				**Follow-up**
Visit Name	**Screening**	**Day 1 (Baseline & 1st Treatment)**	**Day 30**	**Day 90**	**Day 150**	**Day 270**	**Day 330**	**Day 360 ("Switch Day")[2]**	**Day 450**	**Day 510**	**Day 630**	**Day 720 (End of Treatment/ Study)[3]**	**Safety follow-up (last visit +30 days)[4]**
Days	**-28**	**1**	**30**	**90**	**150**	**270**	**330**	**360**	**450**	**510**	**630**	**720**	**750**
Informed consent / assent (as applicable)	X												
Inclusion / Exclusion criteria	X												
Demography	X												
Pregnancy Test (serum)[5]	X												
Pregnancy test (urine)[5]		S						S				S	
Relevant medical history/current medical conditions	X												
Medical history Statin intolerance (if applicable)	X												
Smoking & Alcohol history	X												
Body weight / waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	
Body Height	X	X			X		X			X		X	
Vital Signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam (complete)	S						S					S	

Period	**Screening[1]**	**Part 1 (Double-blind, placebo-controlled)**						**Part 2 (Open-label, single-arm)**				**Follow-up**
Visit Name	**Screening**	**Day 1 (Baseline & 1st Treatment)**	**Day 30**	**Day 90**	**Day 150**	**Day 270**	**Day 330**	**Day 360 ("Switch Day")[2]**	**Day 450**	**Day 510**	**Day 630**	**Day 720 (End of Treatment/ Study)[3]**	**Safety follow-up (last visit +30 days)[4]**
Days	**-28**	**1**	**30**	**90**	**150**	**270**	**330**	**360**	**450**	**510**	**630**	**720**	**750**
Physical Exam (abbreviated)		S	S	S	S	S		S	S	S	S		
12-lead ECG	X						X					X	
Study drug administration[7,8]		X		X		X		X	X		X		
IRT call	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant lipid-lowering therapy	X	X	X	X	X	X	X	X	X	X	X	X	
(Other) Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Surgical/Medical Procedures	X	X	X	X	X	X	X	X	X	X	X	X	
LDL-apheresis recording (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting LDL-C	X	X		X	X	X	X	X	X	X	X	X	
Fasting PCSK9		X		X	X		X	X		X		X	
Full fasting lipid / lipoprotein profile[9]		X			X		X	X		X		X	
Anti-drug antibodies[10]		X			X		X			X		X	
Full chemistry[11]		X					X					X	
Limited chemistry[11]	X		X	X	X	X		X	X	X	X		
Hematology	X	X	X		X		X		X	X		X	
Sexual hormones		X					X					X	
Urinalysis	X	X	X		X		X		X	X		X	

Period	**Screening[1]**	**Part 1 (Double-blind, placebo-controlled)**						**Part 2 (Open-label, single-arm)**				**Follow-up**
Visit Name	**Screening**	**Day 1 (Baseline & 1st Treatment)**	**Day 30**	**Day 90**	**Day 150**	**Day 270**	**Day 330**	**Day 360 ("Switch Day")[2]**	**Day 450**	**Day 510**	**Day 630**	**Day 720 (End of Treatment/ Study)[3]**	**Safety follow-up (last visit +30 days)[4]**
Days	**-28**	**1**	**30**	**90**	**150**	**270**	**330**	**360**	**450**	**510**	**630**	**720**	**750**
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site reaction assessment		X	X	X	X	X	X	X	X	X	X	X	
Neurological Examination		X					X					X	
Tanner staging / menarche		X			X		X			X		X	
[redacted]													
Safety Follow up Call[14]													S

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] Screening / run-in period
[2] Day 360 ("Switch Day") is a shared visit, i.e. the end of Part 1 and the start of Part 2 of the study
[3] For participants who prematurely discontinue the study for any reason [e.g. if a participant's parent(s)/legal representative(s) / a participant (if applicable) decide to prematurely and permanently discontinue the participant from study treatment and decline further follow-up visits] an EOS visit should also be scheduled as soon as possible.
[4] 30 days after the last study visit or 90 days after the last administration of study drug, whatever is longer
[5] Only in females of child-bearing potential (prior to study treatment administration, if applicable)
[6] On Day 1 and Day 360 vital signs will be measured prior to injection and 4 hours post injection; at all other visits, vital signs will be measured only once (prior to injection, if applicable).
[7] Participants will be observed in the clinic for at least 4 hours post injection on Day 1 and Day 360 and for at least 30 minutes post injection for all other dosing visits.

Period	**Screening**[1]	**Part 1 (Double-blind, placebo-controlled)**						**Part 2 (Open-label, single-arm)**					**Follow-up**
Visit Name	**Screening**	**Day 1 (Baseline & 1st Treatment)**	**Day 30**	**Day 90**	**Day 150**	**Day 270**	**Day 330**	**Day 360 ("Switch Day")**[2]	**Day 450**	**Day 510**	**Day 630**	**Day 720 (End of Treatment/ Study)**[3]	**Safety follow-up (last visit +30 days)**[4]
Days	**-28**	**1**	**30**	**90**	**150**	**270**	**330**	**360**	**450**	**510**	**630**	**720**	**750**

[8] For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as possible).
[9] Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, VLDL-C and Apo A1 in addition to the separately listed LDL-C (see Section 8.3 for details)
[10] ADA serum samples will be collected on Day 1 prior to injection and 4 hours after injection. At all other visits, one sample only will be collected.
[11] Diagnosis of diabetes based on fasting plasma glucose (FPG) should be verified by a repeat FPG within 6 weeks of the initial observation
[redacted]
[14] SAEs to be reported to Novartis Safety (see Section 10.1.3 for details)

8.1 Screening

Screening activities (Table 8-1) must be initiated only after the ICF (and assent if applicable) has been signed.

It is not permissible to re-screen a participant if s/he fails the initial screening. In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant is not eligible for the study.

