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Clinical Development

TQJ230/Pelacarsen

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

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
apoB	Apolipoprotein B
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
BL	Baseline
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHD	Coronary heart disease
COVID-19	Corona virus disease of 2019
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CTT	Clinical trial team
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
CCI	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FAS	Full analysis set
GCP	Good Clinical Practice
HbA1C	Hemoglobin A1C
HCT	Hematocrit
HDL-C	High-density lipoprotein-Cholesterol
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IE	Intercurrent event
IRT	Interactive Response Technology

LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LFT	Liver function test
LLOQ	Lower limit of quantification
Lp(a)	Lipoprotein(a)
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram(s)
MI	Myocardial infarction
mL	Milliliter(s)
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCR	Protein-creatine ratio
PCSK9	Proprotein convertase subtilisin kexin type 9
PCSK9i	Proprotein convertase subtilisin kexin type 9 inhibitor
PLT	Platelet
PMM	Pattern-Mixture Model
PRO	Patient Reported Outcomes
PT	Preferred term
QM	Once per month
QW	Every week
Q4W	Once per 4 weeks
RAN	Randomized set
s.c.	Subcutaneous
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard Deviation
SF-36	Short Form 36
SMQ	Standardized MedDRA query
SOC	System organ class
TBIL	Total Bilirubin
TFL	Tables, Figures and Listings
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
VLDL-C	Very-low-density lipoprotein-cholesterol

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses aiming to support the completion of the Clinical Study Report (CSR) for the CTQJ230A12302 study. The clinical development program might be further supported by exploratory analyses not identified in the present SAP. Any post-hoc or unplanned analyses, not identified in this SAP will be clearly indicated as such if they are included in the respective CSR.

The following study reference documents and versions are available at the time of finalization of this SAP:

- Study protocol: V03 (protocol amendment 3), content final dated 09-Nov-2023.
- Case Report Forms (CRFs): Version 2.0.

1.1 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 subcutaneously (s.c.) Q4W compared to placebo significantly reduces the rate of lipoprotein apheresis in patients with hyperlipoproteinemia(a) and established cardiovascular disease (evidence 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.

The study consists of:

- A screening period of approximately 2 weeks, during which participants will continue to take their lipid-lowering background therapy (if applicable). Two lipoprotein apheresis sessions prior to randomization will be performed on a weekly basis.
- A double-blind treatment period of 52 weeks consisting of weekly visits until the end of study.

If all eligibility criteria are met, participants will be randomized in 1:1 allocation ratio to either subcutaneous injections of TQJ230 80 mg or placebo and receive study treatment as defined in the protocol. It is planned to randomize 46 participants. The randomization will not be stratified. The sponsor will provide investigational and control drugs as pre-filled syringes for s.c. injection.

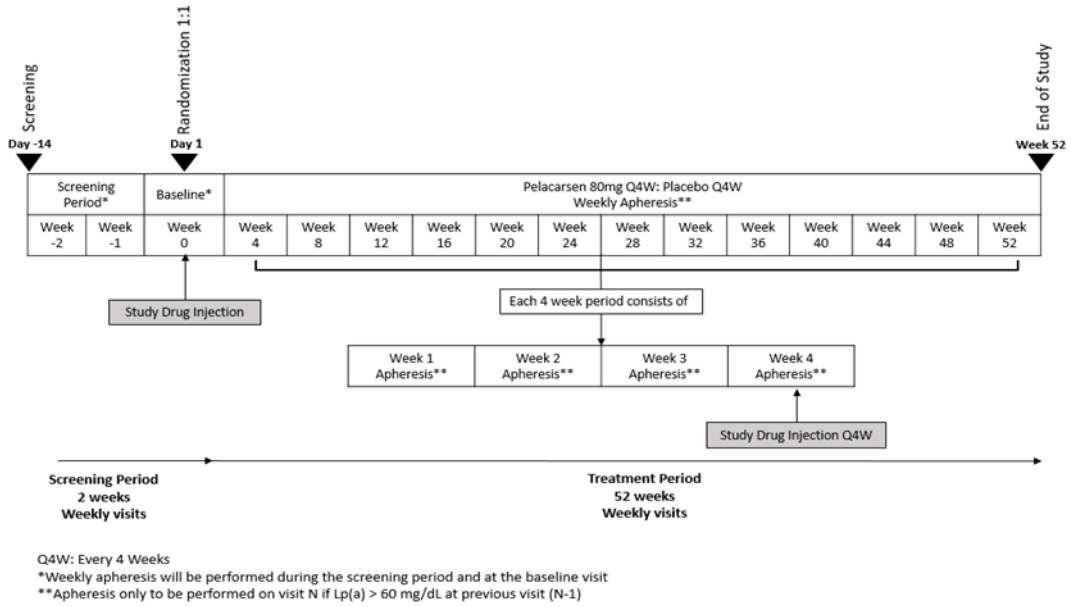
A graphical representation of the study design can be found in Figure 1-1. No interim analyses are planned.

Table 1-1 Investigational and control drugs

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Pelacarsen (TQJ230) 80mg	Solution for injection in prefilled syringe	Subcutaneous injection	Double blind	Global
Placebo	Solution for injection in prefilled syringe	Subcutaneous injection	Double blind	Global

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Placebo (training kits)	Solution for injection in prefilled syringe	Subcutaneous injection	Open label	Global

Figure 1-1 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)

1.2 Study objectives, endpoints and estimands

Table 1-2 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	**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

Objective(s)	Endpoint(s)
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	• 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 • Evaluate pre- and post-lipoprotein apheresis Lp(a) levels • Evaluate the change in expanded lipid profile parameters • Evaluate quality of life	**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 • 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

1.2.1 Primary estimand

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 participants 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 estimand defined by this question has the following attributes:

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
Endpoint	Rate of lipoprotein apheresis sessions performed over double-blind 52-week period normalized to the weekly lipoprotein apheresis schedule
Treatments of interest	The randomized treatment (the investigational treatment pelacarsen (TQJ230) 80mg or placebo s.c. Q4W administration)
Intercurrent events	Treatment policy strategy: - Discontinuation of study treatment: data collected after this intercurrent event (IE) will be used for analysis.

