NOVARTIS

Clinical Development

KJX839/ Inclisiran

CKJX839A12402 / NCT05192941

Efficacy, safety, tolerability and quality of life of ongoing individually optimized lipid-lowering therapy with or without inclisiran (KJX839) – a randomized, placebo-controlled, double-blind multicenter phase IV study in participants with hypercholesterolemia

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 1
Release date:	20-Mar-2025
Number of pages:	54

Template Version 4.0, Effective from 23-Apr-2021

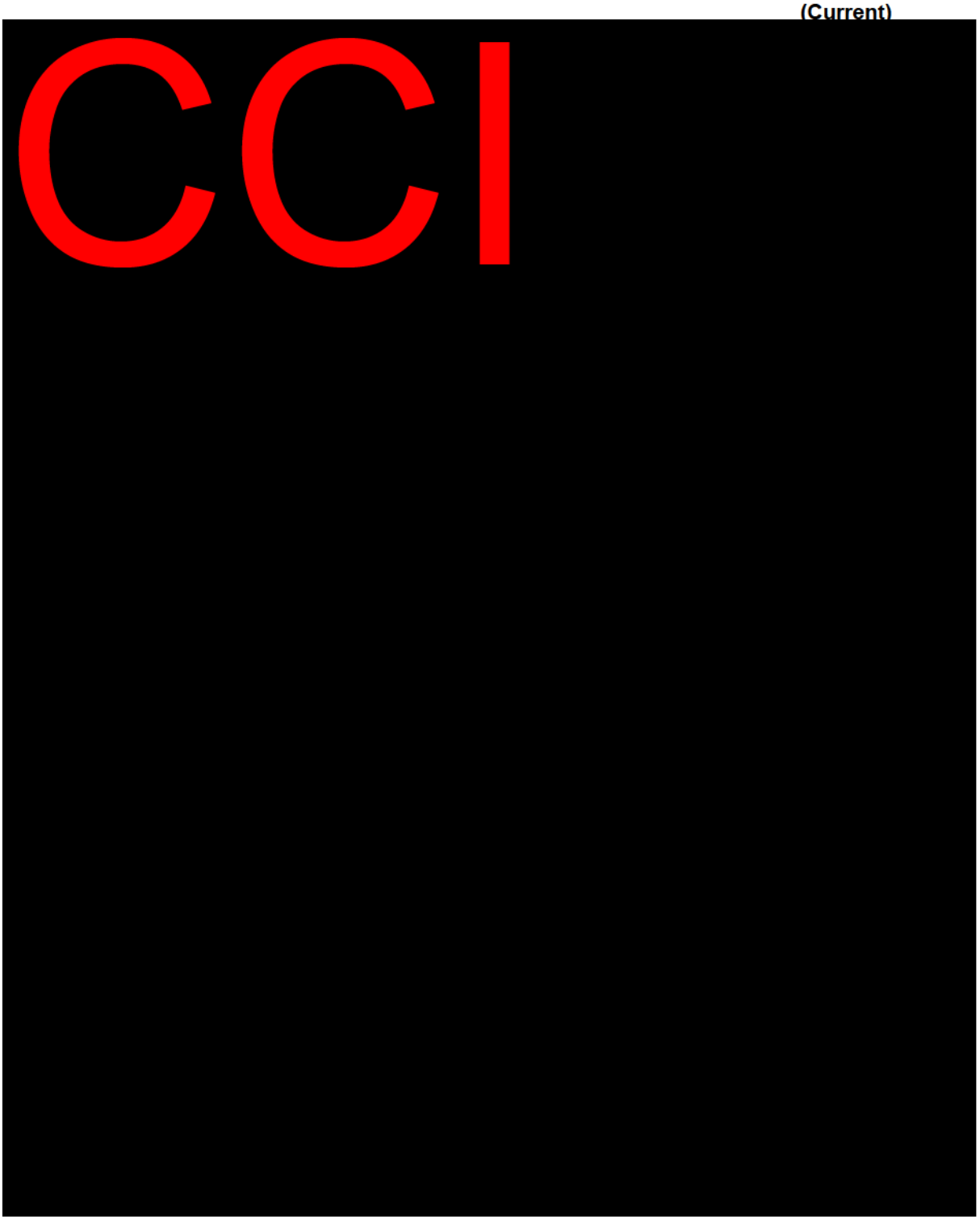
Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
CCI				

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
CCI				

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
CCI				

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)



Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
CCI				

Table of contents

List of tables

List of figures

List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AP	Angina Pectoris
ApoB	Apolipoprotein B
AR1	First order autoregressive
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AxMP	Auxiliary Medicinal Product
CI	Confidence interval
CK	Creatine kinase
CMH test	Cochrane-Mantel-Haenszel test
Covid-19	Corona virus disease 2019
Cox ph	Cox proportional hazard
CRO	Clinical research organisation
CRS	Case retrieval sheet
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovasculat disease
DBL	Database lock
DBP	Dyastolic blood pressure
DM	Diabetes mellitus
EAS	European Atherosclerosis Society
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
eq	Equal to
ESC	European Society of Cardiology
ESS	Eligible screened set
FAS	Full analysis set
FCS	Fully conditional specifications
FIML	Full information maximum likelihood
FPFV	First patient, first visit
GSRS	Gastrointestinal Symptom Rating Scale
HbA1c	Hemoglobin A1c

HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
ICF	Informed Consent Form
IRT	Interactive Response Technology
J2R	Jump to reference
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapy
Lp(a)	Lipoprotein a
LSM	Least square means
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiovascular Event
MacNew	MacNew Heart Disease Quality of Life Questionnaire
MAR	Missing (conditionally) at random
MCID	Minimal clinically important difference
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed model for repreated measures
MNAR	Missing not at random
MTD	Maximum tolerated dose
OR	Odds ratio
PAD	Peripheral artery disease
PCS	Physical component summary
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDS	Programming Dataset Specification
PT	Preferred term
Qx	Quantile x (here: first [25%] and third [75%])
RAN	Randomized set
RDO	Retrieved Drop Out
RIS	Run-in set
RR	Rate ratio
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCR	Screened set
SE	Standard error
SF-36	Short-Form health survey
SF-BPI	Short-Form Brief Pain Inventory
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries

SOC	System organ class
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal range
WIQ	Walking impairment questionnaire

1 Introduction

This document describes the detailed statistical methodology for the study CKJX839A12402, a randomized, placebo-controlled, double-blind multicenter phase IV study in adult participants with hypercholesterolemia to determine efficacy, safety, tolerability, and quality of life of ongoing individually optimized lipid-lowering therapy with or without inclisiran (KJX839).

The content of this Statistical Analysis Plan (SAP) is based on the amended clinical trial protocol No. CKJX839A12402, Version 03, 2-Sep-2024. All decisions regarding final analysis, as defined in this SAP document, have been made prior to the database lock (DBL) of the study data. The final clinical study report (CSR) will be prepared after the final DBL.

1.1 Study design

This interventional study is a double-blind, placebo-controlled multicenter study in adult participants (both sexes) with very high or high cardiovascular risk (as defined by the cardiovascular risk categories in the 2019 ESC/EAS guidelines for management of dyslipidemias (Mach et al 2020)) who do not meet their individual low-density lipoprotein cholesterol (LDL-C) target despite being treated with their individual maximum tolerated dose (MTD) of a statin, and if applicable, further lipid-lowering therapy (LLT).