8.1.1 Information to be collected on screening failures

Participants for whom an ICF was signed and who are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on an appropriate eCRF. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure participants. If the screen failure participant experienced a SAE during the screening phase (see SAE section for reporting details), SAE information must additionally be collected. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

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

8.2 Participant demographics/other baseline characteristics

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

Participant demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity, relevant medical history/current medical condition present before informed consent was signed (where possible, diagnoses and not symptoms will be recorded), concomitant lipid-lowering therapy, as well as relevant laboratory tests.

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

8.3 Efficacy

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

All efficacy biomarkers will be analyzed at a Central laboratory(ies). Participants will be in a fasted state for all efficacy laboratory assessments. At dosing visits, specimens for the analysis of efficacy biomarkers must be collected prior to study drug administration. Details regarding the collection, processing, shipping and storage of the samples will be provided in a Laboratory Manual. The Laboratory Manual will also provide details about prioritization when blood volume is restrictive (Section 16.7 (Appendix 7)).

8.3.1 LDL-cholesterol

The primary efficacy assessment will be LDL-C. Samples for LDL-C will be collected at screening and on Days 1, 90, 150, 270, 330, 360, 450, 510, 630 and 720 (Table 8-1).

After randomization (Day 1) until the Day 360 visit, the results from the LDL-C laboratory assessments must be blinded to participants, investigator staff, persons performing the assessments, and the CTT.

In participants receiving LDL-apheresis, LDL-C must be measured immediately before the scheduled apheresis treatment.

8.3.2 Other efficacy biomarkers

Other efficacy assessments will include:

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

Samples for these additional efficacy biomarkers will be collected on Days 1, 90 [redacted], 150, 330, 360, 510 and 720 (Table 8-1).

After randomization (Day 1) until the Day 360 visit, the results from the efficacy laboratory assessments must be blinded to participants, investigator staff, persons performing the assessments, and the CTT.

[redacted]

[redacted]

8.3.5 Appropriateness of efficacy assessments

LDL-C reduction, which is an effect of the mechanism of action of inclisiran, is a well-defined biomarker and standard assessment in clinical trials, and the primary endpoint of the study. LDL-C reduction is an accepted surrogate for CV risk reduction, e.g. for statins and PCSK9-blocking monoclonal antibodies. While multiple factors contribute to the development of ASCVD, strong and consistent evidence from genetics, epidemiology, Mendelian randomization studies, and randomized trials, have established that among these factors, LDL-C is not merely a biomarker of increased risk, but a causal and modifiable factor in ASCVD (Ference et al 2017).

Laboratory tests and other assessments related to the secondary [redacted] are in line with the expected efficacy of inclisiran. [redacted]

8.4 Safety

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

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

A complete physical examination will be performed at the screening visit, the Day 330 visit and at the Study Completion (EOS) visit. An abbreviated physical examination will be performed at other study visits detailed in Table 8-1. Details on what is included in the complete and abbreviated physical exams and the requirements to perform vital signs assessment and height / weight measurements are provided in Table 8-2.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	**A complete physical examination** will include the examination of height, weight, general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, vital signs, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Tanner staging (Section 8.4.4.1) will additionally be performed at selected visits. **A short physical examination** will include the examination of general appearance and vital signs as well as other examinations based on Investigator discretion. Height and weight will additionally be assessed as per the Schedule of Assessment. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to informed consent signature must be recorded on the appropriate eCRF that captures Medical history. Significant findings made after informed consent signature, which meet the definition of an AE, must be recorded as an AE.
Vital signs	Vital signs include blood pressure and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.2 (Appendix 2).
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Height should be taken using a calibrated stadiometer.

8.4.1 Laboratory evaluations

Specimens will be obtained at the time points detailed in the Assessment Schedule (Table 8-1). Details on what is included in hematology, chemistry, sexual hormones, and urinalysis

laboratory evaluations are provided in Table 8-3. Efficacy laboratory assessments (e.g. LDL-C) are described in Section 8.3.

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

Clinically notable laboratory findings are defined in Section 16.2 (Appendix 2).

A table, which provides the maximum, allowable blood-draw volumes by weight, can be found in Section 16.7 (Appendix 7). The Laboratory Manual will also provide details about prioritization when blood volume is restrictive.

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, basophils, eosinophils, monocytes, lymphocytes), platelet count
Chemistry	**Full chemistry:** AST, ALT, ALP, GGT, total bilirubin, direct and indirect bilirubin (if total bilirubin >2xULN), C(P)K, bicarbonate, uric acid, creatinine, blood urea nitrogen (BUN), eGFR*, sodium, potassium, calcium, phosphate, chloride, albumin, total protein, glucose (fasting)**, HbA_{1C} **Limited chemistry:** ONLY: AST, ALT, ALP, GGT, total bilirubin [fractionated bilirubin (if total bilirubin >2x ULN)], C(P)K, creatinine, eGFR*, glucose (fasting)**, HbA_{1C}
Anti-drug antibodies	see Section 8.4.1.1
Sexual hormones	Gonadal hormones (estradiol for females and testosterone for males), luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol and dehydroepiandrosterone (DHEA)
Urinalysis	Dipstick measurements for: specific gravity, pH, glucose, protein (total), ketones, bilirubin, urobilinogen, nitrite, hemoglobin (blood), leukocytes esterase If dipstick measurement results are positive (abnormal), microscopic examination will be performed
Pregnancy test	Serum / Urine pregnancy test (see Section 8.4.3)
Other	Tryptase (only as required***)

* eGFR will be calculated using the Schwartz age-specific eGFR formula as follows:

- For height in cm and serum creatinine (sCr) in mg/dL: eGFR (mL/min/1.73 m^2) = 0.413 x (height/sCr)
- For height in cm and sCr in µmol/L: eGFR (mL/min/1.73^2) = 36.5 x (height/sCr)

** Diagnosis of diabetes based on FPG should be verified by a repeat FPG within 6 weeks of the initial observation
*** Should a participant develop anaphylaxis on days when inclisiran is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as possible)

8.4.1.1 Anti-drug antibodies

Serum samples for the analysis of formation of ADA will be collected at the time points detailed in the Assessment Schedule (Table 8-1).

