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TQJ230 (Pelacarsen)

Clinical Trial Protocol CTQJ230A12302 / NCT05305664

A randomized, double-blind, placebo-controlled, multicenter trial assessing the reduction of the rate of lipoprotein apheresis after treatment with pelacarsen (TQJ230) compared to placebo in patients with hyperlipoproteinemia(a) and established cardiovascular disease undergoing weekly lipoprotein apheresis in Germany

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List of abbreviations

CCI	[redacted]
CCI	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
aPTT	Activated partial thromboplastin time
ACR	Albumin creatinine ratio
ASO	antisense oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under concentration-time curve
BfArM	Bundesinstitut fuer Arzneimittel und Medizinprodukte
BL	Baseline
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary Artery Disease
CABG	Coronary artery bypass graft
CFR	Code of Federal Regulations
CHD	coronary heart disease
CIOMS	Council for International Organizations of Medical Sciences
CMO & PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
COVID-19	Corona virus disease of 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTIS	Clinical Trials Information System
CT Scan	Computerized tomography scan
CTT	Clinical trial team
CV	Cardiovascular
CVD	cardiovascular disease
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DILI	Drug-induced liver injury
DGfN	Deutsche Gesellschaft für Nephrologie
dL	deciliter(s)

DLT	Dose Limiting Toxicity
DMC	Data monitoring committee
CCI	[redacted]
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EOT	End of Trial
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
eSource	Electronic Source
FAS	Full analysis set
G-BA	Gemeinsamer Bundesausschuss
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
HbA1C	Hemoglobin A1C
HCT	Hematocrit
HCP	Healthcare professional
HDL-C	High-density lipoprotein-Cholesterol
HIV	Human immunodeficiency virus
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for use
IgA	Immunoglobulin A
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
IMP	Investigational medicinal product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol

LFT	Liver function test
Lp(a)	lipoprotein(a)
LPLV	Last participant last visit
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	myocardial infarction
mL	milliliter(s)
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NOAEL	No observed adverse effect level
NSD	Needle safety device
NYHA	New York Heart Association
OLE	Open Label Extension
PAD	peripheral artery disease
PCI	Percutaneous coronary intervention
PCR	Protein-creatinine ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
PLT	Platelet
PRO	Patient Reported Outcomes
PT	prothrombin time
PTA	Post Trial Access
QM	Once per month
QMS	Quality management system
QW	Every week
Q4W	Once per 4 weeks
R Value	ALT/ALP x ULN
RAN	Randomized set
RBC	Red blood cell(s)
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBP	Systolic Blood Pressure
SCR	Screened set
SD	Standard deviation
SF-36	Short Form 36
SiRNA	Small interfering ribonucleic acid
SMQ	Standardized MedDRA query
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 diabetes mellitus
TBIL	Total bilirubin

ULN	upper limit of normal
CCI	[redacted]
VLDL-C	Very low-density lipoprotein cholesterol
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and eCRFs into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	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
Masking	A process to keep the information, e.g. a laboratory value, hidden after randomization to reduce information bias

Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO):	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)/Opposition	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/ or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol

to use of data/biological samples	required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.
Unblinding	Unblinding is the process by which study drug code is broken
Lipoprotein apheresis	Lipoprotein apheresis is indicated and reimbursed in Germany for patients with isolated elevated Lp(a) defined as Lp(a) > 60 mg/dL, LDL-cholesterol in normal range and progressive cardiovascular disease documented clinically and by imaging techniques (Gemeinsamer Bundesausschuss [G-BA] 2020).

Protocol summary

Protocol number	CTQJ230A12302
Full Title	A randomized, double-blind, placebo-controlled, multicenter trial assessing the reduction of the rate of lipoprotein apheresis after treatment with pelacarsen (TQJ230) compared to placebo in patients with hyperlipoproteinemia(a) and established cardiovascular disease undergoing weekly lipoprotein apheresis in Germany
Brief Title	A multicenter trial assessing the impact of lipoprotein(a) lowering with pelacarsen (TQJ230) on the rate of weekly lipoprotein apheresis sessions in patients with hyperlipoproteinemia(a) and established cardiovascular disease in Germany
Acronym	Lp(a) FRONTIERS APHERESIS
Sponsor and Clinical Phase	Novartis – Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Phase III study to test the hypothesis that treatment with pelacarsen (TQJ230) 80 mg Q4W compared to placebo significantly reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established cardiovascular disease currently undergoing lipoprotein apheresis in Germany on a weekly schedule Lipoprotein apheresis to date is the only approved therapeutic option for cardiovascular (CV) risk reduction in patients with severely elevated Lp(a) levels and history of myocardial infarction, stroke, symptomatic PAD or symptomatic CAD in Germany. Lipoprotein apheresis is an expensive, burdensome, and time-consuming procedure. The current study (CTQJ230A12302) will investigate if treatment with pelacarsen (TQJ230) 80 mg Q4W vs placebo reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established CV disease
Primary Objective(s)	Demonstrate superiority of pelacarsen (TQJ230) compared to placebo in reducing the rate of lipoprotein apheresis sessions in patients with hyperlipoproteinemia(a) and established CVD during 52 weeks of treatment
Secondary Objectives	• Demonstrate superiority of pelacarsen (TQJ230) compared to placebo in reducing the time to lipoprotein apheresis avoidance • Demonstrate superiority of pelacarsen (TQJ230) vs placebo in avoiding the performance of any lipoprotein apheresis in the last 40 weeks of the study • Demonstrate superiority of pelacarsen (TQJ230) vs placebo in lowering Lp(a) after 52 weeks
Study design	Randomized, placebo-controlled, double-blind, multicenter trial
Study population	Patients with hyperlipoproteinemia(a) and established cardiovascular disease (CVD); currently undergoing lipoprotein apheresis, 46 patients males and females; age 18 to 80 years, both inclusive
Key Inclusion criteria	• Patients currently undergoing lipoprotein apheresis for isolated Lp(a) on a weekly schedule in Germany for ≥ 12 months prior to screening with at least 35 sessions within the past 52 weeks prior to randomization • Lipoprotein(a) (Lp(a))> 60 mg/dL at screening • Spontaneous prior myocardial infarction (MI): ≥ 3 months prior to the screening visit, and/or • Ischemic stroke: ≥ 3 months prior to the screening visit, and/or • Clinically significant symptomatic peripheral artery disease (PAD) • Clinically significant symptomatic coronary artery disease (CAD)
Key Exclusion criteria	• Uncontrolled hypertension • Heart failure New York Heart Association (NYHA) class IV

	• History of malignancy of any organ system • History of hemorrhagic stroke or other major bleeding • Platelet count <140,000 per mm3 at screening • Active liver disease or hepatic dysfunction • Significant kidney disease • Pregnant or nursing women
Study treatment	Pelacarsen (TQJ230) Placebo
Treatment of interest	Reduction of the rate of lipoprotein apheresis after treatment with pelacarsen (TQJ230) compared to placebo
Efficacy assessments	Lipoprotein Apheresis, Lipoprotein(a)
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory assessments in blood and urine
Other assessments	Patient-reported outcomes (SF-36 questionnaire), patient preference questionnaire
Data analysis	The primary endpoint rate of lipoprotein apheresis treatments over the double-blind 52 week period will be analyzed using a generalized linear model with the logit link under binomial distribution, including treatment as a factor and baseline Lp(a) level as a covariate. The superiority of pelacarsen compared to placebo in reducing the rate of lipoprotein apheresis treatments is established if the 1-sided p-value from this model is less or equal to 0.025. The time to lipoprotein apheresis avoidance (at least 24 weeks of no lipoprotein apheresis until end of study) will be analyzed using a Cox-regression model with treatment as a factor. The total avoidance of lipoprotein apheresis from week 12 to week 52 will be analyzed using a logistic regression model with treatment as a factor. The change from baseline to week 52 in log-transformed Lp(a) (pre-apheresis) will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline log-scale Lp(a) as a covariate. The hypothesis testing for the secondary endpoints will be performed only after the null hypothesis for the primary endpoint is rejected. Hommel testing method will be used to test the three secondary hypotheses to ensure the type I error control
Key words	Lipoprotein(a), cardiovascular disease, apheresis

Amendment 3 (09-Nov-2023)

Short summary of the amendment rationale and major changes



Major and minor revisions are made to:





IRBs/IECs

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

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

Amendment 2 (04-Oct-2023)

Short summary of the amendment rationale and major changes

The protocol is being amended CCI and to provide CCI .CCI Additional revisions are made to align the trial with the upcoming European Union Clinical Trials Regulation (EU CTR) as well as editorial changes for clarity and consistency in the protocol text.

Major and minor revisions are made to:

CCI

IRBs/IECs

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

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

Amendment 1 (24-May-2023)

Short summary of the amendment rationale and major changes

This amendment is aimed at CCI that became effective on CCI to CCI . The amendment changes will also provide for a better characterization of CCI .

The protocol amendment also included changes to the inclusion criteria to increase the enrollment rate for this study and meet the recruitment commitment.

The amendment will require local Health Authorities and Ethics Committees/Institutional Review Boards approval.

Major and minor revisions are made to:

CCI


CCI

1 Introduction

1.1 Background

Lipoprotein(a) [Lp(a)] is a human lipoprotein consisting of glycoprotein apolipoprotein (a) (apo(a)) covalently linked to a low-density lipoprotein (LDL)-particle containing apolipoprotein B-100 (apoB) (Klingel et al 2019). Blood concentrations of Lp(a) are primarily genetically determined (Kronenberg 2016) and elevated Lp(a) levels have been established as an independent, causal risk factor for cardiovascular diseases (CVD) (Klingel et al 2019, Tsimikas 2017) The pathogenic mechanisms through which Lp(a) contributes to cardiovascular risk are mainly proatherogenic, prothrombotic and proinflammatory (Tsimikas 2017). In a large biobank analysis, individuals with a one standard deviation (SD) lower Lp(a) (one standard deviation in Lp(a) defined as 28 mg/dL) were shown to be associated with a risk reduction for coronary heart disease (CHD) by 29%, peripheral vascular disease by 31% and stroke by 13% (Emdin et al 2016). Currently, no pharmacotherapy for lowering of Lp(a) levels to reduce cardiovascular risk is available. In patients with severely elevated Lp(a) levels, lipoprotein apheresis offers a therapeutic option for Lp(a) management.

Lipoprotein apheresis is an extracorporeal therapy to reduce lipoprotein levels (Lp(a) as well as LDL-cholesterol (LDL-C)) in the blood, reducing the risk for a cardiovascular (CV) event. Germany is the country with most extensive use of lipoprotein apheresis for treatment of patients with hyperlipoproteinemia (a) in the world. Lipoprotein apheresis is reimbursed for patients with isolated elevated Lp(a), defined as Lp(a) > 60 mg/dL, LDL-cholesterol in normal range and progressive cardiovascular disease as documented clinically and by imaging techniques (Gemeinsamer Bundesausschuss [G-BA] 2020).