This is a treatment strategy study where the participants are both randomized to inclisiran vs placebo and also simultaneously switched to rosuvastatin, and then have their LLT individually optimized by investigators.

The study design is depicted in Figure 1-1. The study consists of:

- A Screening period of approximately 14 days for all participants.
- An optional Run-in period of up to 120 days as indivually applicable.
- An optional additional baseline period of approximately 10 days as indiviually applicable for required labs.
- A Treatment period of 360 days (excluding a safety follow-up call 30 days after the end of treatment (EOT) visit or at least 90 days after last investigational treatment in case of early study discontinuation).

After signing the study Informed Consent Form (ICF), screening starts and will be used to determine participants' eligibility. If a participant meets all inclusion/exclusion criteria the participant is qualified to either proceed to the optional run-in phase or directly for randomization. Participants being treated with their MTD of statin at screening can directly undergo randomization at baseline, whereas participants treated with a statin dose that is not considered to be the participant's MTD will enter the run-in period. The screening period will be approximately 14 days for all participants.

A participant who enters screening and is determined not eligible will be considered as a screen failure. The investigator may re-screen the participant at a later time if he/she thinks that the participant's condition can fulfill all the eligibility criteria. A participant may only be rescreened once, and a minimum of 2 weeks must elapse between screening and re-screening visits.

An optional run-in period of up to 120 days takes place if the participant has not yet reached its individual MTD of statin therapy (definition see Section 3.2 in Protocol). Participants who meet their individual LDL-C target in the run-in period will be considered a run-in failure. Also, participants who do not reach a MTD up to Day 120 will be considered a run-in failure. These run-in failures will not be eligible for randomization or re-screening and will be discontinued from the study.

The double-blind treatment period begins with a subcutaneous injection of either inclisiran or placebo based on the participant randomization (randomization ratio 1:1, stratified for cardiovascular risk categories, Day 1). In addition, at baseline all participants will be switched from their individual statin to rosuvastatin, which is considered open label study treatment in this trial.

In a double-blind setting, the participant will be subcutaneously injected with 300 mg inclisiran sodium or placebo at Day 1, 90 and 270 during the treatment period by a delegated healthcare professional at the study site.

The baseline visit may be split into two visits planned approximately 10 days apart (Day -10, Day 1). The first visit on Day -10 will only be applicable for participants not randomized within 7 days from screening and for participants coming from run-in. Day -10 visit will only consist of lab draws for confirmation of eligibility.

At the Day 1 visit, all participants will additionally be switched from their individual statin to rosuvastatin. As per local SmPC, the recommended start dose for rosuvastatin is 5 mg/day or 10 mg/day. Considering local SmPC, the investigator will choose the appropriate rosuvastatin start dose level for a particular participant. Participants already treated with rosuvastatin prior to baseline will continue treatment with their individual MTD of rosuvastatin, if in accordance with the investigator.

If after the rosuvastatin titration to an individual MTD, a participant's individual LDL-C is not at target in either treatment arm, the LLT must be further escalated (see Protocol section 3.3 for further information).

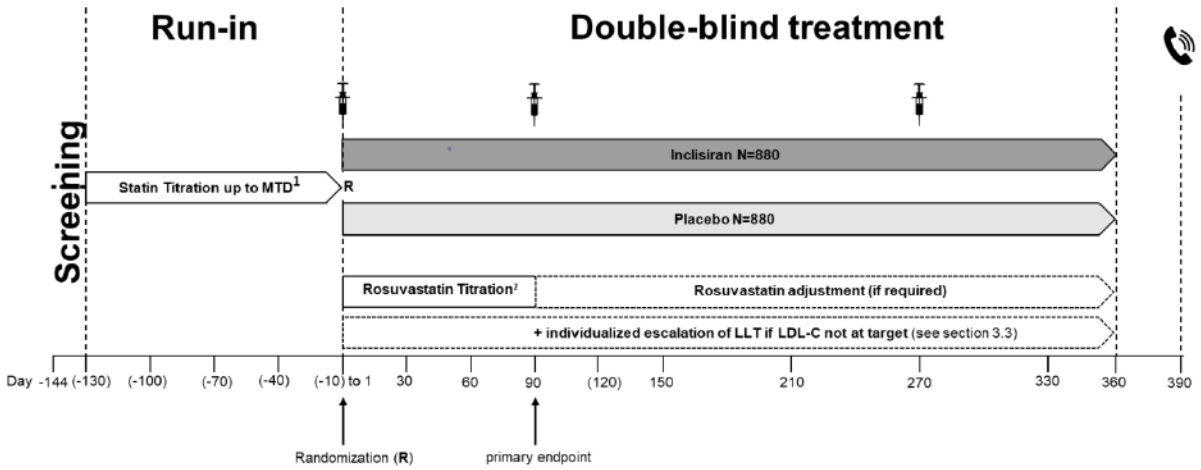
All randomized and/or treated participants will have a safety follow-up call conducted 30 days after last study visit or at least 90 days after last investigational treatment in case of early study discontinuation.

The overall study duration will be at least 360 days but can be longer depending on individual screening and run-in period time.

Around 1760 participants who meet the eligibility criteria will be randomized 1:1 at baseline. Since 35% of participants are expected to be screening or run-in failures, approximately 2700 participants are anticipated to be screened.

No interim analysis is planned for this study.

Figure 1-1 Study design



[1] Duration of the Statin Titration period during the run-in can be shorter than the depicted 120 days (see Protocol section 3.2)

[2] Duration of the Rosuvastatin Titration period during the double-blind treatment period can be shorter or longer (broken line arrow) than the depicted 90 days in both treatment arms (see Protocol section 3.4)

Notes: All days in parenthesis represent optional visits. A mandatory safety follow-up phone call must be given at Day 390.

1.2 Study objectives, endpoints and estimands

The study objectives and endpoints can be found in Table 1-1 (or Table 2-1 in Protocol).

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s) • To demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on reaching a participant's individual LDL-C target as defined in 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020).	**Endpoint(s) for primary objective(s)** • Proportion of participants achieving individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at Day 90.
Secondary objective(s) To demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on:	**Endpoint(s) of secondary objective(s)**

• Reducing mean LDL-C levels over the double-blind study period.	• Relative change (percentage from baseline to mean LDL-C level over the double-blind treatment period.
• Muscle-related adverse events.	• Proportion of participants experiencing at least one muscle-related adverse event (AE) as defined in the Standardized MedDRA Queries (SMQ) rhabdomyolysis / myopathy from Day 1 to Day 360.
• Annualized number of days pain is experienced using pain diary.	• Proportion of participants experiencing self-reported pain. • Annualized number of days participants experiencing self-reported pain from baseline to Day 360.
• Pain-related quality of life at Day 360 using the Short-From Brief Pain Inventory (SF-BPI).	• Change from baseline in SF-BPI pain severity score to Day 360. • Change from baseline in SF-BPI pain interference score to Day 360. • Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to Day 360. • Proportion of participants with clinically relevant change in SF-BPI pain interference score from Baseline to Day 360.
Exploratory objective(s)	**Endpoints(s) for exploratory objective(s)**
CCI	


CCI

1.2.1 Primary estimand(s)

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

The primary clinical question of interest is: What is the effect of inclisiran versus placebo on top of an ongoing individually optimized LLT on achieving the individual LDL-C target at Day 90 in very high risk and high risk participants as defined in the 2019 ESC/EAS guidelines for the treatment of dyslipidemias (Mach et al 2020).