On Day 1, ADA serum samples will be collected prior to injection and 4 hours after injection. At all other visits, one sample only will be collected.

The results from ADA after the first administration of study drug until the Day 360 visit must be blinded to participants, investigator staff, persons performing the assessments, and the CTT.

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

8.4.2 Electrocardiogram (ECG)

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

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

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially before administration of study treatment.

Any identifier details must be redacted e.g. participant initials, date of birth.

Clinically significant abnormalities must be recorded on the eCRF as either Medical history/Current medical condition or AEs as appropriate.

8.4.3 Pregnancy

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female adolescent participants who are menarchal or who become menarchal during the study.

Serum/urine pregnancy tests will be performed for all female adolescents of child-bearing potential according to the Assessment Schedule (Table 8-1). A positive urine pregnancy test should be confirmed with a serum pregnancy test. Additional pregnancy tests may be performed at the investigator's discretion during the study and/or if requested by local requirements.

Participants becoming pregnant must be discontinued from study drug. However, a participant may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

All menarchal adolescents and their parent(s)/legal representative(s) should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age as well as, factors such as precocity, socio(educational) economic and familial background. These discussions with the participant and her parent(s)/legal representative(s) are therefore best performed by investigators familiar with the adolescent participant and her family and should be guided by

requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the participant and her parent(s)/legal representative(s). The privacy of the participant should be considered in accordance with the local law and ethics.

8.4.4 Other safety evaluations

8.4.4.1 Pubertal development

In addition to the assessment of height, weight and sexual hormones (see Section 8.4.1), the following parameters will be monitored to evaluate pubertal development, at the time points detailed in the Schedule of Assessment (Table 8-1):

- Menarche (in females)
- Tanner staging of sexual development (in males and females)

Tanner staging will performed by a physician who (re-)familiarized him/herself with the Tanner stage assessment (in case needed). The results (stages 1-5 for the respective characteristics) will be recorded on an appropriate eCRF. Once a participant reaches Tanner stage 5, evaluations can be discontinued. For females, the date of menarche will also be recorded on an appropriate eCRF.

8.4.4.2 Neurological evaluation

A full neurological evaluation will be performed as per the Schedule of Assessment (Table 8-1). This should include assessment of motor function, sensory function, tone and reflexes and cerebellar function as detailed in Section 16.5 (Appendix 5).

Clinically significant abnormalities must be recorded on the eCRF as either Medical history/Current medical condition or AEs as appropriate.

8.4.4.3 Injection site reactions

Injection site reactions (ISRs) should be monitored at each visit from the randomization (Day 1) visit onwards (Table 8-1) and through additional contacts with the participant between visits as needed. 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.

8.4.4.4 Anaphylactic reactions

Potential anaphylactic reactions should be assessed by Sampson criteria (see Section 16.6 (Appendix 6)). If Samson criteria are positive, confirmation by elevation of tryptase in blood plasma should be obtained within 30 minutes of the onset of anaphylaxis (or as soon as possible).

8.4.4.5 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:

- HbA_{1c} becomes ≥6.5% and/or
- Two consecutive values of FPG are ≥126 mg/dL (7.0 mmol/L)
- If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will need to be collected

'Worsening of glycemic control' should be reported as AE on the eCRF in participants with a medical history of disease (HbA_{1c} ≥6.5% at baseline) when:

- HbA_{1c} increases from baseline >0.5%
- New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level

8.4.5 Appropriateness of safety measurements

The safety assessments selected for this trial are standard for this indication/adolescent population. They take into consideration safety data from adult studies and consultations with Health Authorities and are in accordance with guidelines (ICH Harmonised Guideline Addendum to ICH E11 (ICH E11 (R1) 2017)).

8.5 Additional assessments

[redacted]

8.5.2 Biomarkers

No exploratory biomarkers will be evaluated in this study. The assessment of lipids/lipoproteins and PCSK9 is discussed in Section 8.3.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the participant's parent(s)/legal representative(s) / participant (if applicable) 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. After study treatment discontinuation, participants should remain in the study and complete other study visit procedures as per the Assessment Schedule, unless consent is withdrawn (Section 9.1.2), preferably in writing.

Study treatment must be discontinued under the following circumstances:

- Participant's parent(s)/legal representative(s) / participant (if applicable) decision
- Pregnancy
- Use of prohibited treatment as per details in the prohibited treatment section (Table 6-2)
- Following emergency unblinding
- Any situation in which study participation might result in a safety risk to the participant
- Severe and persistent (>14 days despite appropriate treatment) reactions at the injection site and any confirmed anaphylactic reactions
- Unexplained increases in transaminases (ALT or AST) or total bilirubin as follows:
  - ALT or AST >5x ULN
  - ALT or AST >3x ULN for more than 2 weeks
  - ALT or AST >3x ULN and (total bilirubin >2x ULN or INR >1.5)
  - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - The investigator should evaluate to see if other causes for the laboratory abnormalities are immediately apparent, such as obstructive gall bladder or bile duct disease, viral or alcoholic hepatitis, malignancy involving the liver, congestive hepatopathy, other hepatotoxins or heritable disorders.
- Unexplained C(P)K values >5x ULN confirmed by repeat test when the C(P)K elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction

- Any other laboratory abnormalities that, in the judgment of the investigator, prevents the participant from continuing study treatment

In addition, adolescent females who gain child-bearing potential during the study and are unwilling to comply with the requirements for contraception as outlined in Section 5.2 will be excluded from receiving further study drug.

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.

Study treatment may be restarted at the discretion of the investigator, if the reason for discontinuation has resolved. Every effort should be made to restart study treatment, if deemed appropriate by the investigator. Study treatment is **not** allowed to be re-started following initiation of prohibited medication that requires study drug discontinuation (Table 6-2).