The procedure lowers Lp(a) acutely by 60-80% per session, however, due to a continuous endogenous production rate of Lp(a), a re-equilibration of levels occurs fairly quickly; levels return to pre-session concentrations within 3-5 days in the majority of patients, leading to a time-averaged reduction of 30-35% if lipoprotein apheresis is performed weekly. This procedure is invasive, laborious, time-consuming and expensive (Thompson and Parhofer 2019). While a randomized controlled study to demonstrate the efficacy of lipoprotein apheresis in the treatment of this population has not been performed, lipoprotein apheresis for isolated elevated Lp(a) was demonstrated to be effective in reducing CV risk based on data from a prospective observational multicenter study (Leebmann et al 2013). Additionally, lipoprotein apheresis is associated with a significant decrease in health-related quality of life and a significant increase in physical complaints (De Gucht V, Cromm K, Julius U, et al., 2018).

Pelacarsen (TQJ230) is an antisense oligonucleotide (ASO) that lowers Lp(a) by reducing the synthesis of apo(a). Apo(a) is primarily synthesized in the liver and subsequently covalently linked to the apoB-100 component of LDL-C forming Lp(a) lipoproteins. Pelacarsen (TQJ230) is currently under investigation for cardiovascular risk reduction in patients with elevated Lp(a) levels and established cardiovascular disease. In a Phase II study, treatment with pelacarsen (TQJ230) resulted in dose-dependent reductions of the Lp(a) levels from baseline of up to 80% (20 mg every week) at 6 months of exposure in patients with established cardiovascular disease and screening Lp(a) levels of at least 60 mg/dL. 98% of patients treated with pelacarsen

(TQJ230) 20 mg subcutaneously (s.c.) every week attained a Lp(a) level of ≤ 50 mg/dL at 6 months of exposure (Tsimikas S et al 2020). A pivotal Phase III study, testing the hypothesis that treatment with pelacarsen (TQJ230) 80 mg QM significantly reduces the risk of major CV events in patients with established CVD and elevated levels of Lp(a) is currently ongoing.

Pelacarsen (TQJ230) is a novel approach to decrease Lp(a) with the convenience of a once monthly self-administered subcutaneous injection and may significantly improve lives by offering a less burdensome and time-consuming alternative to lipoprotein apheresis. In addition, it will likely provide lower steady state levels of Lp(a) with less variability than lipoprotein apheresis. The pelacarsen (TQJ230) lipoprotein apheresis study will investigate if treatment with pelacarsen (TQJ230) 80 mg Q4W vs placebo reduces the rate of lipoprotein apheresis.

1.2 Purpose

CTQJ230A12302 study is a randomized, placebo-controlled, double-blind Phase III study to test the hypothesis that treatment with pelacarsen (TQJ230) 80 mg Q4W compared to placebo significantly reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established cardiovascular disease (evidenced by history of myocardial infarction, history of ischemic stroke,symptomatic peripheral artery disease [PAD] or clinically significant symptomatic coronary artery disease [CAD]) currently undergoing lipoprotein apheresis in Germany on a weekly schedule.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective • Demonstrate superiority of pelacarsen (TQJ230) compared to placebo in reducing the rate of lipoprotein apheresis sessions in patients with hyperlipoproteinemia(a) and established CVD during 52 weeks of treatment	**Endpoint for primary objective** • Rate of lipoprotein apheresis sessions performed over 52 weeks normalized to the weekly lipoprotein apheresis schedule
Secondary Objectives • Demonstrate superiority of pelacarsen (TQJ230) compared to placebo in reducing the time to lipoprotein apheresis avoidance • Demonstrate superiority of pelacarsen (TQJ230) vs placebo in avoiding the performance of any lipoprotein apheresis in the last 40 weeks of the study • Demonstrate superiority of pelacarsen (TQJ230) vs placebo in lowering Lp(a) after 52 weeks	**Endpoints for secondary objectives** • Time to lipoprotein apheresis avoidance (where lipoprotein apheresis avoidance is defined as at least 24 weeks of no lipoprotein apheresis until end of study) • Total avoidance of lipoprotein apheresis from week 12 to week 52 • Change from baseline to week 52 in the log-transformed Lp(a) (measured prior to planned lipoprotein apheresis)
Exploratory Objectives • Evaluate rate of lipoprotein apheresis at defined periods of time • Evaluate avoidance of the performance of any lipoprotein apheresis in the last 28 weeks of the study	**Endpoints for exploratory objectives** • Rate of lipoprotein apheresis sessions from week 12 to week 52 and week 24 to week 52 normalized to the weekly lipoprotein apheresis schedule

Objective(s)	Endpoint(s)
• Evaluate pre- and post-lipoprotein apheresis Lp(a) levels • Evaluate the change in expanded lipid profile parameters • Evaluate quality of life	• Total avoidance of lipoprotein apheresis between week 24 to week 52 • Time-averaged Lp(a) levels • Percent change in total cholesterol, LDL-C, High-density lipoprotein-Cholesterol (HDL-C), non-HDL-C, Very-low-density lipoprotein-Cholesterol (VLDL-C), apoB and triglycerides (pre- lipoprotein apheresis) from baseline to week 52 • Change from baseline to week 52 in the physical and mental health summary scores for the SF-36 questionnaire and a patient preference questionnaire

2.1 Primary estimand

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

The primary clinical question of interest is:

What is the effect of pelacarsen (TQJ230) (80 mg s.c. Q4W) versus placebo on lipoprotein apheresis session reduction in patients with hyperlipoproteinemia(a) and established cardiovascular disease (evidenced by history of myocardial infarction, history of ischemic stroke, symptomatic PAD, or clinically significant symptomatic CAD) currently undergoing lipoprotein apheresis in Germany on a weekly schedule, regardless of treatment discontinuations for any reason and regardless of change in the dose of allowed concomitant medications? The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of additional medications, mirroring the conditions in clinical practice.

The primary estimand is described by the following attributes:

1. Population: Patients with hyperlipoproteinemia(a) and established cardiovascular disease (evidenced by history of myocardial infarction, history of ischemic stroke,symptomatic PAD or clinically significant symptomatic CAD) currently undergoing lipoprotein apheresis in Germany on a weekly schedule.
2. Endpoint: Rate of lipoprotein apheresis sessions performed over 52 weeks double-blind period normalized to the weekly lipoprotein apheresis schedule.
3. Treatment of interest: The randomized treatment (the investigational treatment pelacarsen (TQJ230) 80mg or placebo s.c. Q4W administration).

Handling of intercurrent events:

- Treatment discontinuations for any reason: ignore (treatment policy strategy).
- Unforeseen change in the dose of allowed concomitant medications: ignore (treatment policy strategy).
- Death: use only data obtained prior to death (while alive- strategy).

The summary measure: odds ratio between treatments.

2.2 Secondary estimands

The following secondary estimands are considered:

- The estimand for the time to lipoprotein apheresis avoidance (where lipoprotein apheresis avoidance is defined as at least 24 weeks of no lipoprotein apheresis until the end of the study) is defined by the same population and treatment attributes as the primary estimand (see Section 2.1), with the endpoint attribute being: Time from randomization to occurrence of total lipoprotein apheresis avoidance. The summary measure used is hazard ratio between treatments.
- The estimand for the incidence of total lipoprotein apheresis avoidance from week 12 to week 52 is defined by the same population and treatment attributes as the primary estimand (see Section 2.1), with the endpoint attribute being: Proportion of patients without lipoprotein apheresis treatment from week 12 to week 52. The summary measure used is odds ratio between treatments.
- The estimand for the change from baseline to week 52 in the log-transformed Lp(a) is defined by the same population and treatment attributes as the primary estimand, with the endpoint attribute being: the change from baseline to week 52 in log-transformed Lp(a). The summary measure used is the difference in mean change from baseline to week 52 in log-transformed Lp(a).

The intercurrent events identified for the primary estimand also apply to the three secondary estimands and will be handled with the same strategy described in Section 2.1, except that the intercurrent event of death will be handled differently: a patient who dies prior to week 52 will be considered as failure for time to lipoprotein apheresis avoidance and total lipoprotein apheresis avoidance (composite strategy). And for change from baseline to week 52 in Lp(a), multiple imputation will be used to impute the week 52 endpoint which is missing due to death (hypothetical strategy).

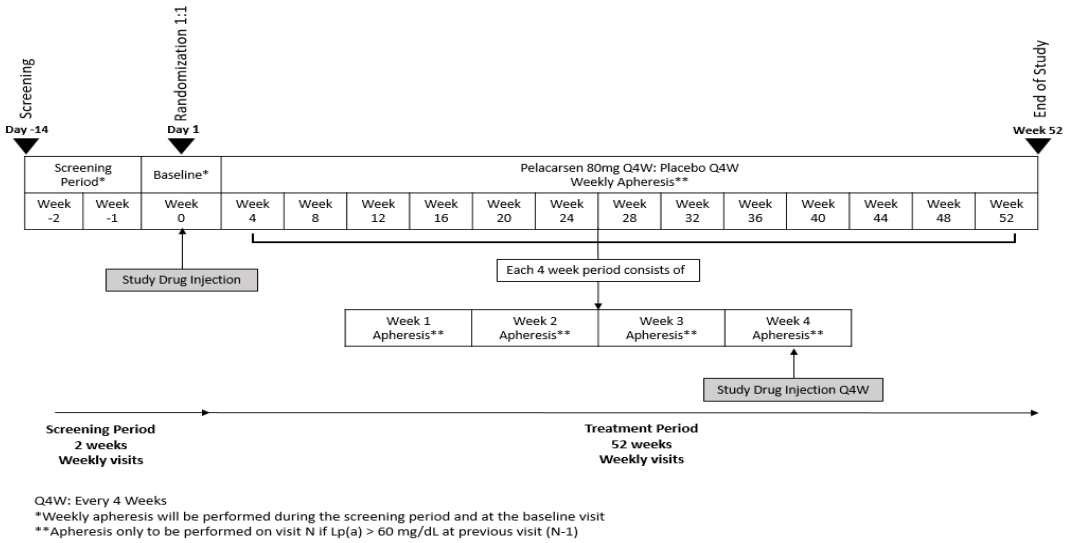
3 Study design

CTQJ230A12302 is a randomized, placebo-controlled, double-blind, multicenter Phase III study to test the hypothesis that treatment with pelacarsen (TQJ230) 80 mg s.c. Q4W compared to placebo significantly reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established cardiovascular disease (evidenced by history of myocardial infarction, history of ischemic stroke,symptomatic PAD or clinically significant symptomatic CAD) currently undergoing lipoprotein apheresis in Germany on a weekly schedule.

The study will consist of a screening period of approximately 2 weeks, followed by a double-blind treatment period of 52 weeks (Figure 3-1): after a 1:1 randomization, patients will continue their weekly visits to the sites, however, lipoprotein apheresis will only be performed on visit N if Lp(a) measured on previous visit (N-1) is above 60 mg/dL. As an objective, the

rate of lipoprotein apheresis treatments over 52 weeks normalized to the weekly lipoprotein apheresis schedule will be assessed.

Figure 3-1 Study design



Q4W: Every 4 Weeks
*Weekly apheresis will be performed during the screening period and at the baseline visit
**Apheresis only to be performed on visit N if Lp(a) > 60 mg/dL at previous visit (N-1)

3.1 Screening period

The screening visits should be timed with a regular scheduled lipoprotein apheresis sessions. Eligible patients, after signing the informed consent form (ICF), will have blood samples taken at ~week -2 and at ~week -1 for the central laboratory (prior to and after lipoprotein apheresis) and continue their planned weekly lipoprotein apheresis sessions. Patients should continue to take their lipid-lowering background therapy (if applicable). A total of two lipoprotein apheresis sessions will be performed prior to randomization.