	- Unforeseen change in permitted concomitant medications (change in dose or start of a lipid-lowering medication): data collected after this IE will be used for analysis. While alive strategy: Death: only data obtained prior to death will be utilized
Summary measure	Odds ratio of treatments of interest conditioning on baseline log transformed Lp(a)

1.2.2 Secondary estimand(s)

The following secondary estimands attributes are considered with the same population and treatment of interest with primary estimand, which will not be repeated herein:

Estimand	Endpoint	Intercurrent events	Summary measure
Time to lipoprotein apheresis avoidance (where lipoprotein apheresis avoidance is defined as at least 24 consecutive weeks of no lipoprotein apheresis until the end of the study)*	Time from randomization to occurrence of total lipoprotein apheresis avoidance	Same as primary estimand, with the following exception: A patient who prematurely discontinues from study or dies prior to week 52 will be considered as apheresis avoidance failure (composite strategy)	Hazard ratio between treatments
Total avoidance of lipoprotein apheresis from week 12 to week 52	Proportion of patients without lipoprotein apheresis treatment from week 12 to week 52	Same as primary estimand, with the following exception: A patient who prematurely discontinues from study or dies prior to week 52 will be considered as failure (composite strategy)	Odds ratio between treatments
Change from baseline to week 52 in the log-transformed Lp(a)	Change from baseline to week 52 in log-transformed Lp(a)	Same as primary estimand, with the following exception: A patient who prematurely discontinues from study or dies prior to week 52 will have his missing Lp(a) data at week 52 imputed (hypothetical strategy)	Difference between the treatments in mean change from baseline to week 52 in log-transformed Lp(a)

* At the latest, time to lipoprotein apheresis avoidance from randomization can be achieved on week 28. If a participant has an apheresis session after week 28, it is impossible to subsequently have 24 consecutive weeks without apheresis until EOS, given that the study lasts for 52 weeks. Participants with one or more apheresis sessions after week 28 visit will be considered as apheresis avoidance failures. The time to apheresis avoidance success is defined as the date when the start of apheresis avoidance is achieved, i.e. the date of the first visit with no apheresis followed by no further apheresis sessions at subsequent visits until the end of the study. As an

example, in the following sequence the success for the time to apheresis avoidance endpoint would be on the date of week 23 visit: patient receives apheresis on weeks 1 to 10; patient does not receive apheresis on weeks 11 to 21; patient receives apheresis on week 22; patient does not receive apheresis on weeks 23 to 52.

For time to lipoprotein apheresis avoidance, as described on the table above, participants with a premature EOS or death event will be considered to having failed for this endpoint and they will be censored at EOS/death time.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Reporting department according to the study protocol Section 12 using R version 3.6.1 or above and/or SAS 9.4.

In general, continuous variables will be summarized descriptively by presenting n, mean, median, standard deviation (SD), quartiles, minimum and maximum, while categorical variables will be summarized descriptively by presenting count and percentage in each category.

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 period and all data collected up to and including week 52 study visit are cleaned.

The analysis cut-off date will be defined in SAP amendment before database lock. No centers/stratification factors will be considered for this study.

2.1.1 General definitions

Study treatment or study drug

In future sections through this document, “study treatment” or “study drug” will be used to refer to pelacarsen (TQJ230) or pelacarsen-matching placebo as assigned to a participant at randomization.

Screening period

Screening period is defined as the period starting from the date of signed informed consent until date of randomization.

Date of first administration of study drug/treatment

Date of first administration of study drug/treatment is defined as the date on which the study drug/treatment is injected for the first time in the study.

Baseline assessment

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

Post-baseline assessment

Post-baseline assessments are defined as those assessments that will be collected after the first dose of double-blind treatment. When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

- Absolute change from baseline: post-baseline value – baseline value.
- Percentage change from baseline: (absolute change from baseline/baseline value)*100

Study day

Study day is defined relative to the analysis reference date, which is the randomization visit date. The study day for a scheduled or unscheduled visit on or after the analysis reference date is defined as:

Study day = (Date of visit) – (Analysis reference date) + 1

The study day for a visit before the analysis reference date is defined as:

Study day = (Date of visit) – (Analysis reference date)

The analysis reference date will be study day 1, and the date directly prior to the analysis reference date is defined as study day -1 (there is no study day 0).

Double-blind period

Double-blind period refers to the period from date of first administration of study drug to study end date.

On-Treatment period

On-treatment period refers to the period from the date of first injection of study drug to 16 weeks (112 days) after the date of the last actual injection of any study drug in the study, the death of the participant, or the participants study end date, whichever comes first.

Study end date

Study end date is defined as the last date of the participant reported in the study (study completion visit date, the last event date, or the last assessment date, whichever comes last).

Lp(a) tests used in analysis

Central lab will provide Lp(a) data from three tests:

Test (Unit)	Comment
Roche (Mass)	Lp(a) data will be reported and analyzed
Roche (Molar)	Lp(a) data will be reported and analyzed
Randox (Mass)	Lp(a) data will be reported and will not be analyzed, but will be used as a diagnostic tool for principal investigators to determine if an apheresis session is deemed necessary.

Unscheduled visits

All data collected at unscheduled visits will not be used in "by-visit" tabulations or graphs, but they will be included in the analyses as appropriate. All data collected at both scheduled and unscheduled visits will be included in data listings.

Laboratory unscheduled visit mapping

If a patient missed a scheduled assessment, the earliest non-missing unscheduled assessment on or after the scheduled visit date and on or prior to the scheduled visit date plus 7 can be mapped to the scheduled visit.

If a collected specimen at the scheduled visit is tested multiple times, the result with the earliest time will be taken as the scheduled assessment.

This visit mapping algorithm only applies to the central laboratory assessments.