The primary estimand is described by the following attributes:

1. **Population:** Adult participants categorized as very high risk or high risk as defined by the CV risk categories in the 2019 ESC/EAS guidelines for the management of dyslipidemias (Mach et al 2020) with elevated LDL-C despite being treated with the individual MTD of statin and, if applicable, also other LLT. Further details about the population are provided in Section 5 of the protocol
2. **Endpoint:** Proportion of participants achieving individual LDL-C target (< 55 mg/dL or < 70 mg/dL) at Day 90. The individual LDL-C target of the participants is determined according to their individual CV risk category.
3. **Treatment of interest:** Inclisiran, compared to placebo, both on top of an ongoing individually optimized LLT. Randomized treatments are the investigational treatment inclisiran or the placebo control treatment. In both treatment arms, participants receive an individually optimized rosuvastatin therapy for reaching the individual LDL-C target and tolerability. If required to achieve their LDL-C target, further individually optimized LLT can be administered. Additional information about the investigational treatment and control treatment are provided in Section 6 of the protocol.
4. **Summary measure:** The odds ratio of achieving individual LDL-C target at Day 90 compared between treatment arms. A larger proportion of participants indicates a superior outcome.

1.2.2 Secondary estimand(s)

The population and the treatment of interest associated with the secondary estimand are the same as for the primary estimand.

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures:

- Relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits).
- Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from Day 1 to Day 360.
- Annualized number of days participants experiencing self-reported pain from Day 1 to Day 360.
- Change from baseline in SF-BPI pain severity score at Day 360.
- Change from baseline in SF-BPI pain interference score at Day 360.
- Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to Day 360.
- Proportion of participants with clinically relevant change in SF-BPI pain interference score from Baseline to Day 360.

The applied summary measure will be described for each endpoint in the respective section. The handling of intercurrent events is described in Section 2.6.3.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by CCI [redacted] on behalf of Novartis using latest version of SAS available with CCI [redacted] according to the data analysis.

Final analysis will be conducted after all participants either completed the study or discontinued early and database was locked. Final analyses will be reported in the Final CSR. No interim analysis is planned for this study.

Unless otherwise stated, summary tables, figures and listings will include all participants of the considered analysis set, respectively.

Categorical data will be presented as frequencies and percentages. For continuous data, number of participants, mean, standard deviation, median, 25th (Q1) and 75th (Q3) percentiles, minimum, and maximum will be presented.

Details on number of decimals displayed are provided in the TFL-Shells.

2.1.1 General definitions

2.1.1.1 Investigational treatment

The investigational drug is inclisiran.

The formulation is 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) in 1.5 mL solution given as subcutaneous injection at Day 1, 90 and 270 by a delegated healthcare professional at the study site. The inclisiran-matching placebo is also given in 1.5 mL solution.

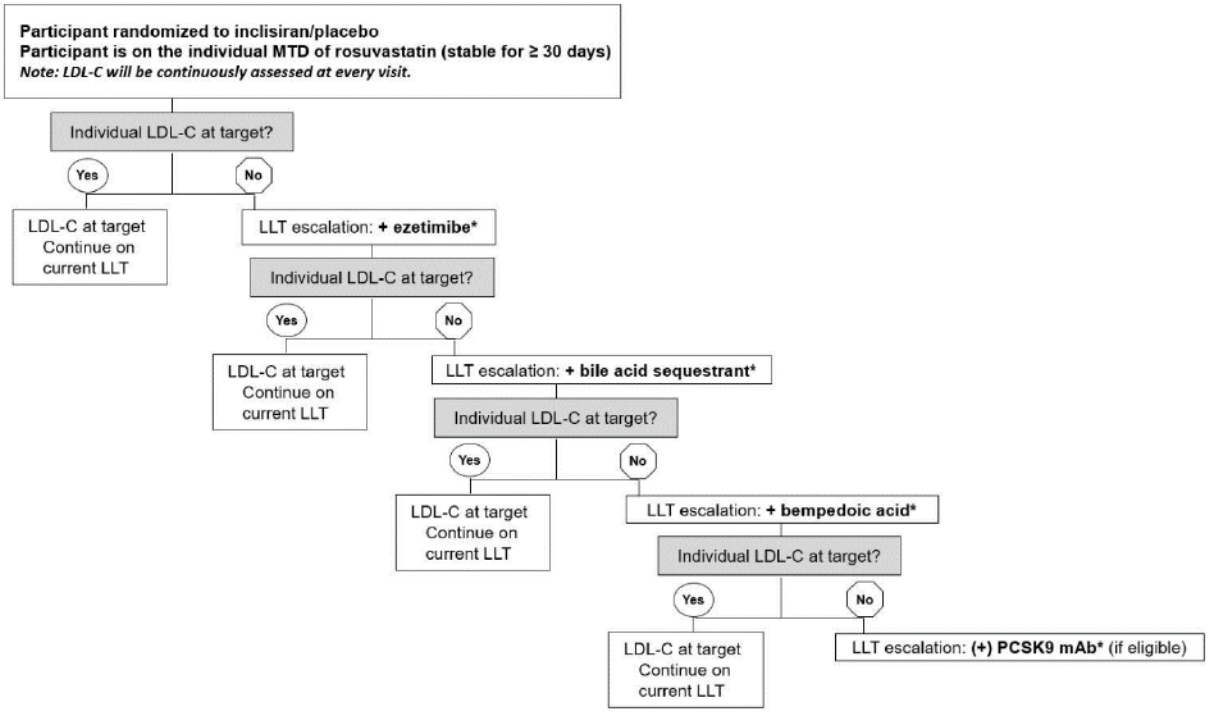
Additionally, at baseline visit all participants' background statin will be switched to rosuvastatin, which is considered open label study treatment and AxMP. Participants already on rosuvastatin at screening can be included up to a maximum of 10%. The starting dose for rosuvastatin will be 5 mg or 10 mg daily (per local SmPC and at discretion of the Investigator), with the dosage up titrated at each visit until the participants MTD or LDL-C target is achieved. Participants already receiving their MTD rosuvastatin prior to baseline will continue on their current dose in the treatment period.

The term blinded investigational treatment is used throughout the document and refer to the injection of double-blind treatment, i.e. Inclisiran/Placebo. The term open label study treatment refers to rosuvastatin.

2.1.1.2 Additional lipid lowering therapies

After randomization, if a participant receives their rosuvastatin MTD for at least 30 consecutive days and the participant is still not at their individual LDL-C target, the LLT must be further escalated as per recommended process (see Figure 2-1 here and Section 3.4 in Protocol for further information).

Figure 2-1 Recommended treatment scheme based on ESC/EAS guidelines in combination with relevant HTA requirements



(+) Please refer to Section 3.4 in Protocol
* If indicated as per (local) SmPC

2.1.1.3 Treatment arms

The study consists of two treatment arms. Study participants will be assigned to one of the following treatment arms based on randomization in a ratio of 1:1:

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

The investigational treatment duration is planned for 360 days.