3.2 Double-blind treatment period

Eligible participants will be randomized to administer either pelacarsen (TQJ230) or placebo and continue their weekly visits throughout the study. As Lp(a) analyses results are only available after a couple of days, Lp(a) from previous visit (N-1) will be used to determine whether lipoprotein apheresis will be performed on the subsequent weekly visit (N). Only in the case that Lp(a) measured on previous visit (N-1) is > 60 mg/dL, lipoprotein apheresis will be performed on week N. If a patient misses 2 or more consecutive visits, an additional blood sample is required before visit N to obtain an Lp(a) value and determine whether apheresis is necessary on visit N. Additionally, Lp(a) samples will be collected post- lipoprotein apheresis at screening, baseline, and QW visits. Starting at baseline and then every 4th visit, subcutaneous injections of pelacarsen (TQJ230) 80 mg Q4W or placebo after lipoprotein apheresis (if conducted) will be administered at site, either by self-administration or by caregiver or site personnel (see Section 6.6.2).

LDL-C will be regularly monitored during the study: LDL-C samples will be collected (pre- and post- lipoprotein apheresis) on a Q4W basis. In case of medically relevant increase in LDL-C values, every effort should be made to reach the individualized baseline LDL-C value (defined as the mean of pre- lipoprotein apheresis measurements taken during the screening phase and at baseline) with appropriate initiation or adjustment of lipid-modifying treatments. In the case that target goals defined in local or international guidelines are not reached, further adjustment of lipid-modifying treatment should be considered. Patients should additionally be instructed to comply with lifestyle changes according to national or international recommendations (Mach et al 2019, Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung e.V., 2020).

4 Rationale

4.1 Rationale for study design

CTQJ230A12302 is designed as a randomized, placebo-controlled, double-blind, multicenter Phase III study to test the hypothesis that treatment with pelacarsen (TQJ230) 80 mg s.c. Q4W compared to placebo significantly reduces the rate of lipoprotein apheresis in patients with established hyperlipoproteinemia(a) and cardiovascular disease (evidenced by history of myocardial infarction, history of ischemic stroke,symptomatic PAD or clinically significant symptomatic CAD) currently undergoing lipoprotein apheresis for isolated Lp(a) in Germany on a weekly schedule. The Phase III Lp(a)HORIZON CV outcome trial (CTQJ230A12301) excludes patients currently being treated with lipoprotein apheresis, or already planned to start lipoprotein apheresis during the study. Additionally, if during the Lp(a)HORIZON study, lipoprotein apheresis becomes indicated according to local practice, study drug must be discontinued. However, to date, lipoprotein apheresis is the only approved therapeutic option for CV risk reduction in patients with severely elevated Lp(a) levels and history of myocardial infarction, stroke, symptomatic PAD or symptomatic CAD in Germany. Lipoprotein apheresis is an expensive, burdensome, and time-consuming procedure. The current study (CTQJ230A12302) will investigate if treatment with pelacarsen (TQJ230) 80 mg Q4W vs placebo reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established CV disease. Lipoprotein apheresis will only be performed on visit N in the case that the Lp(a) value on visit N-1 is > 60 mg/dL. An Lp(a) value of > 60 mg/dL is a level which defines the eligibility for lipoprotein apheresis for isolated Lp(a) in Germany (G-BA 2020)

4.1.1 Rationale for choice of background therapy

No specific background medication is required during the conduct of this study. It is however recommended that CV risk factors, especially control of LDL-C, should be optimally treated according to local practice/guidelines (Mach et al 2020, Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung e.V., 2020). Reimbursement for lipoprotein apheresis for isolated Lp(a) in Germany requires LDL-C blood levels to be within normal range. As lipoprotein apheresis clears LDL-C from the blood, as well as Lp(a), it might be necessary to treat LDL-C pharmacologically in case LDL-C levels rise in patients whom lipoprotein apheresis is omitted due to controlled Lp(a) blood levels, or for other reasons. Therefore, LDL-

C will be monitored on a Q4W basis. For further details on the monitoring and on background therapy optimization, please refer to Section 3.2 and Section 6.2.

4.2 Rationale for dose/regimen and duration of treatment

Pelacarsen (TQJ230) 80 mg Q4W is chosen to provide maximal efficacy with an acceptable safety profile. A once per 4 weeks regimen will decrease the overall burden to the patient associated with more frequent dosing and is expected to provide better local tolerability. This formulation is currently also being tested in the Phase III study (CTQJ230A12301).

CCI

The overall exposure and reductions in Lp(a) between these regimens were similar; therefore, total monthly exposure to pelacarsen (TQJ230) is believed to account for the efficacy of the drug. With regards to safety, there were no pelacarsen-related changes in platelet counts in humans at doses ranging from 20 mg/month to 20 mg/week (equivalent to 80 mg/month; total dose ranging from CCI to CCI mg) relative to placebo (see Section 4.5). The intensive monitoring of platelet counts, up to 52 weeks in the Phase IIb study, did not show confirmed decrease in platelet count below 100,000/mm^3. There was no imbalance in the incidence of any two occurrences of platelet counts < 140,000/mm^3 between any of the individual pelacarsen (TQJ230) treatment groups or pooled pelacarsen (TQJ230) groups, and pooled placebo.

When considering the safety margin for the exposure to pelacarsen (TQJ230) 80 mg QM, the overall exposure (defined by the area under the concentration-time curve [AUC]) is expected to be approximately CCI lower than the no observed adverse effect level (NOAEL) in the chronic monkey study (CCI [based on mg/kg dose], CCI [based on Cmax]).

In the above-mentioned Phase IIb study, the 20 mg QW as well as the 60 mg QM dosing regimen yielded a plateau in Lp(a) blood levels after CCI weeks. As the 80 mg QM dose is expected to provide similar efficacy, it can be extrapolated that the full effect in Lp(a) lowering will have reached steady state after CCI months of treatment. To have clinically meaningful and appropriately powered endpoints, a total treatment duration of 52 weeks was chosen as hyperlipoproteinemia(a) is a chronic disease.

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

CTQJ230A12302 is a placebo-controlled study. Placebo is used to control potential bias in the evaluation of safety and efficacy of the drug. No comparative Lp(a) lowering pharmaceutical treatment has been shown to date to improve outcomes in patients with established CVD and elevated Lp(a); therefore, an active comparator is not included in this study.

A direct comparison of pelacarsen (TQJ230) against lipoprotein apheresis, the only therapeutical option to lower elevated Lp(a), was considered unethical in this high-risk population.

Treatment with pelacarsen (TQJ230) reaches steady state in Lp(a) blood levels only within CCI months. Therefore, 1:1 randomization to pelacarsen (TQJ230) only: lipoprotein apheresis would leave many patients with Lp(a) levels > 60 mg/dL, prior to reaching that steady state, exposing them to an increased risk over time.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

CCI However, exposure to pelacarsen (TQJ230) for up to 12 months in the Phase IIb study and intensive monitoring of platelet count did not show any confirmed decrease in platelets below 100,000/mm^3, nor was there an imbalance in the incidence of any two occurrences of platelet counts < 140,000/mm^3 between pelacarsen (TQJ230) treatment groups, including the highest dose pelacarsen (TQJ230) 20 mg QW and pooled placebo. CCI

Local injection site reactions, local erythema and bruising were reported in the Phase IIb study; however, only one patient discontinued treatment due to this. To minimize the impact of frequent injections, patients in study CTQJ230A12302 will inject study drug every month. In case such events occur, possible treatment is recommended in Section 6.5.7.

Specific dose-limiting toxicity definitions concerning the potential risks of liver events, renal events, and CCI, with guidance for required follow-up and discontinuation of study drug, are included in this protocol (Table 6-3, Table 6-4).

CCI

CCI Section 6.5.2, Table 6-3, Section 6.5.7, Section 6.6.2.1 and subject's updated informed consent form (ICF).



CCI Guidance for prophylaxis and management of specific adverse events (AEs) is provided in Section 6.5.7. For detailed information about potential and identified safety risk please consult the most recent version of the Investigator's Brochure.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study. In general, the risk to participants in this trial is

minimized by compliance with the eligibility criteria, study procedures, and close clinical monitoring.

The benefit a patient might have by participating in the study is the close monitoring of their condition and optimization of treatment of known risk factors during the full duration of the study.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 52 weeks from each participant as part of the study. The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring if a patient meets the follow-up criteria outlined in (Table 6-3 and or Table 6-4).

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

Instructions for sample collection, processing, storage, and shipment information are available in the laboratory manual.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

Approximately 46 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. Signed informed consent must be obtained prior to participation in the study
2. Male and female ≥18 to ≤ 80 years of age at screening
3. Patients currently undergoing lipoprotein apheresis for isolated Lp(a) on a weekly schedule in Germany for ≥ 12 months prior to screening with at least 35 sessions within the past 52 weeks prior to randomization
4. Lp(a) > 60 mg/dL at screening visit week2
5. Stable lipoprotein apheresis technique, volume and duration within 3 months prior to screening and no planned changes to lipoprotein apheresis parameters during the study
6. Established CV disease defined as ANY of the following four conditions:
    1. Spontaneous prior myocardial infarction (either ST-elevation MI or non-ST-elevation MI), which was not the result of percutaneous coronary intervention (PCI) or

coronary artery bypass graft (CABG) and which occurred in the period ≥ 3 months prior to the screening visit. Confirmation of MI is a patient history/patient recollection of signs or symptoms consistent with presentation of MI, and at least one of the following (adapted from Thygesen et al 2018):

- Documentation of cardiac biomarkers that exceed the diagnostic threshold of a local laboratory for MI
- Pathological Q waves on ECG or other ECG changes as defined in Appendix 2
- Imaging evidence of loss of viable myocardium or regional wall motion abnormality in a pattern consistent with an infarction or ischemic etiology
- Identification of a coronary thrombus by angiography at the time of presentation with myocardial infarction

2. History of ischemic stroke (an acute episode of focal cerebral, spinal, or visual dysfunction caused by infarction of central nervous system tissue) having occurred in the period ≥ 3 months prior to the screening visit documented by computerized tomography (CT) scan, magnetic resonance imaging (MRI) or other visualization method. Transient ischemic attack, lacunar infarction or embolic stroke (not of atherosclerotic origin) are not qualifying events
3. Clinically significant symptomatic peripheral artery disease evidenced by intermittent claudication with an ankle-brachial index ≤ 0.90 and/or limb amputation or revascularization due to lower limb ischemia. Thromboangiitis obliterans is not a qualifying event
4. History of clinically significant symptomatic coronary artery disease, evidenced by either typical stable angina pectoris symptoms under mild/moderate exertion (Canadian Cardiovascular Society-class II and III) or unstable angina pectoris symptoms at rest (Canadian Cardiovascular Society-class IV), which required either interventional or surgical coronary revascularization.