Unscheduled visits

All data collected at unscheduled visits will not be used in "by-visit" tabulations or graphs, but they will be included in the following analyses as appropriate.

- Hematology summary of shift from baseline to worst on-treatment post-baseline category
- Chemistry summary of shift from baseline to worst on-treatment post-baseline category
- Hematology - Clinically notable laboratory abnormalities
- Chemistry - Clinically notable laboratory abnormalities
- Newly occurring liver enzyme abnormalities
- Renal events

All data collected at both scheduled and unscheduled visits will be included in data listings.

2.2 Analysis sets

The following analysis populations will be used for statistical analyses:

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

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

The **full analysis set (FAS)** consists of all randomized participants with the exception of those participants 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 participants). Following the intent-to-treat principle, participants will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS.

The safety set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, 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.

Note: Mis-randomized participants are those for whom IRT calls were made by the site either prematurely or inappropriately, prior to confirmation of the participants final randomization eligibility and double-blind medication was not administered to the participant. These participants would subsequently not continue to take part in the study or be followed-up. Mis-randomized participants will not be included in the FAS, but they will be included in the RAN. Further exclusions from the FAS may only be justified in exceptional circumstances (e.g., serious GCP violations).

For the rule of exclusion criteria of analysis sets: See Appendix 5.5.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The SCR will be used to summarize the number of participants screened, completed the screening period, and discontinued prior to screening period completion. The RAN will be used to summarize the number of randomized patients, number of mis-randomized patients and patients who entered FAS. The FAS will be used to summarize the number of participants who completed the double-blind period, the number of discontinued participants prior to double-blind period completion and the reason for discontinuation. The number of participants entering SAF will also be presented.

The SAF will be used to present, by treatment and overall, the number and percentage of participants who completed study treatment, who prematurely discontinued study treatment and the reason for treatment discontinuation. Number of participants with protocol deviations will be tabulated by category and deviation using RAN.

2.3.2 Demographics and other baseline characteristics

The FAS will be used to provide summary statistics by treatment group for the demographics and baseline characteristics, as well as the lipoprotein apheresis treatment history. The following characteristics will be summarized:

- Age [Years]
- Age group (<65 years vs ≥65 years; <75 years vs ≥75 years)
- Sex
- Race
- Ethnicity
- Weight [kg]

- Height [cm]
- Body Mass Index (BMI) [kg/m^2] calculated as weight [kg]/ $height^2$ [m^2]
- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]
- Mean sitting DBP [mmHg]
- Smoking history
- Alcohol history
- Qualifying cardiovascular events as defined below:
  - Myocardial infarction
  - Ischemic stroke
  - Peripheral artery disease
  - Clinically significant symptomatic CAD
- Lp(a) [mg/dL, nmol/L] (only pre-lipoprotein apheresis measurements will be considered)
- Lipid profile (total cholesterol, LDL-C (only pre-lipoprotein apheresis measurements will be considered), non-HDL-C, HDL-C, VLDL-C, triglycerides, ApoB)
- Plasma Glucose
- HbA1c [%]

The SAF will be used to present, by treatment group, the relevant general medical histories by primary system organ class (SOC) and preferred term (PT). Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock.

History of CVD hospitalizations, family history, LDL-C management at randomization. LDL-C management post-randomization and Lp(a) apheresis history at screening will also be summarized by treatment group for the FAS.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The SAF will be used for the following analyses. Unless specified otherwise all the following summaries will be presented by treatment group and overall:

- Duration of double-blind period in days, defined as: date of last known visit on study – date of first dose of treatment + 1.
- Total duration of double-blinded period (patient-years), defined as the sum of patient-years of double-blind period for all participants. Patient-years of double-blind period for each patient is calculated as: (duration of double-blind period in days) / 365.25.
- Duration of on treatment period in days, defined as the time from the first dose date to the earliest date of the following: the last dose date + 112, patient's death date, or patient's study end date.

- Total duration on treatment period (patient-years), defined as the sum of patient-years of treatment for all participants. Patient-years of treatment for each patient is calculated as: (duration of on treatment period in days) / 365.25.
- Number of patients with at least one study treatment interruption which is defined as the case where the study treatment injection is missed, or the recorded dose is zero.
    - Reason for study treatment interruption
- Number of study treatment interruption episodes. Any study treatment interruption interval during which the date of a current injection date minus the previous injection date is larger than 60 days is considered as treatment interruption episode. For each subject, the number of study treatment interruption episodes will be calculated as the number of study treatment interruption intervals described above and the duration (day) of study treatment interruption episodes will be defined as the sum of the length of all intervals of study treatment interruption episodes.
- Duration of exposure, defined as duration of on treatment period minus the duration of study treatment interruption episodes.
- Total duration of exposure (patient-years), defined as the sum of years of exposure for all participants. Patient-years of treatment for each patient is calculated as: (duration of exposure in days) / 365.25.
- Number of doses administrated at each planned drug dispensing visit.

2.4.2 Prior, concomitant and post therapies

The SAF will be used to summarize prior or concomitant medications in separate tabulations based on the coding dictionary used (MedDRA 27.1 and "WHO Drug Dictionary Global B3-202409"). The SAF will also be used to summarize prior or concomitant significant non-drug therapies or procedures. These tables will be presented by treatment group and overall.

For prior or concomitant medications, frequencies and percentages will be presented in alphabetical order by each Anatomical Therapeutic Chemical (ATC) term, then in descending order of frequency in Overall column by preferred term. Same medication will only be counted once. Significant non-drug therapies or procedures will be summarized similarly by SOC and PT.

Prior medications and significant non-drug therapies or procedures are defined as those started or occurred prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used or occurred after the randomization visit. In case a prior medication, non-drug therapy or procedure is still ongoing after the randomization visit, it will be solely considered as concomitant, not prior.