2.1.1.4 Study days

Study days will be calculated with respect to the first dose of investigational treatment.

The first day of administration of investigational treatment (first dose) is defined as Day 1. Day -1 will be the day before Day 1. Day 0 does not exist.

For assessment collected on or after Day 1, the study day is calculated as the difference between the date of assessment and the date of first dose plus 1 (= date of assessment – date of first dose + 1), while the study day for assessments prior to the first dose will be calculated as the difference between the date of assessment and the date of first dose (= date of assessment – date of first dose).

Duration of an event (e.g. adverse event, hospitalization) is calculated as the difference between the end and the start date of the event plus 1 (= event end date – event start date + 1).

2.1.1.5 Baseline

Baseline value is defined as the last non-missing value prior to the start of the treatment period, which means prior to the first injection of the blinded investigational treatment. If the date of assessment is the same as date of first injection but time is not available for comparison, the assessment is assumed to be prior to the administration of blinded investigational treatment. Questionnaires assessments at Day 1 are considered as baseline irrespective of time collected.

Participants pain diary is not collected prior to first injection of the blinded investigational treatment, therefore baseline is not defined for the same.

2.1.1.6 Post-baseline measurements / change from baseline

Post-baseline measurements are defined as assessments performed at and after start of blinded investigational treatment injection.

If absolute change from baseline is of interest, the change will be calculated as the difference between post-baseline value and the baseline value, if both values are not-missing. Relative change from baseline is given as the change from baseline relative to the baseline value times 100 (= [change from baseline / baseline value]*100), if baseline value is not zero and both values are not missing.

2.1.1.7 Visits

Measurements will be collected without windowing as defined in the protocol. Analysis windows will be used for analysis of the data as outlined in Table 2-1.

Based on the study day a scheduled or unscheduled visit is performed, the visit will be allocated to the analysis visit within the corresponding analysis visit window. E.g., if the Day 30 visit of a participant is delayed and occurs on day 33 it will be allocated to analysis visit Day 30. In the case of deviations from the visit schedule, or due to unscheduled visits, several assessments of a participant may fall in a particular analysis window (either scheduled or unscheduled).

If two measurements are allocated to the same analysis window and one is scheduled and the other unscheduled, the scheduled visit will be prioritized regardless of the difference to the target day (even if the unscheduled visit is closer to target day). If at least two scheduled or at least two unscheduled visits are allocated to the same analysis window, the measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart (e.g., one day before target date and one day after) and both are either scheduled or unscheduled the last one will be used.

In case an analysis visit for a specific assessment is not planned (e.g., vital signs at Day 60), the time span (in days) between two visits is split equally and mapped to the former or consecutive analysis visit window, respectively.

The mapped visits will be used in the 'by visit' analysis as allocated. However, the listings will contain all information regardless if the collected data is based on a mapped or not-mapped, scheduled or unscheduled visit.

Table 2-1 Analysis visit windows based on study days

	Analysis window (study days)								
Analysis Visit	SF-BPI, GSRS, Clinical chemistry (if also in Limited Chemistry)	Clinical Chemistry (and not in Limited Chemistry)	Fasting lipid profile (includes LDL-C for efficacy analyses)	Hematology, Urinalysis	Fasting Lp(a)	PCSK9	Vital signs	SF-36	WIQ, Mac New, TSQM
Pre-dose	<= 1 pre-dose	<= 1 pre-dose	<= 1 pre-dose	<= 1 pre-dose	<= 1 pre-dose	<= 1 pre-dose	<= 1	<= 1	<= 1
Day 30	30 [1 post-dose, 45]	.	.	.	.	.	30 [2, 60]	.	.
Day 60	60 [46, 75]	.	60 [1 post-dose, 75]	.	.	.	.	.	.
Day 90	90 [76, 120]	90 [1 post-dose, 120]	90 [76, 120]	.	90 [1 post-dose, 225]	.	90 [61, 120]	90 [2, 150]	90 [2, 225]
Day 150	150 [121, 180]	150 [121, 180]	150 [121, 240]	150 [1 post-dose, 255]	.	.	150 [121, 180]	.	.
Day 210	210 [181, 240]	210 [181, 240]	.	.	.	.	210 [181, 240]	210 [151,285]	.
Day 270	270 [241, 300]	270 [241, 300]	.	.	.	.	270 [241, 300]	.	.
Day 330	330 [301, 345]	330 [301, 345]	330 [241, 345]	.		.	330 [301, 345]	.	.
EOS/EOT (Day 360)	360 [>=346]	360 [>=346]	360 [>=346]	360 [>=256]	360 [>=226]	360 [>=1 post dose]	360 [>=346]	360 [>=286]	360 [>=226].

2.1.1.8 Cardiovascular risk category

Randomization was stratified by cardiovascular (CV) risk category ("very high" and "high").

The stratification of “high” and “very high” for cardiovascular risk used in the statistical analysis will be programmatically derived based on eCRF data as the last assessment of CV risk prior to first dose of double-blind treatment. The stratification factor recorded at randomization will not be used in the statistical analysis. Strata recorded in the IRT data, and derived strata (from data reported on the eCRF) will be listed and flagged if discrepant.

Whenever “CV risk category” is mentioned throughout the remainder of this document, this refers to the derived CV risk category prior to first dose of double-blind treatment, if not specified otherwise.

2.1.1.9 Last contact date

The last date of contact is defined as the latest date out of assessment dates and event/medication start and end dates. In case of death, autopsy dates will not be considered in determining the last contact date.

2.1.1.10 Reflexive LDL-C

The endpoints involving LDL-C will use a reflexive LDL-C approach. When both calculated and beta-quantified LDL-C are available, calculated LDL-C will be used unless triglycerides are greater than 400 mg/dL or calculated LDL-C is less than 40 mg/dL. When only calculated LDL-C or beta-quantified LDL-C is available but not both, the available one will be used. Only measurements from central lab will be used for the analyses.

2.2 Analysis sets

The **screened set (SCR)** consists of all participants who signed the 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 **run-in set (RIS)** consists of all participants who enter the run-in phase.

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 who received at least one dose of blinded investigational treatment. 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 blinded investigational treatment. Participants will be analyzed according to the blinded investigational treatment received. A participant who receives any amount of double-blind inclisiran throughout the study will be analyzed within the inclisiran treatment group for the safety analyses. Concomitant use of commercially available inclisiran during the study will

not be considered, those are considered as part of the intercurrent events. The SAF will be used for the analyses of safety and tolerability variables.

Additionally, the **AP set** is a subset of the FAS and includes participants with a diagnosis of angina pectoris at baseline, i.e. participant has a recorded medical history of stable angina or unstable angina. and the **PAD set** is a subset of the FAS and includes participants with a diagnosis of peripheral artery disease at baseline, i.e. participant has a recorded medical history of peripheral artery disease.

2.2.1 Subgroup of interest

Subgroup analysis for the following subgroups will be conducted for primary and the secondary endpoints:

- Age groups (18 – <65 years, 65 – < 75 and ≥75),
- Sex (male, female),
- CV risk category (very high risk, high risk).