5.2 Exclusion criteria

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

1. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) ≥ 160 mmHg and/ or diastolic blood pressure (DBP) ≥ 100 mmHg (mean of 3 measurements for each SBP and DBP assessment) at the screening visit
2. Treatment with stable dose of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (evolocumab, alirocumab) for less than 12 weeks before randomization
3. Between screening visit and randomization visit (Day1): myocardial infarction, stroke, coronary or lower limb re-vascularization, major cardiac or non-cardiac surgery. The participant can be re-screened 3 months after the relevant event/procedure
4. Treatment with niacin ≥ 2000 mg (2 g) daily in the 3 months before the screening visit; niacin in multi-vitamins is allowed
5. Planned or expected cardiac, cerebrovascular or peripheral artery surgery or coronary revascularization

6. Heart failure New York Heart Association (NYHA) class IV at screening visit or at randomization visit
7. History of hemorrhagic stroke or other major bleeding, or if occurring between screening visit and randomization visit
8. Severe concomitant non-CV disease that is expected to reduce life expectancy to less than 5 years, at screening visit or at randomization visit
9. Known active severe infection or major hematologic, metabolic, gastrointestinal or endocrine dysfunction (e.g. uncontrolled thyroid dysfunction or uncontrolled diabetes mellitus) in the judgment of the investigator, at screening visit or at randomization visit
10. History of malignancy of any organ system (other than localized basal cell carcinoma or squamous cell carcinoma of the skin, or in situ cervical cancer), treated or untreated, within the past 5 years, or if diagnosed between screening visit and randomization visit, regardless of whether there is evidence of local recurrence or metastases
11. Platelet count <140,000 per mm^3 from central laboratory test at screening visit, confirmed by a second central laboratory test prior to the randomization visit
12. Estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73m^2 from central laboratory test at screening visit, confirmed by a second central laboratory test prior to the randomization visit; or patient on dialysis
13. Significant glomerular disease (including but not limited to immunoglobulin A (IgA) nephropathy, diabetic nephropathy, systemic lupus erythematosus, etc.) with urinary protein-creatinine ratio (PCR) > 500 mg/g (56.6 mg/mmol) at screening visit, confirmed by a second central laboratory test prior to the randomization visit
14. Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal (ULN) from central laboratory test at screening visit, confirmed by a second central laboratory test prior to the randomization visit
15. Total bilirubin ≥ 1.5 times the ULN from central laboratory test at screening visit confirmed by a second central laboratory test prior to the randomization visit, or patients with known Gilbert syndrome, independent of the total bilirubin value at screening visit
16. Positive Human immunodeficiency virus (HIV), Hepatitis C screening or Hepatitis B Surface Antigen tests from central laboratory test at screening visit
17. Any other conditions, at screening visit or between screening visit and randomization visit, which in the opinion of the investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
18. Treatment with an oligonucleotide or small interfering ribonucleic acid (SiRNA) within 9 months before screening visit. Treatment with inclisiran if first injection occurred within 30 days prior to randomization
19. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
20. Use of other investigational drugs within 5 half-lives of screening visit or within 30 days, whichever is longer

21. Unwillingness or inability (e.g. physical or cognitive) to comply with study procedures and schedule
22. Pregnant or nursing (lactating) women
23. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 16 weeks after the last dose of the investigational drug. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

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

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, is she considered not of childbearing potential.

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

6 Treatment

6.1 Study treatment

Participants will be randomized 1:1 to administer subcutaneous injections of pelacarsen (TQJ230) 80 mg or placebo Q4W. Injections may be self-injected or administered by a caregiver with the injection device TQJ230 Needle Safety Device (NSD) at site or administered by the study site personnel at randomization and subsequently once monthly at the

corresponding site visits. For details on how injections should be performed, please refer to Section 6.6.2.

6.1.1 Investigational and control drugs

The dispensation unit (handed out to the patients) is one prefilled syringe, with either active drug or placebo, contained in a sealed blister with label, packed in a carton box with a booklet and temper evident seal. This dispensation unit is supposed to stay together, not being opened, until the participant is ready for the treatment administration using this unit.

Table 6-1 Investigational and control drug

Treatment Title	Pelacarsen (TQJ230)	Placebo	Training kit
Treatment Description	Solution for injection in pre-filled syringe, 80 mg; once monthly	Solution for injection in pre-filled syringe, 0 mg; once monthly	Solution for injection in pre-filled syringe; 0 mg; only for training purposes
Type	Drug	Placebo	Placebo
Dose Formulation	Solution for injection in pre-filled syringe	Solution for injection in pre-filled syringe	Solution for injection in pre-filled syringe; only for training purposes
Unit Dose Strength(s)	80 mg/0.8 mL	0 mg/0.8 mL	N/A
Dosage Level(s)	80 mg; once monthly	0 mg; once monthly	N/A
Route of Administration	Subcutaneous injection	Subcutaneous injection	N/A Only for training purposes
Use	Experimental	Experimental	Training kit
Investigational Medicinal Product (IMP)	Yes	Yes	No
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study treatment will be provided as a carton box with a tamper evident seal containing one pre-filled syringe packed in a blister. The carton box and the blister containing the pre-filled syringe will be labelled per country requirements. Double Blind	Study treatment will be provided as a carton box with a tamper evident seal containing one pre-filled syringe packed in a blister. The carton box and the blister containing the pre-filled syringe will be labelled per country requirements. Double Blind	Training kit will be provided as a carton box with a tamper evident seal containing one pre-filled syringe packed in a blister. The carton box and the blister containing the pre-filled syringe will be labelled per country requirements for demonstration purposes. Open Label

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

Participant will be assigned at the baseline visit to one of the following two treatment groups in a 1:1 ratio

- Pelacarsen (TQJ230) 80 mg s.c. Q4W
- Corresponding placebo.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the participant.

For participants who in the opinion of the investigator are still deriving clinical benefit from pelacarsen (TQJ230), every effort will be made to continue provision of study treatment.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies used by the participant in the 3 months prior to randomization must be recorded in the prior/concomitant medications/ significant non-drug therapies or procedures electronic case report form (eCRF) pages independent if these will be continued during the study or not. Each concomitant drug must be individually assessed against all exclusion criteria. All medications, procedures, and significant non-drug therapies (including physical therapy, lifestyle instructions and blood transfusions) administered after the participant was enrolled into the study must also be recorded in the corresponding eCRF pages as specified in Table 8-1. New concomitant drug must be assessed against prohibited medication prior to its initiation. Doses of lipid-lowering and anti-platelet drugs should be recorded throughout the entire duration of the study.

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.

In case medically relevant increase in LDL-C values as a result of omission of lipoprotein apheresis (apheresis reduces LDL-C as well as Lp(a)), or for any other reason, every effort should be made to reach the individualized baseline LDL-C value (defined as the mean of pre-lipoprotein apheresis measurements taken during the screening phase and baseline) with appropriate initiation or adjustment of lipid-lowering treatments. In case target goals defined in local or international guidelines are not reached, further adjustment of lipid-lowering treatment should be considered. Patients should additionally be instructed to comply with lifestyle changes according to local and international recommendations (Mach et al 2020, Deutsche Gesellschaft für Kardiologie – Herz-und Kreislaufforschung e.V., 2020).

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

It is recommended that participants participating in the trial or their caregivers inform healthcare professionals not involved in the study of the potential risk of thrombocytopenia, so that any concomitant therapy which may result in thrombocytopenia and/or bleeding (e.g. heparin, oral anti-coagulants, anti-platelet drugs, direct thrombin inhibitors, Factor Xa inhibitors, niacin treatment) is managed appropriately and participants should be closely monitored. A participant card with information about the potential risk of bleeding will be provided to participants at the randomization visit.

Treatment with inclisiran, if commercially available, for the treatment of elevated LDL-C is allowed if the first injection occurred at a minimum of 30 days prior to randomization or when initiated during the trial. It is not to be considered a prohibited concomitant medication. Because inclisiran may have its own associated side effects, in particular injection site reactions, it is important to be able to differentiate these from any potential reactions from the study drug, pelacarsen (TQJ230). Therefore, inclisiran should be given in an alternate injection site from the study drug injection and should be offset by at least 7 days (plus or minus) from administration of study drug, while adhering to protocol visit windows. The patient should report any adverse reactions to the Primary Investigator/Study Coordinator.

COVID-19 vaccines (including messenger ribonucleic acid (mRNA) vaccines) may be used at any time and are not to be considered prohibited concomitant medication. Because the COVID-19 vaccination may have its own associated side effects, it is important to be able to differentiate these from any potential reactions from study drug (such as an injection site reaction). It is recommended that the study drug administration should be given at an alternate injection site from the COVID-19 vaccination and study drug injection should be offset at least 7 days (plus or minus) from the COVID-19 vaccination while adhering to protocol visit windows. The patient should report any adverse reactions to the Primary Investigator/Study Coordinator.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed:

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Oligonucleotide other than Pelacarsen (TQJ230) or SiRNA treatment*	Full Trial duration	Discontinue study treatment
Niacin ≥2000 mg (2g) daily**	Full Trial duration	Discontinue study treatment
Other investigational treatments	Full Trial duration	Discontinue study treatment
* Treatment with inclisiran is allowed if the first injection occurred at a minimum of 30 days prior to randomization or when initiated during the trial (see Section 6.2.1). ** Niacin in multi-vitamins is allowed		

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 patient is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No. 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 is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

At the randomization visit, 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 for administration to the participant.

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

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

6.4 Treatment blinding

Participants, investigator staff, persons performing the assessments, and the clinical trial team (CTT) will remain blinded to the identity of the treatment from the time of randomization until database lock, 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. 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. (3) Results from central Lp(a) measurements after the randomization visit should be masked for participants, investigator staff, persons performing the assessments, and the CTT. Unblinding a single participant at site for

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

6.5 Dose escalation and dose modification

6.5.1 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs with pelacarsen (TQJ230) and meets any of the criteria included in Table 6-3.

For liver abnormalities, the following two categories have to be considered during the course of the study (irrespective of whether classified/reported as AE/serious adverse event (SAE)):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of AE/SAE and other relevant eCRF pages.

6.5.2 Dose modifications

A list of conditions that may require temporary study drug interruption or permanent study drug discontinuation are listed in Table 6-3.

1. *Recommended* dose interruption or permanent study drug discontinuation are left at the discretion of the investigator.
2. Deviations to *mandatory* dose interruptions or permanent drug discontinuation are not allowed.

These dose changes must be recorded on the appropriate eCRF page.

Table 6-3 Criteria for study drug temporary interruption or permanent discontinuation and re-initiation of study drug due to toxicities.

Worst toxicity	Dose modifications for study drug
Investigations (Hematologic)	
Thrombocytopenia	
PLT < 140,000- 75,000/mm^3	Mandatory: repeat measurement (central lab) within 7 days from awareness of the abnormal result. If confirmed, monitor platelet (PLT) count every 7-10 days (central lab) until platelets recover to ≥140,000/mm^3. Continue with next study treatment administration only if PLTs are ≥140,000/mm^3.
PLT < 75,000 - 50,000/mm^3	Mandatory: repeat measurement (central lab) within 7 days from awareness of the abnormal result.