Participants who discontinue study treatment or for whom the participant's parent(s)/legal representative(s) / participant (if applicable) decide that they do not to wish the participant to participate in the study further, should NOT be considered withdrawn from the study UNLESS informed consent was withdrawn (see Withdrawal of informed consent, Section 9.1.2). **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's parent(s)/legal representative(s) / participant / pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, the participant's parent(s)/legal representative(s) or with another pre-designated person. 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 and/or via telephone/email contact:

- New / concomitant treatments
- AEs/SAEs

Where possible, all clinic visit assessments should be performed according to Table 8-1.

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

If discontinuation occurs because the treatment code has been broken, please refer to the Emergency breaking of treatment code section (Section 6.6.3).

9.1.2 Withdrawal of informed consent

Participants' parent(s)/legal representative(s) / participants (if applicable) may voluntarily withdraw consent for the participant to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant's parent(s)/legal representative(s) / participant (if applicable):

- Does not want the participant to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participants' parent(s)/legal representative(s) / participants (if applicable) therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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

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

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the Assessment Table (Table 8-1).

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

Any adolescent's (for whom the parent(s)/legal representative(s) provided informed consent) request to be withdrawn from the study should be respected and discussed in detail with the participant's parent(s)/legal representative(s) and the local investigator before acting upon the request.

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 / participant's parent(s)/legal representative(s), e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until the end of each study part while due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

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

9.2 Study completion and post-study treatment

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

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

The decision whether there will be a post-study treatment with inclisiran in pediatric patients with HoFH will not occur before an adequate benefit-risk assessment. Should the assessment be positive and a post-study treatment be initiated, participants who complete the trial may have the opportunity to join such post-study treatment.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events 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 in the AE eCRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:

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

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported

4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding with study treatment

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

- Dose not changed
- Drug interrupted/withdrawn

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

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

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory abnormalities are included in Section 16.2 (Appendix 2).

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

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

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after informed consent was provided and until 30 days after the last study visit (or 90 days after the last administration of study drug, whatever is longer) must be reported to Novartis Safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAE reporting time frames are as follows:

1. Screen failures: SAEs occurring after informed consent was provided until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized participants: SAEs collected between time informed consent was provided until 30 days after the last study visit (or 90 days after the last administration of study drug, whatever is longer) must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Any SAE experienced after the 30 days period following the last study visit (or 90 days after the last administration of study drug, whatever is longer) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the participant's parent(s)/legal representative(s) / participant (if applicable) must be asked to read and sign a pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be

followed up until one year after the baby was due to be born to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

Please refer to Table 16-3 (Section 16.3 (Appendix 3)) 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 (Section 16.3 (Appendix 3)). Requirements for follow-up of potential DILI cases is provided in Section 6.5.2.1.

- Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin, direct and indirect bilirubin, PT/INR, ALP, GGT, GLDH, albumin and C(P)K) 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 an appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant, if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Renal safety monitoring

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

Every renal laboratory trigger or renal event as defined in Table 16-6 (Section 16.4 (Appendix 4)) should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-7 (Section 16.4 (Appendix 4)).

10.2.3 Other safety monitoring

The frequency and severity of the AEs listed below will be monitored during the study. They will be reviewed by the DMC at regular intervals.

- ISRs (see also Section 8.4.4.3), hypersensitivity reactions and immune-mediated reactions
- Hepatobiliary AEs and liver-related biochemical abnormalities (see also Section 6.5.2.1 and Section 10.2.1)
- Musculoskeletal AEs and muscle-related biochemical abnormalities (e.g. C(P)K)
- Neurological or psychiatric AEs
- New onset of diabetes or worsening of glycemic control in diabetics (see also Section 8.4.4.5)

10.2.4 Data Monitoring Committee

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

It is anticipated that the DMC will review safety data 90 days after all participants received the first injection of study drug and every 3 months thereafter until EOS, unless requested otherwise by the DMC.

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

10.2.5 Steering Committee

The Steering Committee (SC) will be established comprising representatives associated with the trial, but not being members of the DMC. Novartis representatives from the Global Clinical Team can be present at the SC meetings.

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

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

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

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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, ECGs, 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 signed ICF and the original signed assent form, if applicable (a signed copy is given to the participant's parent(s)/legal representative(s)/ participant (if applicable)).

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

Details of the statistical analysis and data reporting will be summarized in the Statistical Analysis Plan (SAP) document finalized before data lock. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Efficacy and safety analyses of Part 1 data will be performed after all participants have completed the Day 360 visit or discontinued prior to the Day 360 visit. All available data from the clinical database will be included in the analysis. This analysis will be unblinded and reviewed by the CTT.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises of all randomized participants with the exception of those mis-randomized participants who did not receive study drug. Mis-randomized participants are defined as not qualified for randomization and are inadvertently randomized into the study. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. The FAS will be used in analyses for the primary, secondary, [redacted] objectives.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received. This will be the primary population for the safety analyses.

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented. For continuous data, the 1st and 3rd quartile will also be presented by treatment group.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group. Histories of statin intolerance and underlying genetic mutation will be summarized by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below.

The number of participants dosed at each dosing visit, number of study doses administered, duration of exposure in days, and dose administered will be summarized by treatment group. The number of study doses administered will be summarized by study part and overall (Parts 1 and 2 combined).

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

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

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

12.4.1 Definition of primary endpoint and estimand

The primary estimand is defined in Section 2.1. The primary endpoint is the percentage change in LDL-C from the pre-dose baseline measurement to the Day 330 visit.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will summarize change from baseline using summary statistics to characterize change from baseline in LDL-C by treatment group and the difference between treatment groups at the Day 330 time point. No formal hypothesis testing is planned.

12.4.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events are expected.

12.4.4 Handling of missing values not related to intercurrent event

The primary endpoint will not have missing data imputed. Only data from the Day 330 visit time point and baseline data needed to evaluate change from baseline in LDL-C will be included in the primary analysis.