Subgroup analyses will be conducted using the analyses as for primary and secondary endpoints which are included in the testing hierarchy including a subgroup and treatment-by-subgroup factor into the respective statistical analysis model (for negative binomial regression and logistic regression) and subgroup and treatment-by-subgroup, visit-by-subgroup and visit-by-treatment-by-subgroup factor (for MMRM). The estimates for the respective subgroup and corresponding 95% CI will be presented.

Subgroup analyses will only be performed if each subgroup includes more than 10 participants and additionally for binary outcomes if in at least one subgroup 10 events occurred. If there are still convergence issues for the subgroup analyses after considering all steps for in case of non-convergence (see Section 5.5), age categories may be combined.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants screened, randomized and included in the FAS will be presented by treatment group and overall for the SCR.

The reasons for discontinuation prior to randomization (including screening and run-in failures) will be provided for the SCR and RIS. Mis-randomized participants will be considered as screening/run-in failures.

The number and proportion of participants who completed the study, who discontinued the study and the reason for discontinuation from study will be presented in a study disposition table for each treatment group and overall based on the RAN.

The number of participants included in each analysis set will be presented by treatment group using SCR, corresponding percentages will be based on RAN. Participants excluded from analysis sets will be listed with reasons for exclusion.

For each protocol deviation, the number and percentage of participants in RAN for whom the deviation applies will be tabulated by category and deviation term. In addition, a listing of participants with protocol deviations will be provided.

Number and percentage of participants not meeting inclusion/exclusion criteria will be summarized for participants discontinuing prior to randomization.

2.3.2 Demographics and other baseline characteristics

The following participant demographic and baseline characteristics will be summarized descriptively by treatment group for the FAS:

- Age (years)
- Age groups (18 - <25 years, 25 - <45 years, 45 – <65 years, 65 - < 75 and ≥75),
- Age groups (18 – <65 years, 65 – < 75 and ≥75),
- Sex (male, female, unknown, undifferentiated),
- Country (Germany, Estonia, Latvia, Czech Rep, Spain, France, Poland, Bulgaria)
- Height (cm)
- Body weight (kg)
- BMI (kg/m^2), calculated as weight in kg divided by (height in m)^2
- BMI group (< 18.5 kg/m^2, 18.5 - <25 kg/m^2, 25-<35 kg/m^2, => 35 kg/m^2)
- Statin use at baseline visit (% of participants on respective statin),
- Statin dose intensity at baseline visit
- CV risk category (high, very high)
- CV disease history, including but not limited to the following:
    - Myocardial Infarction
    - Unstable Angina
    - Stable Angina
    - Ischemic Stoke
    - Non-Ischemic Stroke
    - Trans ischemic Attack
    - Peripheral Artery Disease
    - Prior PCI
    - Prior stent implantation (Coronary)
    - Prior CABG
    - Primary Dyslipidaemia/ Hyperlipidaemia
    - Familial Hypercholesterolemia
    - Hypertension
    - Heart Failure
    - Atrial Fibrillation
    - Supraventricular Tachycardia

    - Diabetes Mellitus
    - Diabetic Retinopathy
    - Diabetic Nephropathy
    - Diabetic Neuropathy
- Alcohol history (Current, Never, Former)
- Smoking and vaping history (Current, Never, Former)
- Fasting Lipid profile
    - Lp(a) (nmol/L)
    - ApoB (µmol/L)
    - LDL-C (mg/dL)
    - HDL-C (mmol/L)
    - non-HDL-C (mmol/L)
    - total cholesterol (mmol/L)
    - triglycerides (mmol/L)
- relevant laboratory tests (Central lab)
    - AST (U/L)
    - ALT (U/L)
    - total bilirubin (µmol/L)
    - CK (U/L)
    - Creatinine Clearance (U/L)
    - eGFR (mL/min/1.73m^2),
    - fasting glucose (mmol/L)
    - HbA1c (%)
- vital signs
    - SBP (mmHg),
    - DBP (mmHg),
    - Pulse (bpm)

Baseline values corresponding to laboratory measurements in the lipid panel refer to assessments collected on Day 1 of the study (before the first administration of the blinded investigational treatment).

2.3.3 Medical history

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) terminology using the most recent version at the time of database lock.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT) and treatment group based on FAS.

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

2.4.1 Investigational treatment / compliance

The duration of the double-blind treatment period will be computed as the time from the first dose of double-blind treatment to the earliest date out of

- last contact date or
- the participant's death or
- the participant's study completion visit (EOS) date.

The on-treatment period duration will be computed as the time from the first first dose of double-blind treatment to the earliest date out of

- the last injection plus exposure attributable time length of 180 days or
- last contact date or
- the participant's death or
- the participant's study completion visit (EOS) date.

This algorithm reflects intended observation period and the planned treatment schedule and the exposure attributable period of the blinded investigational treatment. The duration of the double-blind treatment period and the duration of the on-treatment period will be summarized for the SAF by treatment group descriptively including by duration categories. The duration categories are given by the number of blinded investigational treatment injections (1 to 3).

The participantyears of exposure will be calculated as the sum of duration of on-treatment period for all participants in days divided by 365.25.

The number of participants with dose adjustments (interruptions or permanent discontinuation) and the reasons will be summarized by treatment and all dosing data will be listed.

The number of study injections administered will also be summarized by treatment group.

2.4.2 Open-label study treatment – AxMP (rosuvastatin)

The duration of exposure to open label study treatment (rosuvastatin) will be computed as the time from the first to the last administration of rosuvastatin excluding interruptions (i.e. minus number days where dose interruption is reported). The duration of exposure will be summarized as for the blinded investigational treatment.

The mean daily administered dose of rosuvastatin averaged over time for an individual participant and over investigational treatment arm will be reported for the double-blind treatment period as well as for the on-treatment period. Interruptions are considered with a dose of 0 mg. For every visit, the number of participants by dose of rosuvastatin administered will be presented. Additionally, the reason for reaching their rosuvastatin MTD will be reported by the number of participants for every specific reason by visit and by investigational treatment arm.

The number of participants with dose adjustments (interruptions or permanent discontinuation) and the reasons will be summarized by treatment and all dosing data (dose level and mean dose) will be listed.

2.4.3 Prior and concomitant lipid lowering therapy

Prior medications and significant non-drug therapies are defined as any medication and significant non-drug therapies taken prior to the first dose of double-blind treatment (i.e. started and stopped prior to first dose). Concomitant medications and significant non-drug therapies are defined as those used during the double-blind period (i.e. started or stopped after first dose of double-blind treatment). Medications taken at date of first dose of double-blind treatment are considered as concomitant.

Prior and concomitant lipid lowering therapy will be summarized for the SAF in separate tables and separate from the standard prior and concomitant medication reporting, based on the coding dictionary used. Lipid lowering medications will be presented in alphabetical order, by preferred terms (PT) and grouped by Anatomical Therapeutic Chemical (ATC) class. ATC class refers to the 4th level ATC class. Tables will show the overall number and percent of participants receiving at least one drug of a particular preferred term and at least one drug in a particular ATC class. A participant with multiple medications with the same preferred term is only counted once towards the total of the preferred term. Summaries will be separate for prior medications and concomitant medications. Additional summary is provided for medications taken at Day 1.