Identified medication classes

Furthermore, the following classes of medications at time of randomization and during the on-treatment period will be identified using the ATC and PT and summarized separately:

- Anti-ischemic agents
    - Beta blockers

  - Intravenous or oral nitrates
  - Calcium channel blockers
- Anti-thrombotic agents
  - Acetylsalicylic acid (aspirin)
  - Anti-thrombotic drugs (excluding aspirin)
- Angiotensin Converting Enzyme inhibitors (ACEIs)
- Angiotensin Receptor Blockers (ARBs)
- Angiotensin Receptor Neprilysin Inhibitors (ARNIs)
- Lipid-lowering agents
  - Statins
  - Ezetimibe
  - PCSK9 inhibitors or Inclisiran
- Diuretics
  - Thiazide diuretics
  - Loop diuretics
- Anti-diabetic medications
  - Insulin
  - Metformin
  - Thiazolidinediones
  - SGLT-2 inhibitors
  - DPP4 inhibitors
  - GLP-1 receptor agonists
  - Sulfonylurea
  - Fixed Combinations of Oral Blood Glucose Lowering Drugs
  - Other oral hypoglycemic agents
- Proton pump inhibitors
- Anticoagulants

The precise definition of these medication classes will be provided in the TFLs document.

2.5 Analysis supporting primary objective(s)

The FAS will be used for the primary efficacy analyses.

2.5.1 Primary endpoint(s)

The primary endpoint of the study is the rate (proportion) of actual over planned apheresis sessions over the double-blind 52-week treatment period.

2.5.2 Statistical hypothesis, model, and method of analysis

The fractional logit model (Papke et al 1996) will be used to model the rate (proportion) of actual over planned apheresis sessions. This model does not assume any distribution as it is a quasi-likelihood method. Let $\boldsymbol{Y_i}$ be the rate of apheresis sessions per patient and $\boldsymbol{x} = (\boldsymbol{trt}, \boldsymbol{Lp(a)})$ be a $\mathbf{1} \times \mathbf{2}$ vector of explanatory variables. Assuming independent observations $\{(\boldsymbol{x_i}, \boldsymbol{Y_i}): \boldsymbol{i} = \mathbf{1}, \mathbf{2}, \ldots, \boldsymbol{N}\}$, where $\mathbf{0} \leq \boldsymbol{Y_i} \leq \mathbf{1}$ and $\boldsymbol{N}$ be the total number of patients, the rate can be modeled as:

$$E(Y_i \mid \boldsymbol{x_i}) = \mathrm{G}(\boldsymbol{x_i\beta})$$

$$\mathrm{G}(\boldsymbol{x_i\beta}) = \frac{\exp(\beta_0 + \beta_1 * trt_i + \beta_2 * Lp(a)_i)}{1 + \exp(\beta_0 + \beta_1 * trt_i + \beta_2 * Lp(a)_i)},$$

where G is the logistic function, β_0 is the model intercept, β_1 and β_2 are the regression coefficients for the treatment indicator (noted as trt) and baseline log transformed Lp(a) (noted as Lp(a)) respectively. Given this setting, the estimation procedure can be based on a Bernoulli quasi-likelihood method, i.e., the log-likelihood is defined as

$$l_i(\boldsymbol{b}) = Y_i log[G(\boldsymbol{x_i b})] + (1 - Y_i) log[1 - G(\boldsymbol{x_i b})],$$

and the quasi-maximum likelihood estimator of $\boldsymbol{\beta}$ is obtained by solving the maximization problem:

$$max_b \sum_{i=1}^{N} l_i(\boldsymbol{b}).$$

As stated in the original paper, robust standard errors need to be obtained through a valid estimate of the asymptotic variance of $\widehat{\boldsymbol{\beta}}$.

In the above specified model, the conditional odds ratio between the lipoprotein apheresis odds of a participant at a post-baseline visit in the pelacarsen (TQJ230) treatment arm (λ_{TQJ230}) against the corresponding odds in the placebo arm ($\lambda_{placebo}$) is given by exponentiating β_1. The interpretation as an odds ratio is valid here since the expected apheresis rates can be viewed as estimates of the probability to undergo an apheresis session at any given week (Baum 2008).

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

$$H_0: \frac{\lambda_{TQJ230}}{\lambda_{placebo}} > 1 \; versus \; H_A: \frac{\lambda_{TQJ230}}{\lambda_{placebo}} \leq 1.$$

Statistical analysis will be carried out using fractional regression with logistic function, including treatment as a factor and baseline log transformed Lp(a) level as a covariate. The p-value, conditional 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 one-sided p-value from this model is less than, or equal to 0.025. To allow for better interpretability, the conditional effect in the outcome under treatment and control will be derived and presented.

In case of missing apheresis information, the missing apheresis session will be imputed. 100 complete Lp(a) data sets will be created and then the missing apheresis session will be imputed. Each complete apheresis data set will be analyzed with the above model, and the estimates of log(conditional odds ratio) and its standard errors will be derived. The pooled log(conditional odds ratio) and its standard error will be obtained using Rubin's rule (Rubin 1987) via SAS PROC MIANALYZE based on the 100 imputed data sets; then the pooled conditional odds ratio and its 95% CI will be further derived by exponentiating the pooled log(conditional odds ratio) and its 95% CI, respectively.

2.5.3 Handling of intercurrent events

Handling of intercurrent events has been defined in Section 1.2.1.

In cases that following treatment discontinuation, data collection cannot be maintained leading to premature study discontinuation, lipoprotein apheresis at visits missed following premature study discontinuation will be imputed as "occurred".

If a patient dies, no imputation after death will be performed.

2.5.4 Handling of missing values not related to intercurrent event

For missing lipoprotein apheresis data that are not related to treatment discontinuation, we will follow the below approach:

- Direct imputation of lipoprotein apheresis data based on the Lp(a) value measured at the previous visit (≤ 60 or > 60 mg/dL) will be performed. Specifically, and similarly to the weekly apheresis decisions performed by the principal investigators as per protocol, lipoprotein apheresis will be imputed as having occurred on visit N for which the apheresis data are missing, if the Lp(a) value at visit N-1 is > 60 mg/dL. Lipoprotein apheresis will be imputed as not occurred on visit N for which the apheresis data are missing if the Lp(a) value at visit N-1 is ≤ 60 mg/dL.
- For all missing values that cannot be imputed with a single value by the previous step, multiple imputation is performed. The multiple imputation is done under a Missing at Random (MAR) assumption separately for the two treatment groups. Details are specified in Section 5.5.1.