12.4.5 Sensitivity analyses for primary endpoint/estimand

No sensitivity analyses are planned.

12.4.6 Supplementary analysis

Supplementary analyses of LDL-C percent change from baseline to Day 330 may be performed in select subgroups.

Details of any supplementary analyses that will be performed, including subgroups included in this analysis, will be specified in the SAP.

12.4.7 Supportive analyses

A linear mixed-effects model for repeated measures (MMRM) analysis will be used as a covariate-adjusted analysis of the difference in percent change from baseline to Day 330 in LDL-C. The MMRM will include fixed effects for treatment, visits, interaction between

treatment and visits, and baseline LDL-C. The Restricted Maximum Likelihood (REML) estimation approach will be used with covariance structure set as "Unstructured". Two-sided 95% confidence intervals for the difference between treatment groups will be provided. Full details of the supportive analysis will be provided in the SAP.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary efficacy endpoints include:

- Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1)
- Percent change and absolute change in LDL-C from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in Apo B from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in Lp(a) from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in non-HDL-C from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in total cholesterol from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in triglycerides from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in HDL-C from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in VLDL-C from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in Apo A1 from baseline to each assessment time up to Day 720 (Year 2)
- Percent change and absolute change in PCSK9 from baseline to each assessment time up to Day 720 (Year 2)

Descriptive summaries by treatment group will be presented.

12.5.2 Safety endpoints

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

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

In particular, summary tables for adverse events (AEs) will summarize only treatment emergent AEs.

Adverse events

The number (and percentage) of participants with treatment emergent adverse events in Part 1 and Part 2 will be summarized in the following ways:

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

The number (and percentage) of participants with treatment emergent serious adverse events in Part 1 and Part 2 will be summarized in the following ways:

- by treatment, primary system organ class and preferred term alphabetically.
- by treatment, primary system organ class and preferred term alphabetically for treatment emergent serious AEs related to study drug.

A separate summary will be provided for adverse events leading to death.

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

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

Vital signs

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

Baseline and change from baseline in height, weight, and BMI will be assessed using age- and sex-adjusted z-scores and summarized by treatment group.

Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit. Shift tables using the low, normal, or high classification will be used to compare baseline to the worst on-treatment value by treatment group for Part 1 and overall. The number (and percentage) of participants meeting clinically significant criteria will be provided by treatment group for Part 1 and overall.

Immunogenicity

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

Other safety evaluations

Baseline Tanner stage will be summarized by treatment group. Shift from baseline in Tanner stage and menarche in female participants without menarche at baseline will be summarized by treatment group.

12.5.3 Biomarkers

Analyses of PCSK9 and lipids/lipoproteins are discussed in Section 12.5.1. No additional biomarkers will be evaluated in this study.

[redacted]

[redacted]

12.7 Interim analyses

Interim analyses are planned for the monitoring of participants' safety and will be performed following the schedule specified in Section 10.2.4. Interim safety analyses before the unblinding for the analysis of Part 1 of the study will be performed by an independent statistician/programmer who will not be involved in the trial conduct. The interim results will be reviewed by the independent DMC.

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size for this study was selected based on feasibility.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF(s), written assent form (if applicable), consent/assent 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 European Union Drug Regulating Authorities Clinical Trials (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 that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) 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

References are available upon request

Baigent C, Keech A, Kearney PM, et al (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet; 366:1267-78.

Barkas F, Liberopoulos EN, Kostapanos MS, et al (2015) Lipid target achievement among patients with very high and high cardiovascular risk in a lipid clinic. Angiology; 66(4):346-53.

Bertolini S, Pisciotta L, Rabacchi C, et al (2013) Spectrum of mutations and phenotypic expression in patients with autosomal dominant hypercholesterolemia identified in Italy. Atherosclerosis; 227: 342–348.

Blom DJ, Harada-Shiba M, Rubba P, et al (2020) Efficacy and safety of Alirocumab in adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol; 76(2):131-42.

Casula M, Tragni E, Catapano AL (2012) Adherence to lipid-lowering treatment: the patient perspective. Patient Prefer Adherence; 6:805-14.

Clinical Trials Facilitation and Coordination Group CTFG (2020). Recommendations related to contraception and pregnancy testing in clinical trials. Version 1.1. (Online): https:www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf (Accessed 15-Feb-2023).

Cuchel M, Bruckert E, Ginsberg HN (2014) Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J; 35:2146-57.

Davidson MH, Maki KC, Pearson TA, et al (2005) Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. Am J Cardiol; 96:556-63.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute (2011) Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics; 128 Supp 5:S213-S256.

Ference BA, Ginsberg HN, Graham I, et al (2017) Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J; 38(32):2459-72.

Fitzgerald K, White S, Borodovsky A, et al (2017) A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. N Engl J Med; 376(1):41-51.

Giugliano RP, Pedersen TR, Park J-G, et al (2017) Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet; 390:1962-71.

Go AS, Mozaffarian D, Roger VL, et al (2014) Heart disease and stroke statistics-2014 update: a report from the American Heart Association. Circulation; 129:e28-e292.

Grundy SM, Cleeman JI, Bairey Merz CN, et al (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation; 110:227-39.

Howie SRC (2011) Blood sample volumes in child health research: review of safe limits. Bull World Health Organ; 89:46-53.

ICH Harmonized Guideline Addendum to ICH E11 (2017) Clinical investigation of medicinal products in the pediatric population E11 (R1). (Internet) Available from: database.ich.org/sites/default/files/E11_R1_Addendum.pdf (Accessed 10 Jun 2020).

Jameson K, Zhang Q, Zhao C, et al (2014) Total and low-density lipoprotein cholesterol in high-risk patients treated with atorvastatin monotherapy in the United Kingdom: analysis of a primary-care database. Curr Med Res Opin; 30(4):655-65.

Jones PH, Nair R, Thakker KM (2012) Prevalence of dyslipidemia and lipid goal attainment in statin treated participants from 3 data sources: a retrospective analysis. J Am Heart Assoc.; 1(6):e001800.