The number of participants on any of the four considered LLT medications (ezetimibe, bile acid sequestrants, bempedoic acid, PCSK9 mAb) will be summarized by visit for both investigational treatment arms. Furthermore, the number of participants for whom the protocol-recommended lipid-lowering therapy escalation was not followed will be reported by reason for not following for every visit. Additionally, the number of participants reaching their LDL-C target under LLT escalation will be provided by visit, investigational treatment and rosuvastatin dose. Duration of exposure to LLT medication will be computed and summarized by type of LLT concomitant medication used. Duration of exposure is derived as the total number of days the respective LLT was taken by the participant between first dose of double-blind treatment and last contact date.

2.4.4 Prior, concomitant and post therapies

Prohibited concomitant medications as mentioned in Table 6-3 of the protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized by preferred term.

Prior and concomitant medications (excluding LLTs) will be summarized for the SAF in separate tables based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms (PT) and grouped by ATC class. Tables will show the overall number and percent of participants receiving at least one drug of a particular preferred term and at least one drug in a particular ATC class. A participant with multiple medications with the same preferred term is only counted once towards the total of the preferred term.

Summaries will be provided separately for prior medications and concomitant medications. Additional summary will be provided for medications taken at Day 1.

2.5 Analysis supporting primary objective(s)

The primary objective is to demonstrate the superiority of inclisiran on top of ongoing individually optimized LLT compared to placebo on top of ongoing individually optimized LLT on reaching a participant's individual LDL-C target.

2.5.1 Primary endpoint(s)

The primary endpoint for this study is the proportion of participants at Day 90 achieving their individual LDL-C target of less than 55 mg/dL or less than 70 mg/dL, i.e. <55 mg/dL for participants with very high cardiovascular risk and <70 mg/dL for participants with high cardiovascular risk. The participant-individual LDL-C target depends on their cardiovascular risk category at time of the LDL-C measurement and will be evaluated according to the most recent assessment of CV risk as determined by the investigator. Accordingly, the achievement of the participant-individual LDL-C target forms a binary response variable for LDL-C target ("achieved"/"not-achieved") and will be analyzed in the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary null hypothesis to be rejected is that the odds regarding participants achieving their individually optimized LDL-C target at Day 90 are equal between treatment groups and therefore independent of the injection of inclisiran or placebo.

The primary null hypothesis and the alternative hypothesis tested can be described as:

$$H_{01}: OR := \frac{(p_1(1-p_1))}{(p_0(1-p_0))} \leq 1 \; vs. \; H_A: OR > 1$$

with p_1 and p_0 the proportion of participants achieving their individually optimized LDL-C target in the inclisiran (p_1) or placebo (p_0) group, respectively. If the null hypothesis cannot be rejected no conclusion regarding a superior effect of inclisiran to reach the individual LDL-C target can be drawn.

For the primary analysis, the odds ratio between inclisiran vs. placebo of the participants achieving their individual LDL-C target at Day 90 will be estimated using a logistic regression model. Treatment and CV risk category will be included as factors in the model. The odds ratio, associated 95% confidence interval (CI), and one-sided p-value will be estimated. Details on testing procedure are described in Section 2.6.2.5.

The number and percentage of participants achieving the individual LDL-C target at Day 90 will be presented for each treatment group derived from data as observed after accounting for intercurrent events as described in Section 2.5.3. The odds ratio, associated 95% CI, and one-sided p-value will be derived from multiply imputed data.

2.5.3 Handling of intercurrent events

The general strategy to account for different intercurrent events is summarized in Table 2-2. Additional explanation is given in the following:

1. **Discontinuation of investigational treatment:**
   Follow-up information after permanent discontinuation of investigational treatment, Retrieved Drop Out (RDO) data will be collected at regular study visits and will be included in the analysis, with treatments as assigned at randomization (treatment policy strategy). If no RDO data are collected missing data will be imputed using jump to reference as described in Section 5.5.3.
2. **Death:**
   For participants who die no subsequent LDL-C value can exist, therefore only pre-death data will be considered. For deceased participants the last value measured before death will be included into the analysis (while alive strategy).
3. **Use of PCSK9 targeting non-study medication or lipid apheresis:**
   It could occur that participants are switched to PCSK9 targeting therapy after discontinuation of study medication or receive lipid apheresis. For the primary estimand participants who use PCSK9 targeting non-study medication or lipid apheresis will be considered as not achieving their LDL-C target (composite strategy).
4. **COVID-19 pandemic impact on study:**
   For the primary estimand collected data will be included in the analysis. The treatment groups will be kept as assigned at randomization (treatment policy strategy). All observed data are used for the analyses, missing data are imputed as described in Section 2.5.4.

Table 2-2 Account for different post randomization events for the primary endpoint reaching LDL-C target at day 90

Intercurrent event	Strategy
Permanent discontinuation of investigational treatment	*Treatment policy strategy*
Death	*While alive strategy*
Use of PCSK9- targeting non-study medication* or lipid apheresis	*Composite strategy*
COVID-19 pandemic impact on study	*Treatment policy strategy*

** evolocumab, alrocumab or commercially available inclisiran*

Change in background medication essentially concerns change in LLT during optimization. A change in background medication is therefore not considered as an intercurrent event because it is part of the treatments compared.

If an assessment at a visit is affected by multiple intercurrent events, strategy for the intercurrent events occurring will be applied considering the following order of decreasing importance: first composite, followed by while alive and treatment policy.

2.5.4 Handling of missing values not related to intercurrent event

Missing values will be imputed by multiple imputation. In a first step the continuous LDL-C level will be imputed by m = 100 imputations based on FAS. From the imputed continuous LDL-C level the binary response variable will be derived against the individual LDL-C target and analyzed with the methods described in the related section. Results will be combined according to Rubin's rules on the log scale. The imputation model will impute missing values based on all observed values taking into account strategy applied for the respective intercurrent event. The imputation model will include randomized treatment arm and CV risk category. Details are described in Section 5.5.3.

2.5.5 Sensitivity analyses

As sensitivity analysis the primary analysis will be repeated excluding participants with a protocol deviation (PD) concerning risk category criteria not met. The following PDs are considered for exclusion of participants:

- INCL03: "Cardiovascular risk category criteria not met"
- INCL04a: "Very high risk criteria and LDL-C target met"
- INCL04b: "High risk criteria and LDL-C target met"

2.5.6 Supplementary analyses

2.5.6.1 Relative risk and absolute risk difference

Additionally, the relative risk as well as absolute risk difference and their 95% confidence intervals will be estimated from a Cochran-Mantel-Haenszel test (CMH) stratified for CV risk category . Analysis is based on data as observed after accounting for intercurrent events as described in Section 2.5.3.

2.5.6.2 Exploratory endpoints

2.5.6.3 PCSK9 targeting non-study medication or lipid apheresis supplementary analysis

With a supplementary analysis the impact of allowing the use of PCSK9 targeting non-study medication or lipid apheresis will be investigated. Therefore, the individual LDL-C target of participants receiving PCSK9 targeting non-study medication or lipid apheresiswill not be

considered a treatment failure (composite strategy). For this supplementary strategy the primary analysis will be repeated but LDL-C values observed during or after the use of a PCSK9 targeting non-study medication or lipid apheresis will be evaluated according to participant-individual LDL-C target as measured.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The population and the treatment of interest associated with the secondary estimand are the same as for the primary estimand (see Section 1.2.1).