2.5.5 Sensitivity analyses

Two sensitivity analyses will be performed for the primary endpoint as follows:

1. While on-treatment strategy will be used to re-analyze the primary endpoint by considering all follow-up data until treatment discontinuation.
2. Apheresis treatment information impacted by protocol deviations will be imputed. Please see the detailed information in Section 5.1.5

2.5.6 Supplementary analyses

In addition, the treatment effect of pelacarsen (TQJ230) vs placebo in reducing the rate of lipoprotein apheresis will also be expressed in terms of marginal risk difference and marginal

relative risk for better facilitating the data interpretation and communication, using the standardized estimator method (also known as average treatment effect) (Steingrimsson et al 2017). The standardized estimator method estimates the average treatment effect and works as in the following steps within each imputed data set that deployed for the primary analysis:

1. Use the above generalized linear model to
   a. predict the rate of lipoprotein apheresis under TQJ230 treatment for all study participants (regardless of their originally assigned treatment arm).
   b. predict the rate of lipoprotein apheresis under placebo treatment for all study participants (regardless of their originally assigned treatment arm).
2. Obtain the population rates for TQJ230 and placebo, respectively, by taking the average of all predictions from step (1a) and of all predictions from step (1b).
3. Calculate the estimated risk difference, relative risk, and odds ratio based on the population rates from step (2).
4. Obtain the standard error for each estimate in step (3) via bootstrapping (non-parametric, sampling with replacement, stratified by arm) by repeating steps (1) to (3) 1000 times for each bootstrap sample.

Then the pooled point estimate (risk difference, relative risk, and odds ratio) and its standard error based on the 100 imputed data sets will be obtained using Rubin's rule (via SAS PROC MIANALYZE). Finally, the point estimates and their 95% CIs will be presented.

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 binomial distribution, including treatment, use of PCSK9i (yes/no) at baseline, and the interaction of treatment by the use of PCSK9i at baseline as factors and baseline log transformed Lp(a) level as covariate. The same approach for handling intercurrent events and/or missing data for primary analysis will be adopted

The descriptive summary for the number of lipoprotein apheresis treatments, and rate of lipoprotein apheresis treatments over the double-blind 52-week treatment period normalized to the weekly schedule based on the observed data, will be presented by treatment.

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

2.6 Analysis supporting secondary objectives

The FAS will be used for the secondary efficacy analyses.

2.6.1 Secondary endpoint(s)

The secondary endpoints for this study have been provided in Section 1.2.2.

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary hypotheses will be tested only if the primary hypothesis is rejected. 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.

The three secondary hypotheses will be tested using the Hommel testing method that adjusts for multiplicity (Hommel 1988). Briefly, the one-sided p-values obtained from the statistical models applied on the three secondary endpoints will be ordered, together with their corresponding null hypotheses. Let $p(1) \leq p(2) \leq p(3)$ and H(1), H(2) and H(3) be the ordered p-values and their corresponding null hypotheses respectively. The Hommel test will be performed as follows:

- Step 1: if $p(3) \leq \boldsymbol{\alpha = 2.5\%}$, then reject all three hypotheses; otherwise, do not reject H(3) and proceed to step 2.
- Step 2: if $p(2) \leq \boldsymbol{\alpha/2}$, then reject H(2) and H(1); otherwise, do not reject H(2) and proceed to step 3.
- Step 3: if [$p(2) \leq \boldsymbol{2\alpha/3}$ and $p(1) \leq \boldsymbol{\alpha/2}$] or [$p(1) \leq \boldsymbol{\alpha/3}$], then reject H(1).

In terms of statistical modelling, the following approaches will be used:

- Time to lipoprotein apheresis avoidance: A Cox-regression model with treatment as factor and baseline log transformed Lp(a) as covariate will be used. Ties will be handled using the Efron method. Given that week 28 is the maximum time allowed for a participant to succeed in this endpoint, all participants not having achieved lipoprotein apheresis avoidance at week 28 will be censored (refer to appendix 5.4 for censoring rule). The estimated conditional hazard ratio, its 95% confidence interval and the p-value from this model will be provided. The cumulative incidence rate of lipoprotein apheresis avoidance over time for each treatment group will be estimated by the Kaplan-Meier method and the Kaplan-Meier curve will be presented by treatment group.
- Total avoidance of lipoprotein apheresis from week 12 to week 52: Total avoidance will be represented with a binary yes/no variable and analyzed using a logistic regression model with treatment as a factor and baseline log transformed Lp(a) as a covariate. The estimated conditional odds ratio, its 95% confidence interval and the p-value from this model will be presented.
- Analysis of change from baseline to week 52 in the log-transformed Lp(a) measured before any planned lipoprotein apheresis session: An analysis of covariance (ANCOVA) model with treatment as a factor and baseline log(Lp(a)) as a covariate will be utilized. The estimates and the two-sided 95% confidence intervals will be provided for the geometric mean ratio to baseline at week 52 in both treatment groups, and for the geometric mean ratio (pelacarsen / placebo) at week 52. Furthermore, 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.

2.6.3 Handling of intercurrent events

The handling of intercurrent events has been provided in Section 1.2.2.

For the change from baseline to week 52 in the log-transformed Lp(a) secondary endpoint, missing Lp(a) data at week 52 will be multiple imputed based on a control-based Pattern-Mixture Model (PMM). Jump to reference approach will be utilized (Carpenter et al 2013), details can be referred to Section 5.5.2.1. 100 imputed datasets will be created. Each dataset will be analyzed using the above ANCOVA model. 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. From these outcomes, a pooled estimate and standard error will be derived using the Rubins rule (Rubin 1987), based on which p-values and 95% confidence intervals will be obtained via SAS PROC MIANALYZE. The final estimates will then be back transformed to the original scale and presented.