Khvorova A (2017) Oligonucleotide Therapeutics - A New Class of Cholesterol-Lowering Drugs. N Engl J Med; 376(1):4-7.

Kolansky DM, Cuchel M, Clark BJ, et al (2008) Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol; 102:1438-43.

Lakoski SG, Lagace TA, Cohen JC, et al (2009) Genetic and metabolic determinants of plasma PCSK9 levels. J Clin Endocrinol Metab; 94:2537-43.

Momper JD, Mulugeta Y, Green DJ, et al (2013) Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr; 167(10):926-32.

Moorjani S, Roy M, Torres A, et al (1993) Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia. Lancet; 341:1303-6.

Mousavi SA, Berge KE, and Leren TP (2009) The unique role of proprotein convertase subtilisin/kexin 9 in cholesterol homeostasis. J Intern Med; 266(6):507-19.

Najam O, Ray KK (2015) Familial Hypercholesterolemia: a Review of the Natural History, Diagnosis, and Management. Cardiol Ther; 4(1):25-38.

Nordestgaard BG, Chapman MJ, Humphries SE, et al (2013) Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease : Consensus Statement of the European Atherosclerosis Society. Eur Heart J; 34(45):3478-90.

Raal FJ, Kallend D, Ray KK, et al (2020) Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med; 382(16):1520-30.

Ray KK, Stoekenbroek RM, Kallend D, et al (2019) Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels: One-Year Follow-up of the ORION-1 Randomized Clinical Trial. JAMA Cardiol; 4(11):1067-75.

Ray KK, Wright RS, Kallend D, et al (2020) Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med; 382(16):1507-19.

Sabatine MS, Giugliano RP, Keech AC, et al (2017) Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med; 376(18):1713-22.

Sampson HA, Munoz-Furlong A, Bock SA, et al (2005) Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol; 115(3):584-91.

Sampson HA, Munoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol; 117(2):391-7.

Santos RD, Gidding SS, Hegele RA, et al (2016) Defining Severe Familial Hypercholesterolaemia and the Implications for Clinical Management: A Consensus Statement From the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol; 4:850-61.

Schwartz GG, Steg PG, Szarek M, et al (2018) Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med; 379(22):2097-107.

Stone NJ, Robinson JG, Lichtenstein AH, et al (2014) 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation; 129 Supp 2:S1-S45.

Thedrez A, Blom DJ, Ramin-Mangata S, et al (2018) Homozygous Familial Hypercholesterolemia patients with identical mutations variably express the LDLR (Low-Density Lipoprotein Receptor): Implications for the efficacy of Evolocumab. Arterioscler Thromb Vasc Biol; 38(3):592-8.

Varghese MJ (2014) Familial hypercholesterolemia: A review. Ann Pediatr Card; 7(2):107-17.

WHO (2017) World Health Organization Cardiovascular diseases. (Internet) Available from: who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Accessed 03 Jun 2020).

Wiegman A, Gidding SS, Watts GF, et al (2015) Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J; 36:2425-37.

Wilemon KA, Patel J, Aguilar-Salinas C, et al (2020) Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia: A Global Call to Action. JAMA Cardiol; 5(2):217-29.

Youngblom E, Pariani M, and Knowles JW (2016) Familial Hypercholesterolemia. Initial posting: January 2, 2014; last update: December 8, 2016. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: ncbi.nlm.nih.gov/books/NBK174884/ (Accessed 27 Jan 2020).

16 Appendices

16.1 Appendix 1: Diagnostic criteria for HoFH

Participants with a genetic diagnosis of HoFH by the following genotype criteria are eligible:

- Documented homozygous or compound heterozygous mutations in both LDLR alleles
  - *Note: Participants with known null (negative) mutations in both LDLR alleles, i.e. double null (negative), are not eligible (see Section 5.2 exclusion criteria)*
- Presence of homozygous or compound heterozygous mutations in Apo B, PCSK9, or low density lipoprotein receptor adaptor protein 1 (LDLRAP1)
- Presence of double heterozygous mutations (i.e. mutations in different genes) in the LDLR, Apo B, PCSK9, or LDLRAP1 alleles (e.g. LDLR/PCSK9)

16.2 Appendix 2: Clinically notable laboratory values and vital signs

Criteria for clinically notable vital signs are defined in Table 16-1:

Table 16-1 Criteria for clinically notable vital signs

Age	SBP [mmHg]	DBP [mmHg]	Heart Rate [beats min^{-1}]
12 years*	< 90, > 130	< 50, > 80	< 50, > 105
>12 years	< 90, > 145	< 55, > 90	< 45, > 95
* criteria for 6-12 years			

Criteria for clinically notable laboratory values are defined in Table 16-2:

Table 16-2 Clinically notable laboratory abnormalities for selected tests

Parameter	Alert Value
Hematology	
RBC count	>50% increase, >30% decrease
Hemoglobin	>50% increase, >30% decrease or any value <70 g/L (<7 g/dL)
Hematocrit	>50% increase, >30% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Clinical chemistry	
Albumin	<20 g/L (<2 g/dL)
ALT	>150% increase
AST	>150% increase
Bilirubin (Total)	>100% increase
BUN	>50% increase
Calcium	>10% increase, >10% decrease
C(P)K	>300% increase
Creatinine	>50% increase
Chloride	>10% increase, >10% decrease
eGFR	>30% decrease
Glucose	>50% increase, >50% decrease, or any value <3.3 mmol/L (<60 mg/dL)
Potassium	>20% increase, >20% decrease, or any value >5.3 mmol/L (>5.3 mEq/L)
Sodium	>5% increase, or any value >150 mmol/L (>150 mEq/L)
Uric acid	>50% increase

16.3 Appendix 3: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-3 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal	