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures in Table 2-3:

Table 2-3 Endpoints and summary measures of the secondary estimand

Endpoint	Summary Measure
Relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits)	Difference in mean relative change
Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from Day 1 to Day 360	OR (odds ratio)
Annualized number of days participants experiencing self-reported pain from Day 1 to Day 360	Annualized RR (rate ratio)
Change from baseline in SF-BPI pain severity score at Day 360	Difference in mean relative change
Change from baseline in SF-BPI pain interference score at Day 360	Difference in mean relative change
Proportion of participants with clinically relevant change in SF-BPI pain severity score from baseline to Day 360.	OR (odds ratio)
Proportion of participants with clinically relevant change in SF-BPI pain interference score from Baseline to Day 360.	OR (odds ratio)

2.6.2 Statistical hypothesis, model, and method of analysis

For muscle-related AE / SMQ rhabdomyolysis / myopathy the SAF will be used for analysis. For all other secondary efficacy analyses the FAS will be used.

2.6.2.1 Mean relative change in LDL-C

The null hypothesis to be rejected for the relevant secondary endpoint is:

- H_{02}: The mean relative changes from baseline in LDL-C level, averaged over all post baseline visits during the double-blind treatment period, are equal between treatment groups.

The relative change (percentage change) from baseline in LDL-C level averaged over the double-blind treatment period will be analyzed using a mixed model for repeated measures (MMRM) including treatment group, CV risk category, scheduled visit and the interaction of treatment group with scheduled visit as factors and baseline LDL-C level and the interaction of baseline LDL-C level with scheduled visit as covariates. To allow adjustment for correlations between time points within participants, an unstructured variance-covariance structure will be used. The null hypothesis of equal mean changes between both groups to the average over all post baseline visits will be tested by an appropriate linear contrast of the variable treatment and treatment by visit interaction.. The adjusted mean change from baseline as well as the treatment difference and their corresponding 95% confidence intervals will be presented.

Least square means of each treatment group and estimated treatment differences at visits and corresponding 95% confidence intervals will be tabulated and presented graphically.

2.6.2.2 Proportion of muscle-related adverse events

The null hypothesis to be rejected for the relevant secondary endpoint is:

- H_{03}: The odds regarding participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from Day 1 to Day 360 are equal between treatment groups.

Muscle-related AEs are defined by the SMQ rhabdomyolysis / myopathy (covering narrow and broad search). The proportion of participants experiencing at least one muscle-related AE from Day 1 to Day 360, i.e. occurring between first dose of double-blind treatment up to the minimum of last contact date and Day 360 visit date, will be analyzed in a logistic regression model. Treatment and CV risk category will be included as factors in the model. The odds ratio and its 95% confidence interval (CI) and p-value will be estimated.

Additionally, the relative risk as well as absolute risk difference and their 95% confidence intervals will be estimated from a Cochran-Mantel-Haenszel test (CMH) stratified for CV risk category.

2.6.2.3 Annualized number of days with pain

Participant reported secondary endpoints are the number of days participants experiencing self-reported pain (at its worst in the last 24 h on a numeric rating scale from 0 (no pain) to 10 (pain as bad as you can imagine)) from Day 1 to Day 360 as reported in the electronic diary. A day with pain is defined as a day with a numeric score > 0. The annualized count (number of days pain) for each participant is calculated as the total counts during the study divided by the total individual observation time of that participant in the double-blind treatment period (between first dose of double-blind treatment up to the minimum of last contact date and Day 360 visit date) where pain diary was completed, multiplied by 365.25.

The null hypothesis to be rejected for the relevant secondary endpoint is:

- H_{04} : The annualized mean number of days pain is experienced is equal between both treatment groups.

The number of pain days experienced will be analyzed using a negative binomial model with the number of observed pain days as the dependent variable and treatment group and CV risk category as fixed-effect factors and the logarithmic follow-up duration (days between first dose of double-blind treatment up to the minimum of last contact date and Day 360 visit date where diary was completed) in years as the off-set. The annualized occurrence rates (i.e. number of pain days per year) and their 95% confidence intervals estimated from the model will be provided by treatment group. The treatment comparison will be performed through the estimated occurrence rates. The occurrence rate ratio and its 95% confidence interval will be provided.

If the negative binomial model fails to converge a quasi-Poisson model will be used instead.

Proportion of patients without any day with pain will be displayed descriptively where pain diary was completed.

2.6.2.4 Change from baseline in SF-BPI score (pain severity and pain interference)

Participant reported secondary endpoints are the mean change from baseline in Short-Form Brief Pain Inventory (SF-BPI) at Day 360 in pain severity and pain interference score.

The null hypothesis to be rejected for the relevant secondary endpoints are:

- H_{05} : The mean change from baseline in SF-BPI pain severity score to Day 360 is equal between treatment groups.
- H_{06} : The mean change from baseline in SF-BPI pain interference score to Day 360 is equal between treatment groups.

The SF-BPI is a self-administered standardized fifteen items questionnaire that assesses how pain interferes with or influences a participant's life. The query period covers the past 24 hours and takes 5 minutes for the participant to complete (see also Section 8.5.1.1 in Protocol).

The pain severity and interference scores will be derived for each visit between screening and EOT/EOS (Day 360). To derive the pain severity score the average of the four items concerning pain intensity will be taken. Accordingly, the pain interference score will be calculated as the average of the seven items concerning pain interference. Both scores will be between 1 and 10. The remaining items do not contribute to the scoring. An overall score is not defined.

If there is missing data for a participant and the available data is more than 50% for the corresponding domain (3 of 4 [pain severity] or 4 of 7 [pain interference], respectively), the missing items will be imputed using the mean score of the non-missing item scores. Else no imputation will be done and the domain score will be imputed according to the general handling of missing values as described in Section 2.6.4.

The higher the scores, the poorer is the condition of the participant. Changes from baseline scores are defined as clinically relevant, if the pain severity score and the pain intensity score change by at least 2 points.

The absolute change from baseline in SF-BPI pain severity score and SF-BPI pain interference score will be analyzed using a mixed model for repeated measures (MMRM) including

treatment group, CV risk category, scheduled visit and the interaction of treatment group with scheduled visit as factors and corresponding baseline SF-BPI score and the interaction of corresponding baseline SF-BPI score with scheduled visit as covariates. To allow adjustment for correlations between time points within participants, an unstructured variance-covariance structure will be used.

The null hypothesis of equal mean changes between both groups at day 360 visits will be tested by an appropriate linear contrast of the variable treatment and treatment by visit interaction. The adjusted mean change from baseline as well as the treatment difference and their corresponding 95% confidence intervals will be presented.

Least square means of each treatment group and estimated treatment differences at visits and corresponding 95% confidence intervals will be presented graphically.

Additionally, the odds ratio between inclisiran vs. placebo of the participants achieving a clinically relevant change in pain severity score and pain intensity score from baseline to Day 360 will be estimated using a logistic regression model. Treatment and CV risk category will be included as factors in the model. The odds ratio and its 95% confidence interval (CI) and p-value will be estimated.

2.6.2.5 Control of Familywise type I error rate

1-sided p-values and alpha level of 0.025 are considered for the testing procedure.