2.6.4 Handling of missing values not related to intercurrent event

- Missing lipoprotein apheresis data that are not related to treatment discontinuation will be multiple imputed following the same strategy with primary analysis. If the multiple imputation from primary analysis is performed, the corresponding multiple imputed Lp(a) and lipoprotein apheresis datasets will be directly utilized for the time to apheresis avoidance and total avoidance secondary endpoints, that is, the imputation will not be performed again for the secondary endpoints.
- For the change from baseline to week 52 in the log-transformed Lp(a) secondary endpoint, missing data not related to an intercurrent event is imputed under a MAR assumption.

2.6.5 Sensitivity analyses

There are no planned sensitivity analyses.

2.6.6 Supplementary analyses

There are no planned supplementary analyses.

2.7 Safety analyses

The SAF will be used in all safety analyses unless otherwise specified. All listings and tables will be presented by treatment group.

2.7.1 Adverse events (AEs)

All AEs, deaths, and serious adverse events will be listed. The MedDRA dictionary will be used for coding AEs. Treatment emergent AEs refer to events started after the first dose of study medication and that took place during the on-treatment period, as defined in Section 2.1.1.

In general, AEs will be analyzed for the following time periods defined below:

Pre-treatment adverse events

Adverse events and serious adverse events occurring between informed consent and first administration of study treatment (pre-treatment) will be summarized by primary system organ class and preferred term for all screened patients.

Adverse events during double-blind period

Adverse events and serious adverse events occurring after first administration of study treatment will be summarized by treatment, primary system organ class and preferred terms for safety set irrespective of how long after last study drug intake.

Treatment emergent adverse events

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

- 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.

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.

Overall summary of treatment emergent adverse events (AEs/SAEs, study medication related AEs/SAEs, AEs leading to drug interrupted, AEs leading to study drug discontinuation) will be summarized by the number and percentage of patients reporting particular events. Percentages will be based on the number of patients in the safety population.

The most common adverse events (>=10% of patients for each preferred term) will be presented by preferred term in descending frequency starting from the most common event. Study medication related AEs/SAEs, AEs leading to drug interrupted, AEs leading to study drug discontinuation, and AEs with fatal outcome will be summarized by treatment, primary system organ class, preferred term.

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by treatment. These events are defined in Section 2.7.1.1 that follows.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population. If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is $\leq$ 1 day gap between the end date of the preceding AE and the start of the consecutive AE.
- more than one occurrence will be counted if there is $>$ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE must be checked in a block, e.g., among AEs in a $\leq$ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest /grouping of AEs

Adverse events of special interest identified in the TQJ230 Development Safety Profiling Plan as representing potential compound and class related risks and general risks will be grouped. These safety topics of interest are evaluated based on a comprehensive analysis of AEs, using pre-defined groups of MedDRA PTs: Standardized MedDRA Query (SMQ) or Novartis MedDRA Query (NMQ).

Treatment emergent adverse events of special interest (AESI) and serious AESI will be summarized by treatment, associated level as defined in the case retrieval strategy, and preferred term. In addition, AESI and serious AESI will be summarized by treatment, preferred term, and maximum severity.

Adverse events of special interest are defined on the bases of an ongoing review of the safety data:

- CCI [redacted]
- Constitutional symptoms and CCI [redacted]
- Inflammatory adverse events
- Injection Site Adverse events
- Thrombocytopenia and bleeding events
- Hepatotoxicity
- Renal toxicity
- Immunogenicity

CCI [redacted] In addition, the events that occurred on the dosing date or one day after the dosing date will be summarized in a separate table.

For each of the above safety topic, the TEAE within the safety topic will be summarized by treatment group, using the numbers and the percentages of patients with at least one event, the Kaplan-Meier estimates for the cumulative incidence rates (one minus survival rates) for time to the first event. Kaplan-Meier plots for the cumulative failure probability will also be provided for each safety topic. Patients without the event will be censored (Section 5.4)

2.7.2 Deaths

All deaths will be listed at the individual participant level.

2.7.3 Laboratory data

All the below-mentioned summaries will be performed using the SAF.

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

Unscheduled visit mapping for laboratory data has been defined in Section 2.1.1.

For the numerical laboratory parameters, if the test value is below the lower limit of quantification (LLOQ), the test value will be imputed by 0.5 x LLOQ; if the test value is above the upper limit of quantification (ULOQ), the test value will be imputed by 1.5 x ULOQ.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, chemistry, and Urinalysis). Descriptive summary statistics (mean, median, standard deviation, Min, and Max) for the change from baseline to each study visit with lab assessment will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

Change from baseline = post baseline value – baseline value

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst value/category during double-blind period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a post-baseline value was normal, low, or high relative to whether the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group.

The frequency and percentage of participants with clinically notable laboratory results after baseline will be tabulated. Clinically notable laboratory results, for those parameters where ranges are available, are given in Table 2-1 below.

Table 2-1 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, > 150mmol/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)

A summary of newly occurring liver enzyme abnormalities compared to baseline will be provided. Liver enzyme abnormalities will be defined as criteria specified in Table 2-2.

Table 2-2 Hepatic events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>1.5xULN; >2xULN
DBL	>1.5xULN; >2xULN
TBL and DBL	TBL>1.5xULN+(DBL>ULN,>1.5xULN or >2xULN) TBL>2x ULN+(DBL>ULN, >1.5xULN or >2xULN)
ALP	>2xULN; >3xULN
(ALT or AST) & (TBL)	ALT or AST >3xULN & TBL >2xULN ALT or AST >5xULN & TBL >2xULN ALT or AST >8x ULN and TBL >2x ULN ALT or AST >10xULN & TBL >2xULN ALT or AST >20x ULN and TBL >2x ULN
ALP & (TBL)	ALP >3xULN & TBL >2xULN
For participants with normal ALT, AST and TBL values at baseline: (AST or ALT) & (TBL and ALP)	(AST or ALT >3xULN) & (TBL> 2xULN and ALP < 2xULN)
For participants with elevated ALT or AST or TBL at baseline: (AST or ALT) & (TBL and ALP)	[(AST or ALT >2xbaseline & >3xULN) or (AST or ALT >8xULN)] & [(TBL>2xbaseline & >2xULN) and ALP < 2xULN]
AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin, DBL = conjugated (direct) bilirubin	

The number of participants with renal events at any point during the study will be summarized as per Table 2-3.