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

	ALT or AST	**Total bilirubin**	**Liver Symptoms**	**Action**
ALT or AST increase without bilirubin increase:				
	If normal at baseline: ALT or AST > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline total bilirubin	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, total bilirubin, direct and indirect bilirubin, PT/INR, albumin, C(P)K, and GLDH in 48-72 hours • Follow-up for symptoms
	If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT or AST > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline total bilirubin	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, total bilirubin, direct and indirect bilirubin, PT/INR, albumin, C(P)K, and GLDH in 48-72 hours • Follow-up for symptoms • Initiate close monitoring and workup for competing etiologies
	If elevated at baseline: ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
	If normal at baseline: ALT or AST > 8 x ULN	Normal	None	

	ALT or AST	**Total bilirubin**	**Liver Symptoms**	**Action**
ALT or AST increase with bilirubin increase:				• Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline
	If normal at baseline: ALT or AST > 3 x ULN	Total bilirubin > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT or AST > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT or AST > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-5 Follow up requirements for liver laboratory triggers

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

16.4 Appendix 4: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-6 Specific Renal Alert Criteria and Actions

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

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

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

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

Table 16-7 Renal event follow-up

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

16.5 Appendix 5: Recommended Neurological Examination

MOTOR FUNCTION

When assessing motor function, from a neurological perspective, the assessment should focus on arm and leg movement. You should consider the following:

1. Muscle size
2. Muscle tone
3. Muscle strength
4. Involuntary movement
5. Posture, gait

Symmetry is the most important consideration when identifying focal findings. Compare one side of the body to the other when performing your assessment.

Assessment of a Conscious Patient

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

Table 16-8 Grade Strength

Grade strength	Description
5	Full range of motion against gravity and resistance; normal muscle strength
4	Full range of motion against gravity and a moderate amount of resistance; slight weakness
3	Full range of motion against gravity only, moderate muscle weakness
2	Full range of motion when gravity is eliminated, severe weakness
1	A weak muscle contraction is palpated, but no movement is noted, very severe weakness
0	Complete paralysis

NB: In a conscious patient, the single best test to quickly identify motor weakness is the "drift test". Have the patient hold their arms outward at 90 degrees from the body. With palms up, have the patient close their eyes and hold the arms for a couple of minutes. "Drifting" will occur if one side is weak.

Lower Extremities

Assess the patient in a supine position. Ask him/her to separate both legs to test for hip abduction. Then ask the patient to bring the legs back together to test for hip adduction. Sit the patient on the side of the bed to assess knee flexion and extension. Ask the patient to flex and extend the knee. If able to do this, apply resistance as these movements are repeated. Test plantar and dorsiflexion by having the patient push down against your hand with their foot and then pull up against your hand with their foot. Remember to compare the left side to the right side.

Upper Extremities

Assess ability to flex elbow (biceps) and straighten (triceps). Assess ability to raise shoulders and return to a resting position. Assess wrist flexion and extension. Test each function with resistance. For focused upper extremity assessment, assess each digit for flexion, extension and lateral movement.

Assessment of an Unconscious Patient

Upper Extremities

1. Observe the patient for spontaneous/involuntary movement.
2. Apply painful stimuli to elicit a motor response (start with central pain; move to peripheral pain if no response occurs).
3. Assess for paralysis of the limb by lifting both arms and releasing them together. If one limb is paralysed it will fall more rapidly than the non paralysed arm.

Lower Extremities

1. Observe for spontaneous/involuntary movement.
2. Apply painful stimuli to elicit a motor response. Begin with central pain. Nailbed or peripheral pain can be attempted if the patient doesn't respond to central pain (caution needs to be used when interpreting peripheral pain as it may stimulate spinal reflex responses vs withdrawal or other more deliberate responses).
3. To assess for paralysis of the one limb you can position the patient on their back and flex the knees so that both feet are flat on the bed. Release the knees simultaneously. If the leg falls to an extended position with the hip externally rotated, paralysis is present. The normal leg should stay in the flexed position for a few seconds and then gradually assume its previous position.

SENSORY FUNCTION

When assessing sensory function remember that there are three main pathways for sensation and they should be compared bilaterally:

1. Pain and temperature sensation.
2. Position sense (proprioception).
3. Light touch.

Pain can be assessed using a sterile pin. Light touch can be assessed with a cotton wisp. To test proprioception, grasp the patient's index finger from the middle joint and move it side to side and up and down. Have the patient identify the direction of movement. Repeat this using the great toe.

Sensory Tests:

A number of tests for lesions of the sensory cortex can be done. Examples include the following:

- **Stereognosis:** The ability to recognize an object by feel. Place a common object in the persons hand and ask them to identify the object.
- **Graphesthesis:** "Draw" a number in the palm of the person's hand and ask them to identify the number.
- **Two-Point Discrimination:** Simultaneously apply two pin pricks to the skin surface. Continually repeat the test while bringing the two pins closer together, until the individual can no longer identify two separate stimuli. The finger tips are the most sensitive location for recognizing two point differences while the upper arms, thighs and back are the least sensitive.

- **Extinction:** Touch the same spot on both sides of the body at the same time (eg, the left and right forearms. Ask the individual to describe how many spots are being touched. Normally, both sides are felt; with sensory lesions the individual will sense only one.
- **Point Locations:** Touch the surface of the skin and remove the stimulus quickly. Ask the individual to touch the spot where the sensation was felt. Sensory lesions can impair accurate identification, even if they retain their sensation of light touch.

TONE and REFLEXES

Upper motor neuron problems (brain and spinal cord) are associated with increased tone. Lower motor neuron problems are associated with decreased tone.

Look at the muscles on each side of the body in pairs. Assess for symmetry of bulk.

Evaluation of the stretch reflexes assesses the intactness of the spinal reflex arc at various spinal cord levels. The limb should be relaxed while applying a short and snappy blow with a reflex hammer. Hold the hammer loosely in a relaxed manner, making a wrist action. Allow the hammer to bounce.

Table 16-9 Reflex responses

Reflex responses	Description
0	No response
1+	Diminished, low normal
2+	Average, normal
3+	Brisker than normal
4+	Very brisk, hyperactive
Lower motor neuron disease is associated with 0 or 1+, upper motor neuron disease is associated with 3+ or 4+.	