Worst toxicity	**Dose modifications for study drug**
	If confirmed: • Temporary dose interruption • Monitor PLT count every 3-7 days (central lab) • Mandatory: permanent study drug discontinuation, if after reintroduction of study drug, the platelet count again falls below 75,000/mm^3. • Restore treatment if no associated bleeding episode and PLTs reach baseline level. Mandatory: permanent study drug discontinuation, if associated clinically relevant non-major bleeding or major bleeding episode.
PLT < 50,000 - 25,000/mm^3	Mandatory: repeat measurement (central lab) within 2-3 days from awareness of the abnormal results. If confirmed: • Permanent study drug discontinuation • Monitor platelet count initially every 2-3 days (central lab) and consider treatment (Section 6.5.7).
PLT < 25,000/mm^3	Mandatory: repeat measurement (central lab) within 2-3 days from awareness of the abnormal results. If confirmed: • Permanent study drug discontinuation • Monitor platelet count initially every 2-3 days (central lab) and consider treatment (Section 6.5.7).
Hepatic investigations (Central laboratory)	
Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Recommendation: Maintain dose level
> 1.5 - 3.0 x ULN	Mandatory: Complete AE/SAE eCRF. Temporary dose interruption. Monitor liver function tests (LFTs) [a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: Restore treatment when total bilirubin ≤ 1.5 x ULN.
> 3.0 - 10.0 x ULN*	Mandatory: Complete AE/SAE eCRF. Monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: Temporary dose interruption. If resolved in ≤ 14 days, then restore study treatment. If resolved in > 14 days, then permanent discontinuation of study treatment. The participant should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 30 days.
> 10.0 x ULN*	Mandatory: Complete AE/SAE eCRF. Mandatory: Permanently discontinue participant from study treatment.

Worst toxicity	**Dose modifications for study drug**
	The participant should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 30 days.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Recommendation: Maintain dose level
> 3.0 - 5.0 x ULN	Mandatory: Complete AE/SAE eCRF. Maintain dose levels. Repeat LFTs[a] as soon as possible, preferably within 2-3 days from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN.
> 5.0 - 10.0 x ULN	Mandatory: Complete AE/SAE eCRF. Temporary dose interruption. Repeat LFTs[a] as soon as possible, preferably within 2-3 days from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. Then: If resolved in ≤ 14 days, restore study treatment. If resolved in > 14 days, then discontinue permanently participant from study treatment.
> 10.0 - 20.0 x ULN	Mandatory: Complete AE/SAE eCRF. Discontinue permanently study drug. Repeat LFTs[a] as soon as possible, preferably within 2-3 days from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline.
> 20.0 x ULN	Mandatory: Complete AE/SAE eCRF. Discontinue permanently study drug. Repeat LFTs[a] as soon as possible, preferably within 2-3 days from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 30 days.
Combined[b] elevations of AST or ALT and total bilirubin (potential Hy's Law case)	
For participants with normal ALT and AST and total bilirubin (TBIL) value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN or jaundice without evidence of cholestasis (defined as ALP < 2.0 x ULN)[c] For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2.0 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2.0 x baseline AND > 2.0 x ULN] or jaundice without evidence of cholestasis (defined as ALP < 2.0 x ULN)	Mandatory: Complete AE/SAE eCRF. Permanently discontinue participant from treatment. Repeat LFTs as soon as possible, preferably within 2 days from awareness of the abnormal results, then with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 30 days. Refer to the Section 6.5.5.1 for additional follow-up evaluations as applicable.
Skin and subcutaneous tissue disorders	
Injection site reaction e.g. erythema, pain, swelling at the injection site	
Mild	May maintain dose frequency or temporary study treatment interruption may be considered. Consider

Worst toxicity	Dose modifications for study drug
	initiating appropriate skin toxicity therapy (e.g. cold compress/ice, antihistamines, Section 6.5.7).
Moderate	May maintain dose frequency, or temporary study treatment interruption may be considered but initiate/intensify appropriate skin toxicity therapy (e.g. cold compress/ice, antihistamines, topical corticosteroids, low-dose systemic corticosteroids, Section 6.5.7).
Severe	Recommendation: If resolved in ≤ 7 days, then proceed with next dose; temporary study treatment interruption may be considered. If resolved in > 7 days (despite appropriate skin toxicity therapy: e.g. cold compress/ice, anti-histamines, topical corticosteroids, low-dose systemic corticosteroids, Section 6.5.7), permanently discontinue treatment at investigator's discretion.
Serious adverse event	Mandatory: Permanently discontinue participant from treatment. Initiate appropriate skin toxicity therapy.
Other adverse events	
Constitutional symptoms (CCI): fever, headache, chills, arthralgia, or joint swelling suspected to be related to the study drug administration	Recommendation: Symptomatic treatment (e.g. acetaminophen/ paracetamol and ibuprofen) prior to and after dosing (Section 6.5.7). If resolved in ≤ 14 days with appropriate therapy at investigator's discretion, then proceed with next dose; temporary study treatment interruption may be considered. If resolved in > 14 days despite appropriate therapy at investigator's discretion, then permanently discontinue participant from treatment. Mandatory: In case of a SAE of constitutional CCI symptoms reported as related to the study treatment, the collection of blood samples to assess CCI should be done at the next study visit
CCI	

CCI

Worst toxicity	Dose modifications for study drug
CCI	

All dose modifications should be based on the worst preceding toxicity.
[a]Core LFTs consist of ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
[b]"Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold
If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment
[c]"Cholestasis" defined as alkaline phosphatase (ALP) elevation (>2.0 xULN and R value <2). For R calculation and interpretation, see Section 6.5.5.1
[d] The investigational drug must not be administered during an episode of active major bleeding (definition in Section 6.5.4)
* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then continue treatment at the discretion of the investigator.

6.5.3 Renal Safety monitoring

Serum creatinine, urinary albumin/creatinine ratio and protein/creatinine ratio will be assessed at time points defined in Table 8-1. Criteria for serum and urinary adverse event and required actions are presented in Table 6-4.

Table 6-4 Renal events and their management

Criteria	Action required
Serum event	
Serum creatinine increase 50% or more (Central laboratory) compared to baseline value	Repeat assessment: send a sample to the Central laboratory within 1-2 days following receipt of the result, if possible. If ≥50% increase is confirmed, and serum creatinine is ≤ULN: perform one additional serum creatinine test 7-10 days after receipt of the confirmatory result. If serum creatinine remains ≤ ULN, then continue monitoring serum creatinine according to the assessment schedule. No treatment interruption. If increase ≥50 % is confirmed and serum creatinine is >ULN: • Temporary dose interruption, unless other cause is diagnosed and corrected. • Monitor serum creatinine every 7-10 days in the first month then monthly and until baseline level reached or stabilization (2 consecutive values ≤ 1.5 x ULN). • Restore treatment when serum creatinine reaches baseline level. • Consider participant hospitalization and specialist consultation.
Urine event	
For patients without dipstick proteinuria or with dipstick proteinuria <3+, at baseline: New dipstick proteinuria ≥ 3+	Send samples to the Central lab, within 1-2 days hours of the dipstick result, if possible, for assessment of albumin-creatinine ratio/protein-creatinine ration (ACR/PCR), Urine sediment microscopy, serum albumin and total protein. If proteinuria (PCR) is <1000 mg/g (<113.2 mg/mmol), repeat ACR/PCR prior to next scheduled study drug administration. Proceed with study treatment if PCR value is <1000 mg/g (<113.2 mg/mmol).
For all patients, independent of presence of proteinuria: Protein-creatinine ratio (PCR) ≥1000 mg/g (≥113.2 mg/mmol)	Send samples to the Central lab, within 1-2 days of the initial result, if possible, for assessment of ACR/PCR, Urine sediment microscopy, serum albumin and total protein. If confirmed proteinuria (PCR) ≥1000 mg/g (≥113.2 mg/mmol), and no other cause is diagnosed and corrected: • Temporarily interrupt study treatment. • Follow-up with PCR and serum creatinine prior to the next scheduled study drug administration, until 2 consecutive PCR are <1000 mg/g (<113.2 mg/mmol). • Continue PCR monitoring according to the assessment schedule. • Restore treatment when 2 consecutive PCR are ≤ 500 mg/g (56.6 mg/mmol).

Criteria	Action required
For all patients: • New dipstick hematuria ≥ 3+ not due to trauma	Perform: Urine sediment microscopy serum creatinine, ACR (all in Central laboratory)
For all renal events: Document contributing factors in the eCRF: co-medication, other co-morbidity conditions, and additional diagnostic procedures performed	

6.5.4 Bleeding events safety monitoring

Participants will be instructed to promptly report any signs or symptoms of bleeding. If a bleeding event occurs, the investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters must be performed, and action with study drug taken, as recommended (Table 6-3). Classification of bleeding events:

Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events (please see below), for example excess bruising, petechiae, or gingival bleeding on brushing teeth.

Definition of Major Bleeding Events (Schulman et al 2005):

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours or leading to transfusion of 2 or more units of whole or red cells.

Definition of Clinically Relevant, Non-Major Bleeding Events (Laporte et al 2017):

- Multiple-source bleeding
- Spontaneous hematoma > 25 cm^2
- Excessive wound hematoma (not injection site related)
- Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
- Spontaneous: rectal bleeding; epistaxis; gingival bleeding; hemoptysis; hematemesis
- Bleeding after venipuncture for > 5 minutes.

6.5.5 Follow-up for toxicities

Participants whose treatment is temporarily interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once per week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. Further guidance and recommendations for the management of toxicities are provided in Section 6.5.2 All participants with unresolved or non-stabilized condition resulting

from dose limiting toxicities (DLTs) must be followed up for adverse events and serious adverse events for 16 weeks following the last dose of the study drug. All participants who have not withdrawn consent should continue follow-up for Lp(a) measurements as per central lab, CV events and other assessments according to Table 8-1, regardless of the study drug status.

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

Participants with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events. 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 (potential Hy's Law case) will require further follow-up as outlined below:

- For participants with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN or jaundice.
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN] or jaundice.

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of ALP liver fraction 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).

In the absence of cholestasis, these participants should be immediately discontinued from study treatment and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Additional testing for other hepatotropic viral infection (Cytomegalovirus (CMV), Epstein-Barr virus (EBV) or Herpes Simplex virus (HSV)), autoimmune hepatitis or liver

biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

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", thus, meeting the definition of SAE and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.5.6 Treatment compliance

Study treatment will be administered either by the patient, a care giver or by site personnel at the baseline visit and thereafter at the Q4W study visits.

6.5.7 Recommended treatment of adverse events

Adverse events should be treated according to local practice and guidelines.

For participants whose platelet count is less than 50,000/mm^3, administration of steroids is recommended. Dosing and duration of steroid treatment is at investigator's discretion.

For participants with injection site reaction, cold compress/ice, antihistamines, local or systemic steroids can be used at investigator's discretion depending on the severity of the reaction (Table 6-3).

For participants who are experiencing CCI [redacted] symptomatic interventions such as acetaminophen/ paracetamol or ibuprofen prior to and after dosing may help to alleviate symptoms.

If a CCI [redacted] occurs when the subject is at the study site, supportive treatment according to standard of care and professional guidelines will be provided depending on the severity of the reaction.

Should a subject have already experienced injection-site reaction(s) and/or CCI [redacted] the Investigator may consider based on clinical judgement prophylactic treatment (e.g. anti-histaminic drug) before future study drug administration to prevent or alleviate the course of a subsequent severe or serious reaction.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant non-drug therapies eCRF page.

6.5.8 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to treat the participants safely. 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. Investigators are encouraged to call the Novartis medical monitor prior to code break if possible. 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 unblinding can be performed at any time.

After emergency unblinding, the study drug should be discontinued. The patient will continue to be followed up in the study unless they withdraw their informed consent (Section 9.1.1 and Section 9.1.2).

6.6 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Table 6-1 under investigational and control drug section.

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

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

6.6.1 Handling of study treatment and additional treatment

6.6.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis country organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of the participating 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.