Table 2-3 Renal events

Parameter	Criterion
Dipstick proteinuria	≥ 3+
Dipstick hematuria	≥ 3+
Protein-creatinine ratio (PCR)	≥1000 mg/g (≥100 mg/mmol)
Serum event	Serum creatine increases 50% or more (central laboratory) compared to baseline value

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Not applicable.

2.7.4.2 Vital signs

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

Descriptive summary statistics (mean, median, standard deviation, Min, Max) for the change from baseline to each post baseline scheduled visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for participants with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline visit – baseline value

The frequency and percentage of participants with clinically notable vital signs (based on the worst values in changes from baseline) will be tabulated. Clinically notable vital sign results are provided in Table 2-4 below:

Table 2-4 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-baseline value compared to baseline value.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable

2.10 Patient-reported outcomes

The absolute values, changes from baseline, and percentage change 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 factor and baseline scores 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.

2.11 Biomarkers

The FAS set will be utilized. There are two biomarker endpoints:

- Time-averaged Lp(a) levels
- Percent change in apoB (pre-lipoprotein apheresis) from baseline to week 52

The time-averaged Lp(a) level at each visit will be calculated using the Kroon formula (Kroon et al 2000):

$$C_{AVG} = C_{MIN} + 0.73(C_{MAX} - C_{MIN}),$$

where C_{MAX} and C_{MIN} are the immediate pre- and post-apheresis Lp(a) levels. All calculated time-averaged Lp(a) levels will be descriptively summarized by treatment using n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum and maximum. Further, the mean and median time-averaged Lp(a) levels will be depicted for each visit by treatment group.

The apoB biomarker will be descriptively summarized in terms of absolute and percentage change from baseline by scheduled visit and treatment.

2.12 Other Exploratory analyses

The FAS will be utilized to perform explanatory analyses for the following endpoints:

- 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.
- Total avoidance of lipoprotein apheresis between week 24 and 52.
- Percentage change total cholesterol, LDL-C, HDL-C, non-HDL-C, VLDL-C and triglycerides (pre-lipoprotein apheresis) from baseline to week 52.

The rate of lipoprotein apheresis sessions will be analyzed using a generalized linear model with logit link based on binomial distribution with treatment as factor and baseline log transformed Lp(a) as covariate, similarly to the primary analysis. The conditional odds ratio and the 95% confidence interval from the models with be presented. The standardized estimation will be calculated and provided as well (see Section 2.5.2).

Total avoidance of lipoprotein apheresis between week 24 and 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 factor and baseline log transformed Lp(a) as covariate. The conditional odds ratio and the 95% confidence interval from the model will be presented.

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

Percentage and absolute changes in total cholesterol, HDL-C, non-HDL-C, VLDL-C and triglycerides (pre-lipoprotein apheresis) will be summarized by scheduled visit and treatment.

Descriptive summary statistics (mean, median, minimum, maximum, geometric mean, and geometric coefficient of variation) for the observed data the change from baseline (mean, median, 1st and 3rd quantiles, minimum, and maximum) to each study visit for pre-apheresis Lp(a) will be presented by visit and treatment group. CCI [redacted]

2.13 Interim analysis

No interim analysis planned.

3 Sample size calculation

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 3-1 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, 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 [redacted] (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 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.

4 Change to protocol specified analyses

No change from protocol specified analyses was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

The partially missing AE start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study PDS.

5.1.3 Concomitant medication date imputation

The partially missing concomitant medication start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study PDS.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.1.4 CCI



5.2 AEs coding/grading

Coding of AE will be done per MedDRA dictionary.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Censoring rules

Table 5-2 Censoring rules for time to apheresis avoidance

Scenarios	Status	Date of Status
Alive, not prematurely discontinued from study, and at least 24 consecutive weeks of apheresis free until end of study (week 52)	Event	the date of the first visit with no apheresis session followed and no further apheresis sessions at subsequent visits until the end of the study
Death or prematurely discontinued from study, or at least one apheresis session after week 28	Censored	The earliest of the following dates: week 28 visit date, death date, end of study date

Note: In case of any missing data, time to apheresis avoidance is derived based on the imputed dataset.

Table 5-3 Censoring rules for time to the first event of the safety topic

Scenarios	Status	Date of Status
Patient had the event between first dosing date and LPLV	Event	The start date of the first event

Patient died or prematurely discontinued study and no event occurred	Censored	Death date or end of study date
Patients didn't die or discontinued study and no event occurred between first dosing date and LPLV	Censored	End of study date

5.5 Statistical models

5.5.1 Analysis supporting primary objective(s)

5.5.1.1 Missing data imputation for Lp(a) measured by Randox assay and utilized in the analysis of apheresis relevant efficacy endpoints

In this section, multiple imputation for Lp(a) measured by Randox assay will be described.

Both missing data related to an intercurrent event and not related to an intercurrent event will be imputed from the imputation model.

A two-step algorithm to impute the missing data is employed following the ideas outlined by Carpenter et al (2013), but instead of using a full Bayesian approach, an approximate Bayesian model is used; and the imputation strategy is MAR.

Then missing apheresis sessions will be imputed based on the rules described in Section 2.5.3 and 2.5.4.

Step 1:

An MMRM model is chosen as the imputation model. This models the joint distribution of each study participant's Lp(a) at different visits through a multivariate normal distribution with a single AR(1) covariance matrix across study arms. Different study participants are modelled as independent. The model includes the following covariates: study treatment, baseline Lp(a), and study treatment by visit interaction.