Biceps Reflex (C5 – C6):

Support the forearm on the examiners forearm. Place your thumb on the bicep tendon (located in the front of the bend of the elbow; midline to the anticubital fossa). Tap on your thumb to stimulate a response.

Triceps Reflex (C7-C8):

Have the individual bend their elbow while pointing their arm downward at 90 degrees. Support the upper arm so that the arm hangs loosely and "goes dead". Tap on the triceps tendon located just above the elbow bend (funny bone).

Brachioradialis Reflex (C5-C6):

Hold the person's thumb so that the forearm relaxes. Strike the forearm about 2-3 cm above the radial styloid process (located along the thumb side of the wrist, about 2-3 cm above the round bone at the bend of the wrist). Normally, the forearm with flex and supinate.

Quadriceps Reflex (Knee jerk) L2 – L4:

Allow the lower legs to dangle freely. Place one hand on the quadriceps. Strike just below the knee cap. The lower leg normally will extend and the quadriceps will contract.

If the patient is supine: Stand on one side of the bed. Place the examiners forearm under the thigh closest to the examiner, lifting the leg up. Reach under the thigh and place the hand on the thigh of the opposite leg, just above the knee cap. Tap the knee closest to the examiner, (the one that has been lifted up with the examiners forearm).

Achilles Reflex (ankle jerks) L5 – S2:

Flex the knee and externally rotate the hip. Dorsiflex the foot and strike the Achilles tendon of the heel. In conscious patients, kneeling on a chair can help to relax the foot.

Heel Lift:

While the patient is supine, bend the knee and support the leg under the thigh. Have the leg "go dead". Briskly jerk the leg to lift the heel of the bed. Normally, the leg will remain relaxed and the heel will slide upward; increased tone will cause the heel and leg to stiffen and lift off the bed.

Babinski Response:

Dorsiflexion of the great toe with fanning of remaining toes is a positive Babinski response. This indicates upper motor neuron disease. It is normal in infants.

CEREBELLAR FUNCTION

The cerebellum is responsible for muscle coordination and balance on the same side. To test cerebellar function use the following tests:

1. Finger to finger test: have the patient touch their index finger to your index finger (repeat several times).
2. Finger to nose test: perform with eyes open and then eyes closed.
3. Tandem walking: heel to toe on a straight line
4. Romberg test: stand with feet together and arms at their sides. Have patient close his/ her eyes and maintain this position for 10 seconds. If the patient begins to sway, have them open their eyes. If swaying continues, the test is "positive" or suggestive of cerebellum problems.

Dizziness that occurs in response to position changes is usually blood pressure initiated. If the patient sways during a Romberg test, but stops when the eyes are opened, the problem is probably visual or CN VIII (vestibular).

16.6 Appendix 6: Sampson Criteria for Diagnosing Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

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

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, painful abdominal cramps, vomiting)

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

a. Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure*

b. Adults: SBP <90 mmHg or >30% decrease from that person's Day 1 reading

*Low SBP for children is age specific and defined as: <70 mmHg from age 1 month to 1 year; <70 mmHg + [2 x age] for age 1 to 10 years; <90 mmHg from age 11 to 17 years.

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

16.7 Appendix 7: Reference table blood volume by weight

Blood volume drawn for the purpose of this study is limited to a maximum of 2.5% of the circulating blood volume per sampling session and to a maximum of 5% over a 4-week period (Table 16-10) (Howie 2011). Investigators may further limit the volume of blood withdrawn based on local institutional guidelines and if the clinical condition of the participant may be adversely affected by removal of the blood volumes stated below. Details of blood volume requirement for [redacted] biomarker and safety samples are provided in the laboratory manual.

Table 16-10 Reference table – blood collection volumes by body weight

Body Weight (kg)	Total blood volume (TBV) of the participant (mL)[1]	Maximum allowable volume (mL) in one blood draw (2.5% of TBV)	Total maximum volume (mL) drawn in a 28-day period (5% of TBV)
20	1600	40	80
21	1680	42	84
22	1760	44	88
23	1840	46	92
24	1920	48	96
25	2000	50	100
26	2080	52	104
27	2160	54	108
28	2240	56	112
29	2320	58	116
30	2400	60	120
31	2480	62	124
32	2560	64	128
33	2640	66	132
34	2720	68	136
35	2800	70	140
36	2880	72	144
37	2960	74	148
38	3040	76	152
39	3120	78	156
40	3200	80	160
41	3280	82	164
42	3360	84	168
43	3440	86	172
44	3520	88	176
45	3600	90	180
46	3680	92	184
47	3760	94	188
48	3840	96	192
49	3920	98	196
50	4000	100	200
51	4080	102	204
52	4160	104	208

Body Weight (kg)	**Total blood volume (TBV) of the participant (mL)[1]**	**Maximum allowable volume (mL) in one blood draw (2.5% of TBV)**	**Total maximum volume (mL) drawn in a 28-day period (5% of TBV)**
53	4240	106	212
54	4320	108	216
55	4400	110	220
56	4480	112	224
57	4560	114	228
58	4640	116	232
59	4720	118	236
60	4800	120	240
61	4880	122	244
62	4960	124	248
63	5040	126	252
64	5120	128	256
65	5200	130	260
66	5280	132	264
67	5360	134	268
68	5440	136	272
69	5520	138	276
70	5600	140	280
71	5680	142	284
72	5760	144	288
73	5840	146	292
74	5920	148	296
75	6000	150	300
76	6080	152	304
77	6160	154	308
78	6240	156	312
79	6320	158	316
80	6400	160	320
1: Assuming a TBV of 80 mL per kg			

For body weights not listed in the Table, use the following formulas to calculate 2.5% and 5% of total blood volume:

- **2.5% of total blood volume = body weight (in kg to the closest 0.5 kg) X 2**
- **5% of total blood volume = body weight (in kg to the closest 0.5 kg) X 4**