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

6.6.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system. During the 52 week treatment period, pelacarsen (TQJ230) or placebo will be dispensed at every Q4W visit following the baseline visit. If a participant is unable to attend the scheduled Q4W study dose visit, the study dose should be administered either 1 week before or after the scheduled study dose visit.

Pelacarsen (TQJ230) can be injected independent of food intake.

Pelacarsen (TQJ230)/placebo is to be administered after performing lipoprotein apheresis (if applicable).

The prefilled syringe, including the safety needle device is designed to deliver the investigational drug or placebo in a safe way, so that the participants or their caregivers can use it in clinic after appropriate instructions by a study site staff member according to the Instructions for Use (IFU).

The first injection will be performed in the context of observed assessment under the supervision of one study site staff member.

At the randomization visit (week 0), the participants will be instructed by the site staff, who will walk them through the IFU on how to self-inject, and an injection pad will be provided as a training device. Participants will then be asked to raise questions if they have any. They will be instructed to refer to the IFU and be handed a placebo-containing injection device to simulate the use on the injection pad. Participants will again be asked to raise any questions, if they have any, and then to proceed with supervised self-injection.

The instruction acts and the review of the injection technique at the randomization visit at the study site should be documented in the source documents. If a patient or caregiver is evaluated by the study staff to be capable of supervised (self-)injection, this must also be documented in the eCRF. In the case that a patient or care provider is not assessed to be capable for supervised (self-)injection at site, training and re-assessment can continue at the following study visits. In the case that during these visits the site staff considers that the patient or care provider become capable for (self-)injection, the assessment must be recorded in the eCRF.

During the supervised self-injection, the observing site staff must exercise judgment and intervene in the self-/caregiver administration should a participant not be acting in a safe or reasonable manner, or any manner which does not fall within the scope of the study objectives.

In such a case, a patient or caregiver cannot be declared capable to self-inject the study drug unsupervised using TQJ230 NSD. Only after a member of the site personnel evaluates and records on the eCRF that the participant or the caregiver can (self)-administer safely and effectively without supervision, can the participant or caregiver proceed with study drug (self-)administration at site. If in the opinion of the study site staff, a patient or their caregiver is not capable to safely and efficiently deliver an injection with TQJ230 NSD unsupervised, the patient will receive the injections by the study personnel.

Any prefilled syringe for which a defect or malfunction is noticed prior to or during the injection at any of the study visits, must be kept at the site until guidance is received from Novartis on whether it should be returned to Novartis or discarded. Additionally, any noticed defect, malfunction, and problem during the injections or product complaints with the prefilled syringe should be recorded in the source document by the site, detailing the issue, the date and the visit number. It should also be reported to Novartis personnel.

6.6.2.1 CCI



CCI

7 Informed consent procedures

The Investigator will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Novartis will provide to investigators in a separate document, a proposed informed consent form, that complies with the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment
- CCI [redacted]

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

CCI [redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

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

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) (+/- 3 days). Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and any adverse event and concomitant medications should be recorded on the CRF.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

CCI



Table 8-1 Assessment schedule

Visit Name	Screening period		Baseline	Treatment period												EOT/ EOS	Weekly visits[1]	Follow-up[7]
Week	**-2**	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**QW**	**68**
Obtain informed consent	X																	
Inclusion/exclusion criteria	X		X															
Demography	X																	
Complete physical exam	S															S		
Brief Physical Exam			S	S	S	S	S	S	S	S	S	S	S	S	S			
Medical history / current medical conditions	X																	
Height	X																	
Weight	X		X													X		
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Smoking history	X																	
Alcohol history	X																	
Hematology	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hematocrit post-lipoprotein apheresis			X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Clinical Chemistry	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eGFR	X	(X)	X													X		
Urinalysis	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinary albumin-to-creatinine ratio and protein-creatinine ratio	X	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hepatitis, HIV Screen	X																	

Pregnancy test (serum)[5]	X															X		
Pregnancy test (Urine)[5]			S	S	S	S	S	S	S	S	S	S	S	S	S			
Lp(a), pre lipoprotein apheresis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipoprotein apheresis	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Lp(a), post lipoprotein apheresis[6]	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Direct LDL-C pre lipoprotein apheresis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Direct LDL-C post lipoprotein apheresis[6]	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
Lipid panel (total cholesterol, non-HDL-C, VLDL-C, HDL-C, triglycerides, apoB) pre lipoprotein apheresis[2]			X			X			X			X				X		
CCI																		
Lifestyle instructions	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Surgical and medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection device use assessment[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		
Patient card with information about potential risk of bleeding			S															
PRO (SF-36)			X			X			X			X				X		

Patient preference questionnaire			X													X		
AE and SAE Collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	S[7]
Study drug administration			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety follow up Call																		S[7]

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

Assessments denoted by parenthesis [(X) or (S)] are only required if lipoprotein apheresis is performed

QW: Every week

1) Weekly visits will be performed from week 0 to week 52

CCI [redacted]

4) Source documentation for all, and eCRF only when participant/caregiver qualifies for self-injection. Once confirmed eligible for self-injection, assessment is no longer required to be performed at subsequent visits

5) Serum and urine dipstick pregnancy test only in women of childbearing potential, prior to study treatment administration

6) Post-lipoprotein apheresis blood draws should be performed prior to the investigational medicinal product (IMP) injection

7) To be conducted 16 weeks after last administration of study treatment. Only applicable to patients who do not roll-over into the OLE study (CTQJ230A12302E1)

8.1 Screening

Screening activities (Table 8-1) must be initiated only after the patient has signed the ICF. Re-screening is allowed only once during the recruitment period, after the screening visit and the patient has been recorded as a screen failure prior to randomization. Patients can be re-screened once for any reason, including failing Lp(a) inclusion criterion at screening.

One time re-screening is acceptable for patients with historically highly elevated Lp(a) values who failed the first screening, to allow for re-confirmation of Lp(a) measurement by central lab.

In the case that a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once as required in Section 5.2. 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 who sign an ICF and are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form (CRF). The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of screen fail confirmation.

Participants who are randomized but fail to be started on treatment, e.g. participants randomized in error, will be considered early terminators. The reason for early termination should be captured on the appropriate disposition CRF.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Participant demographics: year of birth or age, sex, race, predominant ethnicity, and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, as required by Health Authorities, the diversity of the study population needs to be assessed. Further details include relationship status, educational level and working status.

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

8.3 Efficacy

Samples for efficacy assessment will be collected at the timepoints defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

8.3.1 Lipoprotein apheresis

At each visit N during the treatment period, the decision as to whether the patient will undergo lipoprotein apheresis or not is determined by the Lp(a) value from previous visit (N-1). Only in the case that the Lp(a) is > 60 mg/dL on visit N-1, lipoprotein apheresis will be performed on visit N.

8.3.2 Lipid profile

Changes from baseline in the efficacy biomarkers: total cholesterol, LDL-C, HDL-C, non-HDL-C, VLDL-C, apoB, and triglycerides will be assessed.

Lp(a) change from baseline will be reported as Lp(a) particle mass (mg/dL) and molar concentration of apolipoprotein(a) [apo(a)] (nmol/L). Due to the variability in particle mass, arising mainly from differences in apo(a) isoform mass but also from variations in lipid mass, a conversion between the two metrics is not appropriate. Therefore, in this study, the central lab will use two different assay kits to allow Lp(a) reporting in both mg/dL and nmol/L. There will be no calculated conversion between the two metrics.

CCI [redacted]

In addition, investigators and site staff involved in the conduct of this trial and all medical personnel involved in the participant's care and medical management should refrain from obtaining lipid panels between the time from randomization to study completion. If a lipid panel is obtained, all reasonable actions must be taken to ensure the study participant is not informed of the results.

8.3.3 Appropriateness of efficacy assessments

Reduced rate of lipoprotein apheresis sessions has been used in a previous pharmacological study and is considered clinically relevant (Moriarty et al 2016). Laboratory tests are related to the secondary and exploratory endpoints are in line with the expected efficacy of pelacarsen (TQJ230). Exploratory endpoints are hypothesis-generating and exploratory in nature.

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 AE Section 10.1.1.

As per Section 4.6, during a Public Health Emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from randomization except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (BP) and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The mean BP values should be used to determine a participant's eligibility (i.e. at screening and/or baseline). Clinically notable vital signs will be defined in Appendix 1.
Height and weight	Height is obtained in centimeters (cm) and body weight is obtained in kilograms (kg) and rounded to the nearest 0.1 kg. Weight is obtained in indoor clothing, without shoes.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the central laboratory manual.

Clinically notable laboratory findings will be defined in Section 16.1.

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, erythrocyte count, leukocytes count with differentials (neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured. If a result for platelet count is not available (e.g. due to sample clotting), the study site must call the patient for an unscheduled visit and send a new sample to the Central laboratory.
Chemistry	Sodium, potassium, creatinine, urea nitrogen/ urea, uric acid, chloride, calcium, phosphate, alkaline phosphatase, total protein, total bilirubin, AST, ALT, GGT, plasma glucose, HbA1c Estimated glomerular filtration rate (eGFR) will be calculated using the Modification of Diet in Renal Disease formula. If the total bilirubin concentration is increased above 2 times the upper limit of normal, direct and indirect bilirubin should be differentiated.

Test Category	Test Name
	For lipid panel please see Section 8.3.2
Urinalysis	Urinalysis (Blood, Ketones, Glucose, Protein, Bilirubin, Nitrite and Leukocyte esterase) should be performed locally. If any of the result(s) for Blood, Ketones, Glucose, Protein, Bilirubin, Nitrite and Leukocytes from locally performed urinalysis is/are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed by the Central laboratory following an abnormal local urinalysis test and results will be available in the Central laboratory database. Samples for urinary ACR and protein-creatinine ratio will be collected from spot urine (at the timepoints defined in the Assessment Schedule (Table 8-1) and analyzed in the Central laboratory

8.4.2 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test performed at the screening and end of trial visit. Pregnancy testing is not required for post-menopausal women. A urine pregnancy test will be performed prior to each study drug administration, i.e. monthly.

A positive urine pregnancy test requires immediate interruption of study drug and confirmation by serum pregnancy test. If positive upon the confirmation test, the patient must discontinue study drug. They will continue to be followed up in the study unless they withdraw their informed consent (Section 9.1.1 and Section 9.1.2).

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

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.3 Appropriateness of safety measurements

The safety assessments are standard for this indication/patient population.

8.5 Additional assessments

8.5.1 Patient reported outcomes (PRO)

Well-being of participants enrolled in the double-blind treatment period will be assessed with the SF- 36 questionnaire, as well as a patient preference questionnaire. SF-36 assessments will be performed at baseline, week 12, week 24, week 36 and End of Study. Patient preference questionnaire assessment will be performed at baseline and End of Study. The participants must be given the questionnaires to be completed after laboratory assessments and after all clinical

assessments were conducted. The participant should be given sufficient space and time to complete the questionnaire.

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The completed PRO will be reviewed by the investigator and reported if any AE/SAE is observed. The responses stored electronically in the database will be considered the source file.

8.5.2 CCI

CCI

8.5.3 CCI

Upon occurrence of AEs defined in Table 6-3 during study site visits, CCI will be collected as specified in Table 6-3.

CCI

In case of any CCI see Table 6-3), blood sample will be collected CCI CCI t. These blood draws can be combined with next study site visit if scheduled within this permitted time window.