100 estimates of parameters from the MMRM model are obtained by repeatedly applying restricted maximum-likelihood (REML) parameter estimation of the MMRM model to nonparametric bootstrap samples. The bootstrap samples are obtained through resampling stratified by study arm from the original dataset.

The imputation model is fitted to all data observed prior to IE.

Step 2:

Missing data will be imputed under a MAR assumption.

For each of the 100 parameter estimates from Step 1, for each study participants with missing data, the joint distribution of observed and missing data $(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{miss}) \sim MN(\tilde{\boldsymbol{\mu}}, \tilde{\boldsymbol{\Sigma}})$ with mean $\tilde{\boldsymbol{\mu}} = (\tilde{\boldsymbol{\mu}}_{obs}, \tilde{\boldsymbol{\mu}}_{miss})$ and covariance matrix $\tilde{\boldsymbol{\Sigma}}$ is constructed. The mean vector $\tilde{\boldsymbol{\mu}}$ is chosen to reflect the imputation strategy. Then, the missing data is imputed by drawing from

conditional distribution $\boldsymbol{Y}_{miss}|\boldsymbol{Y}_{obs}$ of missing data given the observed values. This results in 100 complete data sets of Lp(a) values.

The multiple imputation described in this section will be implemented using R package rbmi.

Detailed information of the imputation of apheresis is described as follows:

For all apheresis missing data including missing apheresis sessions related to an IE (as described in Section 2.5.3) and missing apheresis sessions not related to an IE (as described in Section 2.5.4) will be imputed applying the following rules:

- No imputation will be performed after death date.
- No imputation will be performed when an apheresis session indicator (decision to perform/not perform apheresis) is present
- If the apheresis indicator is missing, it will be imputed by the following rules:
  1. Following an IE, premature study discontinuation occurred
     - for missing apheresis sessions after the premature study discontinuation, the apheresis indicator will be set to "Yes".
     - For missing apheresis sessions preceding the premature study discontinuation, refer to imputation rule #2 below.
  2. For missing apheresis sessions not related to an IE:
     - The apheresis indicator at the N visit will be set to Yes if the Lp(a) value at the N-1 visit is > 60 mg/dL, otherwise to No (the observed value at the N-1 visit or imputed if the observed value is missing will be used).

5.5.2 Analysis supporting secondary objective(s)

5.5.2.1 Missing data imputation for log-transformed Lp(a) measured by Roche assay and utilized in the analysis of change from baseline to week 52 in log-transformed Lp(a)

In this section, multiple imputation for log(Lp(a)) measured by Roche assay will be described.

Both missing data related to an intercurrent event and not related to an intercurrent event will be imputed from the imputation model.

A two-step algorithm to impute the missing data is employed following the ideas outlined by Carpenter et al (2013), but instead of using a full Bayesian approach, an approximate Bayesian model is used.

Step 1:

An MMRM model is chosen as the imputation model. This models the joint distribution of each study participant's log(Lp(a)) at different visits through a multivariate normal distribution with a single AR(1) covariance matrix across study arms. Different study participants are modelled as independent. The model includes the following covariates: study treatment, baseline log(Lp(a)), and study treatment by visit interaction.

100 estimates of parameters from the MMRM model are obtained by repeatedly applying restricted maximum-likelihood (REML) parameter estimation of the MMRM model to nonparametric bootstrap samples. The bootstrap samples are obtained through resampling stratified by study arm from the original dataset.

The imputation model is fitted to all data observed prior to IE. If post-intercurrent observations would be included in the model fit, then the imputation model would mistakenly estimate mean trajectories based on a mixture of observed pre- and post-intercurrent event data which are not relevant for reference-based imputations. Hence, any observed post-intercurrent event data are considered as missing and excluded for the model fit. However, such observations will not be replaced by imputed data, instead they will be added back to replace the corresponding imputed data, refer to details specified in Step 2.

Step 2:

Missing data not related to an intercurrent event is imputed under a MAR assumption, while missing data related to an intercurrent event is imputed under the jump to reference assumption, as outlined in Sections 2.6.3 and 2.6.4.

For each of the 100 parameter estimates from Step 1, for each study participant with missing data, the joint distribution of observed and missing data $(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{miss}) \sim MN(\tilde{\boldsymbol{\mu}}, \tilde{\boldsymbol{\Sigma}})$ with mean $\tilde{\boldsymbol{\mu}} = (\tilde{\boldsymbol{\mu}}_{obs}, \tilde{\boldsymbol{\mu}}_{miss})$ and covariance matrix $\tilde{\boldsymbol{\Sigma}}$ is constructed. The mean vector $\tilde{\boldsymbol{\mu}}$ is chosen to reflect the jump to reference strategy, that is, for study participants in the treatment arm who have the intercurrent event, the mean response distribution after the intercurrent event is that of the control arm.

Then, the missing data is imputed by drawing from conditional distribution $\boldsymbol{Y}_{miss}|\boldsymbol{Y}_{obs}$ of missing data given the observed values.

Post-intercurrent-event data that was removed as part of Step 1 is now added back in and replaces the corresponding imputed data. This results in 100 complete data sets.

The multiple imputation described in this section will be implemented using R package rbmi.

5.6 Analysis visit mapping rule

EOS visit for patients who died or discontinued study prior to week 52 will be mapped to the actual week using the following formula: week number for EOS visit = integer of (EOS date – randomization date +1)/7. For patients who complete the study, EOS will be mapped to Week 52 visit.

5.7 Rule of exclusion criteria of analysis sets

Table 5-3 Criteria leading to exclusion

Analysis set	Criteria that cause subjects to be excluded
SCR	Not having informed consent
RAN	Not in SCR;

Analysis set	Criteria that cause subjects to be excluded
FAS	Not randomized Not in RAN; Mis-randomized
SAF	No double-blind study drug taken

6 Reference

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