8.5.4 CCI

CCI

CCI

CCI

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of drug-related toxicities requiring study treatment discontinuation (Table 6-3)
- Any laboratory abnormalities that in the judgement of the investigator prevents the participant from continuing study drug administration.

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

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Table 8-1).

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

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

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

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

9.1.2 Discontinuation from study

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

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made, as detailed in the assessment table (refer to Table 8-1).

9.1.3 Lost to follow-up

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

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

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

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

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

It is encouraged that participant provides withdrawal of consent in writing.

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

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

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

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

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 SAE collection follow-up call conducted 16 weeks after last administration of study treatment, unless enrolling into the post-trial access (PTA) OLE study (CTQJ230A12302E1). 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.

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the Investigator's evaluation will be allowed to receive PTA. PTA will be provided as part of the OLE study (CTQJ230A12302E1) for approximately 5 years or until one of the following conditions is met, whichever occurs first: investigator recommends treatment discontinuation, conditions requiring pelacarsen permanent discontinuation (as defined in Section 6.5.2 and Section 9.1) are met, resulting in study discontinuation, product launch/reimbursement are achieved in the relevant indication, treatment fails to achieve registration/reimbursement in the trial participant's country, or the clinical study is discontinued for any other reason.

9.2.1 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to

the protection of the participant's interests. The investigator or sponsor, depending on local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirement

10.1.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. Patient Reported Outcomes are considered as other assessments to detect adverse events, see Section 8.5.1.

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

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

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

- Dose not changed
- Drug interrupted/withdrawn

6. Its outcome
    - not recovered/not resolved;
    - recovered/resolved;
    - recovering/resolving,
    - recovered/resolved with sequelae;
    - fatal; or unknown.

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

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

Adverse event monitoring should be continued for at least 16 weeks following the last dose of study treatment.

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

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

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

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

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

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

A potential Hy's Law case (see Table 6-3) requires expedited reporting and must be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 16 weeks after their last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours after 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.

Must be reported to Novartis:

- SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure.
- SAEs collected between the time that a participant signs the ICF until 16 weeks after the participant's last study visit for randomized patients.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a chief medical office & public 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 (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 16 weeks post-study treatment period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

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

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Newborn will be followed up at approximately 1 month, 3 months and 12 months after birth according to guidelines as there was nothing observed in any studies that would suggest a fetal development risk.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the 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 the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1).

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.

This process is described in Section 6.5.1, where recommendations for follow-up and action required with study drug are also provided. Requirements for follow-up of potential DILI is provided in Section 6.5.5.1.

General rules for follow-up of AEs potentially indicative of liver toxicity are summarized below:

- 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 reported on the unplanned local laboratory 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 Table 6-3), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should be ensured

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

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study: serum events and urine events (Table 6-4).

Renal events should be identified and followed up by the investigator or designated personnel at the trial site as summarized in Table 6-4.

10.2.3 CCI



CCI

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 8 Visit schedule and assessments and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (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 (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate.

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

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

11.2 Database management and quality control

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

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

Randomization codes and data about all study treatment(s) dispensed to the participant and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who

will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. 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. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and good clinical practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis/ clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

This section provides the description of the statistical methods to be used in the evaluation of data collected in the study.

The primary efficacy and safety analyses of the study will be conducted on all patient data at the time when all patients have completed the 52 week planned double-blind treatment and all data collected up to and including week 52 study visit are cleaned.

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

12.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

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

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

The **full analysis set (FAS)** consists of all randomized patients with the exception of those patients who have not been qualified for randomization and have not received study treatment but have been inadvertently randomized into the study (referred to as mis-randomized patients). Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS.

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

12.2 Participant demographics and other baseline characteristics

The number of patients screened, screen failed, randomized, and included in the FAS will be summarized for the screened set, in which the summary for randomized and in the FAS will be provided by the treatment group. The reasons for discontinuation prior to randomization will be provided for screened set as well. The number and percentage of patients in the randomized set who completed the study, who prematurely discontinued the study and the reason for discontinuation will be presented by treatment group and for overall.

The number and percentage of patients with major protocol deviations as well as the criteria leading to data exclusion from analysis will be summarized by treatment group for the randomized set.

Summary statistics will be provided by treatment group for demographics and baseline characteristics for the FAS, including but not limited to the following:

- Age [Years]
- age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years),
- Sex,
- Race,
- Ethnicity,
- Weight,
- Height,

- Body Mass Index (BMI) [kg/m^2], calculated as weight [kg]/height^2 [m^2], from the collected height and weight at Visit 1 (screening visit)
- Vital signs (including sitting pulse [bpm], mean sitting SBP and DBP [mmHg])
- Smoking history,
- Alcohol history,
- Qualifying cardiovascular events,
- Cardiovascular risk factors and other co-morbidities (e.g. T2DM, hypertension etc.),
- Baseline Lp(a) level and lipid profile.

Continuous variables will be summarized using n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study drug unless specified otherwise. For Lp(a) and LDL-C, only pre-lipoprotein apheresis measurements will be considered for baseline.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group in the SAF. The lipoprotein apheresis treatment history will be summarized by treatment group in the FAS separately.

12.3 Treatments

The overall duration on the randomized study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration categories of interest (e.g. at least 3 months, 6 months, 9 months and 1 year).

Duration of exposure to study treatment excluding interruptions will be similarly computed and summarized as above.

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

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.

In addition, the use of medications of interest (e.g. lipid lowering agents, anti-diabetic medications and cardiovascular medications) at time of randomization and during the double-blind period will be summarized separately. The detailed definitions of these medication classes will be provided in a separate statistical analysis plan.

The SAF will be used for the above analyses unless otherwise specified.

12.4 Analysis supporting primary objective

The aim of the primary estimand is to answer the primary clinical question of interest in terms of reducing the rate of lipoprotein apheresis sessions (see Section 2.1) with pelacarsen (TQJ230) as compared to placebo.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the rate of lipoprotein apheresis sessions over the double-blind 52 week period normalized to the weekly schedule, defined as the ratio of the number of actual lipoprotein apheresis treatments performed over the number of planned lipoprotein apheresis treatments according to patients' weekly lipoprotein apheresis schedule.

12.4.2 Statistical model, hypothesis, and method of analysis

The aim is to estimate the treatment effect of the pelacarsen (TQJ230) compared to placebo, for the target population on the primary endpoint of rate of lipoprotein apheresis treatments normalized to the weekly schedule over 52 weeks. The justification of the corresponding primary estimand is detailed in Section 2.1.

The following hypothesis will be tested at the one-sided 2.5% level:

H_0: $\lambda_{TQJ230}/\lambda_{Placebo} \geq 1$ versus H_A: $\lambda_{TQJ230}/\lambda_{Placebo} < 1$

where λ_{TQJ230} is the odds of a participant on lipoprotein apheresis at a post-baseline visit in the pelacarsen (TQJ230) treatment arm and $\lambda_{Placebo}$ is the corresponding odds in the placebo arm.

Statistical analysis will be carried out using a generalized linear model with the logit link under quasi-binomial distribution (to adjust for over-dispersion), including treatment as a factor and baseline Lp(a) level as a covariate. The p-value, odds ratio, and its 95% confidence interval from this model will be presented. The superiority of pelacarsen versus placebo in reducing the rate of lipoprotein apheresis treatment is established if the 1-sided p-value from this model is less than, or equal to 0.025.

In addition, the treatment effect of pelacarsen (TQJ230) vs placebo in reducing the rate of lipoprotein apheresis will also be expressed in terms of risk difference and relative risk for better facilitating the data interpretation and communication, using the standardized estimator method (Steingrimsson et al 2017). The standardized estimator method will use the above generalized linear model fit to first calculate the predicted probability of a participants on lipoprotein apheresis under treatment for all study participants (regardless of actual study arm), then calculate the risk difference and relative risk based on the average of the predictions with the pelacarsen (TQJ230) and placebo arms. The 95% confidence intervals of the risk difference and relative risk will be derived using a nonparametric bootstrap replicated data sets (e.g. 500 - 1000 bootstrapping samples).

12.4.3 Handling of intercurrent events of primary estimand

The primary analysis will account for different intercurrent events as explained in the following:

1. **Discontinuation of study treatment for any reason:** Lipoprotein apheresis treatment data collected after discontinuation of study treatment will be used for analysis (treatment policy strategy).
2. **Unforeseen change in permitted concomitant medications (e.g. change in the dose of lipid-lowering medication; start a lipid-lowering medication, e.g. PCSK9i or inclisiran)**: Lipoprotein apheresis treatment data collected after unforeseen changes in concomitant medications will be used for analysis (treatment policy strategy).

3. **Death: Lipoprotein apheresis treatment data collected prior to death will be used for analysis (while alive strategy).**

12.4.4 Handling of missing values not related to intercurrent event

In cases that following treatment discontinuation, data collection cannot be maintained leading to patients' withdrawal from study follow-up, missing values will be imputed. In particular, missing lipoprotein apheresis treatment information will be imputed as if apheresis "occurred." Therefore, in case of patient dropout before week 52, the actual number of lipoprotein apheresis procedures will be added to the imputed number of the remaining planned treatments according to the weekly schedule.

The occurrence of apheresis for missed apheresis visits that are not related to treatment discontinuation will be imputed. Further details will be provided in the SAP.

In the event that a patient dies prior to week 52, no imputation will be performed. The rate of lipoprotein apheresis is the actual number of lipoprotein apheresis sessions divided by the planned number of lipoprotein apheresis sessions before the death.

12.4.5 Supplementary analysis

The rate of lipoprotein apheresis treatments during the double-blind 52 week period will also be analyzed using a generalized linear model with the logit link under quasi-binomial distribution, including treatment, use of PCSK9i (yes/no) and the interaction of treatment by the use of PCSK9i as factors and baseline Lp(a) level as a covariate. The descriptive summary for the raw number of lipoprotein apheresis treatments, and raw rate of lipoprotein apheresis treatments over the double-blind 52 week period normalized to the weekly schedule, will be presented by treatment.

The number and percentage of participants receiving lipoprotein apheresis treatment over time during the 52 weeks will be summarized descriptively by treatment and by weekly schedule and depicted accordingly.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy endpoint(s)

There are three secondary endpoints defined:

- Time to lipoprotein apheresis avoidance (where lipoprotein apheresis avoidance is defined as at least 24 weeks of no lipoprotein apheresis until end of study)
- Total avoidance of lipoprotein apheresis from week 12 to week 52
- Change from baseline to week 52 in the log-transformed Lp(a) (pre-lipoprotein apheresis)

For each secondary endpoint, the null hypothesis of no treatment difference between pelacarsen and placebo will be tested against the alternative hypothesis that pelacarsen is superior to placebo in reducing the time to lipoprotein apheresis avoidance (or resulting in total avoidance, or in reducing the Lp(a) pre-lipoprotein apheresis level after 52 week treatment). The secondary hypotheses will be tested only if the primary hypothesis is rejected.

The Hommel testing method will be used to test the three secondary hypotheses. Let $p(1) \leq p(2) \leq p(3)$ be the ordered one-sided p-values from the statistical models on the three secondary endpoints as described in the following, and H(1), H(2) and H(3) are the corresponding null hypothesis. Hommel test will be performed as follows:

- Step 1, if $p(3) \leq \alpha$ (=2.5%), then reject all three hypotheses; otherwise accept H(3) and go to step 2.
- Step 2, if $p(2) \leq \alpha/2$, then reject H(2) and H(1); otherwise accept H(2) and go to step 3.
- Step 3, if ($p(2) \leq 2\alpha/3$ and $p(1) \leq \alpha/2$) or $p(1) \leq \alpha/3$, then reject H(1).

All analyses for the secondary endpoints will be performed in the FAS.

Analysis of time to lipoprotein apheresis avoidance

Time to lipoprotein apheresis avoidance (at least 24 weeks of no lipoprotein apheresis until end of study) will be analyzed using a Cox-regression model with treatment as a factor and baseline Lp(a) as a covariate. The estimated hazards ratio and its 95% confidence interval and the p-value from this model will be provided.

The strategy for handling intercurrent events of prematurely discontinuing study treatment and unforeseen changes in permitted concomitant medications is the same as used for the primary endpoint, i.e. lipoprotein apheresis treatment data collected after the occurrence of intercurrent events will be used in analysis. Prematurely discontinued from the study (including death) prior to week 52 will be considered as a failure for lipoprotein apheresis avoidance until end of study.

The cumulative incidence rate of lipoprotein apheresis avoidance for each treatment group will be estimated by the Kaplan-Meier method and the Kaplan-Meier curve will be presented.

Analysis of total avoidance of lipoprotein apheresis from week 12 to week 52

The total avoidance of lipoprotein apheresis from week 12 to week 52 (a binary variable yes/no) will be analyzed using a logistic regression model with treatment as a factor and baseline Lp(a) as a covariate. The estimated odds ratio and its 95% confidence interval and the p-value from this model will be presented.

The strategy handling intercurrent events of prematurely discontinuing study treatment and unforeseen changes in permitted concomitant medications is the same as used for the primary endpoint, i.e. lipoprotein apheresis treatment data collected after the occurrence of intercurrent events will be used in analysis. Prematurely discontinued from the study (including death) prior to week 52 will be considered as a failure for lipoprotein apheresis total avoidance.

Analysis for change from baseline to week 52 in the log-transformed Lp(a) (pre-lipoprotein apheresis)

Baseline Lp(a) is defined as the last non-missing pre-lipoprotein apheresis assessment prior to the first dose of randomized study drug.

The change from baseline to week 52 in log-transformed Lp(a) (pre-lipoprotein apheresis) will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline log-scale Lp(a) as a covariate.

The strategy handling intercurrent events of prematurely discontinuing study treatment and unforeseen changes in permitted concomitant medications is the same as used for the primary endpoint, i.e. pre-lipoprotein apheresis Lp(a) data collected after the occurrence of intercurrent events will be used in the analysis. For patients who discontinue from the study (including death) prior to week 52, the missing Lp(a) data at week 52 will be imputed using the jump to reference approach (Carpenter et al 2013). A large number of imputed datasets (e.g. ≥100) will be created.

Each dataset will be analyzed using the above ANCOVA model. The least squares mean changes in log scale from baseline for each treatment group, the difference in the least squares mean changes in log-scale, and the two-sided 95% confidence interval along with the p-value for the difference will be obtained from each model, then combined using Rubin's rule (Barnard and Rubin 1999). The combined final estimates will then be back-transformed to the original scale and presented.

The absolute change and percent change of Lp(a) from baseline at each post-baseline scheduled visit (pre- lipoprotein apheresis) will be descriptively summarized and presented. The geometric mean of Lp(a) level over time will be depicted by treatment group and by visit.

The above analyses will be performed for Lp(a) data in both units of mg/dL and nmol/L separately.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) include all data from the double-blind period.

Adverse events

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

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

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

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

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by treatment.

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.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Patient reported outcomes

The absolute values and changes from baseline for the SF-36 domain-specific scores and the two summary scores (physical component summary and mental component summary) will be descriptively summarized by visit and treatment.

The change from baseline to week 52 in the two summary scores will be separately analyzed using ANCOVA models with treatment as a factor and baseline score as a covariate. The least square mean changes in each treatment group, the difference of least square means between treatments and its 95% confidence interval and the nominal p-value will be presented.

The above analyses will be performed in FAS patients whose PROs are collected.

The data collected from the participant preference questionnaire will be summarized and presented by treatment as appropriate.

12.6 Analysis of exploratory endpoints

The rate of lipoprotein apheresis sessions from week 12 to week 52, and from week 24 to week 52 normalized to the weekly lipoprotein apheresis schedule will be similarly analyzed respectively as for the primary analysis, using a generalized linear model with logit link based on quasi-binomial distribution with treatment as a factor and baseline Lp(a) as a covariate. Odds ratio and the 95% confidence intervals from the models will be presented.

Total avoidance of lipoprotein apheresis between week 24 and week 52 will be similarly analyzed as for the secondary endpoint of total avoidance of lipoprotein apheresis between week 12 and week 52, using a logistic regression model with treatment as a factor and baseline Lp(a) as covariate. The odds ratio and the 95% confidence interval from the model will be presented.

Time-averaged Lp(a) levels based on all pre- and post-lipoprotein apheresis measurements (calculated using the Kroon formula (Kroon et al 2000)) will be descriptively summarized by treatment using n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum, and maximum. The mean or median time-averaged Lp(a) levels over time will be depicted by treatment group and visit.

Percent change in LDL-C from baseline to week 52 (pre-lipoprotein apheresis value) will be analyzed using an ANCOVA model with treatment as a factor and baseline LDL-C as a covariate. Missing values at week 52 due to prematurely discontinuation from the study

(including death) will be multiply imputed similarly as for the Lp(a) secondary endpoint. Pre-lipoprotein apheresis LDL-C levels over time, as well as time-averaged levels based on pre- and post-lipoprotein apheresis measurements will be similarly summarized and depicted as for Lp(a).

In addition, the absolute changes and percent changes in total cholesterol, HDL-C levels, non-HDL-C, VLDL-C, apoB and triglycerides from baseline over time will be descriptively summarized by scheduled visit and treatment.

All above analyses will be performed in the FAS.

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

It is planned to randomize 46 participants in 1:1 allocation ratio to TQJ230:placebo. The power calculations, for demonstrating the superiority of TQJ230 over placebo in reducing the rate of lipoprotein apheresis sessions at the one-sided 2.5% alpha level, are provided in the following table:

Table 12-1 Power Calculation

Rate of apheresis in TQJ230	Rate of apheresis in placebo	Power	Scenario
20%	60%	66%	Pessimistic
20%	67%	82%	Skeptical
20%	75%	94%	Optimistic

The assumptions on the rate of lipoprotein apheresis sessions used in the calculation are based on the pelacarsen (TQJ230) Phase IIb data (CCI), where it was observed that the mean proportion of visits with Lp(a) values < CCI mg/dL among all post-Baseline visits with Lp(a) measured is around CCI in the placebo group and CCI % in the pelacarsen (TQJ230) CCI (corresponding to 80 mg monthly) group, which suggests a potential CCI apheresis rate in the placebo arm against CCI % in the pelacarsen arm. Further, per inclusion criteria at least 35 apheresis sessions over the 52 weeks prior to randomization (67.3%) are required, with the original version of the protocol requiring at least 40 sessions (76.9%).

Three scenarios on apheresis rates were considered for power calculations given 21 patients per arm, which would require a total of approximately 46 patients assuming a potential 10% dropout. A fixed 20% apheresis rate was assumed for the pelacarsen arm, whereas for placebo, a more conservative 75%, 67% and 60% against the observed phase IIb rate of 84% was used. The middle scenario (67%) is already skeptical given that it is aligned with the minimum apheresis rate required for the year prior to randomization in order for a subject to be enrolled in this study. Importantly, there is no biological evidence to assume that the rate will be smaller during follow-up, which makes the pessimistic scenario (with an assumed 60% apheresis rate in placebo) extremely unlikely. In summary, for the plausible scenarios (skeptical, optimistic) the study has more than 80% / more than 90% power.

Of note, the power considerations given here are generally conservative since they are based on the binomial distribution, whereas the main analysis uses a quasi-binomial model.

N-Query 7.1 was used for the calculations.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals
  for Human Use (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21)

The protocol, protocol amendments, ICF, Investigator's Brochure, [IB], and other relevant documents (e.g. advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required.

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

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

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Directive 2001/20/EC or European regulation 536/2014 for clinical studies (if applicable), European

Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in Clinical Trials Information System (CTIS) public website. In addition, after study completion (defined as Last Participant Last Visit (LPLV)) and finalization of the study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, CTIS etc.).

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

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

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

13.3 Quality Control and Quality Assurance

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

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

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

13.4 Data protection

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

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be

explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

Novartis has appropriate processes and policies in place to handle data breaches including personal data, according to applicable privacy laws. Any data security breach that may impact the confidentiality and protection of study participants' data is recorded and investigated by Novartis as required by applicable laws or regulations and as adequate to the nature of the breach. Upon identification of any potential data security breach, an appropriate Novartis team (depending on nature of the breach) performs an initial assessment. Depending on the nature and type of breach, including the categories of data impacted, the data security breach management process may include investigation of the root cause of the incident, and, on a basis of its outcome, determination of the adequate mitigation actions to address any immediate impact, and corrective and preventive measures to prevent recurrence and mitigate any adverse effects, as applicable. The data security breach is reported to the regulatory authorities and IECs or IRBs, as required by the applicable laws or regulations.

13.5 Data quality assurance

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

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

13.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in, e.g. source data acknowledgment or monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis /CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

13.7 Participant Engagement

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

- Thank You letter
  - Study Start: provide after patient is confirmed eligible for the study
  - End of study (EOS): provide at last treatment visit or last study visit
  - Plain language trial summary - after clinical study report (CSR) publication

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Table 16-1 Vital signs notable range deviations

Vital sign		Notable abnormalities
Pulse (beats/min)		either ≥120 + increase ≥25* or > 130 either ≤50 + decrease ≥30* or < 40
BP (mmHg)	systolic	either ≥180 + increase≥30* or > 200 either ≤90 + decrease≥30* or < 75
	diastolic	either ≥105 + increase≥20* or > 115 either ≤50 + decrease≥20* or < 40
* Refers to post-BL value as compared to BL value.		

Notable laboratory values are defined in Table 16-2:

Table 16-2 Clinically notable laboratory abnormalities for selected tests

Parameter	Criteria (based on a percent change from baseline or change from baseline)
Hematology	
Red Blood Cells (RBC) (total)	>50% increase, >20% decrease
White Blood Cells (WBC) (total)	>50% increase, >50% decrease
Platelet count	>75% increase, < 75,000/mm^3
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
Clinical chemistry	
ALT	>150% increase
AST	>150% increase
Blood Urea Nitrogen (BUN)	≥50% increase
Creatinine	≥50% increase
Total bilirubin	>100% increase
ALP	>100% increase
Sodium	>5% increase, >150 mmol/L, <130 mmol/L
Potassium	absolute values < 3.0 mmol/L, > 5.9 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease, hyper > 2.6 mmol/L
Uric acid	>50% increase
Plasma glucose	>50% increase, < 3.0 mmol/L (54 mg/dL)

16.2 Appendix 2: ECG findings supporting diagnosis of myocardial infarction

Electrocardiographic manifestations suggestive of acute myocardial ischaemia (in the absence of left ventricular hypertrophy and bundle branch block) (Thygesen et al 2018)

ST elevation

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

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

ST-depression and T wave changes

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

Pathological Q waves

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

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

16.3 Appendix 3: CCI





16.4 Appendix 4: CCI




CCI