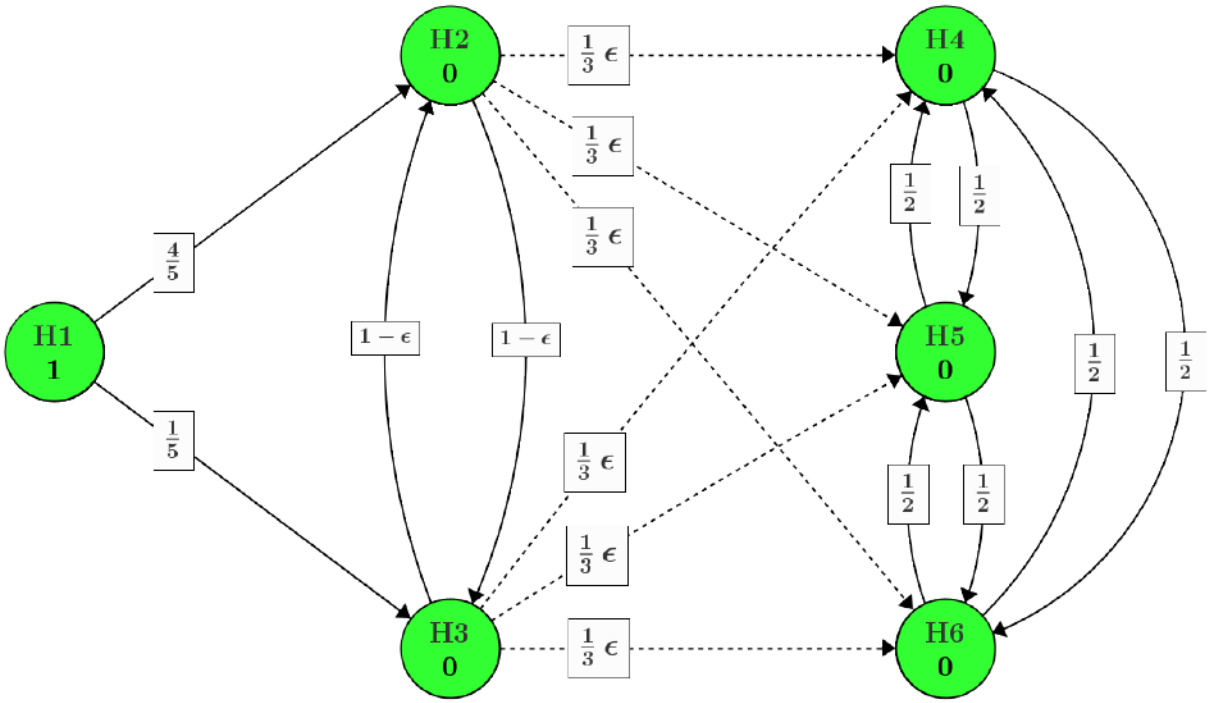
Hypotheses are grouped into three families. The first family contains the primary hypothesis H_{01}. The second family contains two secondary hypotheses H_{02} and H_{03}. The third family contains the remaining secondary hypotheses H_{04}, H_{05} and H_{06}. A hierarchical testing strategy is applied to these three families to control the familywise type I error rate in the strong sense. First H_{01} is tested at level α. If it is rejected, we test the second family using a closed test at level α. If both hypotheses are rejected, we test the third family using the Hommel procedure at level α. When not all hypotheses in a family can be rejected, testing stops at the corresponding family and does not proceed to test the next family.

Within the second family, a closed test procedure based on weighted Simes tests is applied with 80% weight for H_{02} and 20% weight for H_{03}. First the two nominal p-values for the two hypotheses are simultaneously compared to α. If both nominal p-vales are less or equal α, the two null hypotheses are rejected. Otherwise the individual nominal p-values will be compared to the pre-specified weighted alpha. If the p-value for H_{02} is less or equal 0.8α, H_{02} is rejected; if the p-value for H_{03} is less or equal 0.2α, H_{03} is rejected.

Within the third family, the Hommel prodecure is applied. Let the ordered p-values for H04, H05 and H06 be $p(1) \leq p(2) \leq p(3)$ and the corresponding hypotheses H(1), H(2) and H(3). First if p(3) is less or equal α, we can reject all three hypotheses. Otherwise, if p(2) is less or equal $\alpha/2$, we can reject H(2) and H(1). Otherwise, if $p(1) \leq \alpha/3$ or ($p(1) \leq \alpha/2$ and $p(2) \leq 2\alpha/3$) , H(1) is rejected.

For more details see also Figure 2-2.

Figure 2-2 Applied testing procedure



2.6.3 Handling of intercurrent events

For the secondary estimand we consider the same intercurrent events as for the primary estimand (see Section 2.5.3). Except one specific exception described below, the proposed approach for all secondary endpoints for the intercurrent events of discontinuation of investigational treatment, the use of PCSK9 targeting non-study medication or lipid apheresis or the impact of the COVID-19 pandemic is the treatment policy strategy. For the intercurrent event of death a while alive strategy will be applied.

The first secondary endpoint of relative change (percentage change) from baseline to mean LDL-C level over the double-blind study period (averaged over all post baseline visits) will be handled differently for the use of PCSK9 targeting non-study medication or lipid apheresis. For this specific intercurrent event for this endpoint a hypothetical strategy will be applied.

If an assessment at a visit is affected by multiple intercurrent events, strategy for the intercurrent events occurring will be applied considering the following order of decreasing importance: first hypothetical, followed by while alive and treatment policy. For treatment policy, for the remaining missings PCSK-9 (MAR imputation) is considered over second treatment discontinuation (J2R imputation).

2.6.4 Handling of missing values not related to intercurrent event

Missing values will be under a missing at random (MAR) assumption for every secondary endpoint. For the relative change from baseline to the mean LDL-C level over the double-blind study period (first secondary endpoint), the change from baseline in SF-BPI pain severity score at Day 360 (forth secondary endpoint) and the change from baseline in SF-BPI pain interference

score at Day 360 (fifth secondary endpoint) a multiple imputation approach will be applied as described in Section 5.5.3. The annualized number of days participants experiencing self-reported pain from Day 1 to Day 360 (third secondary endpoint) will be handled by normalizing the observation time via the offset function. In case of missing values muscle-related AE / SMQ rhabdomyolysis / myopathy will not be imputed but analyzed according to last known status of the occurrence of an event.

2.6.5 Sensitivity analyses

To investigate the sensitivity to missing values or potentially different observation times in the two study arms, a time to the first experience of at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy will be conducted via a Cox proportional hazards model (see Section 5.5.2.5).

The event-free observation time per participant will be censored at the earlier date out of death date, last contact date and date of visit Day 360. This covers intercurrent event strategies: for participants with an intercurrent event following the while alive strategy (time of censoring will be set to the time of the intercurrent event (i.e. date of death)) and for intercurrent events following the treatment policy strategy no censoring will be assumed for the intercurrent event itself is applied.

2.6.6 Supplementary analyses

2.6.6.1 Descriptive statistics

Descriptive summaries will be provided for the secondary endpoints.

2.6.6.2 CCI

CCI

2.6.6.3 CCI

CCI

2.6.6.4 CCI

2.6.6.5 Subgroup analysis

Regarding subgroup analysis for secondary endpoints see Section 2.6.1.

2.7 Safety analyses

All safety parameters will be analyzed based on the SAF, including the secondary safety endpoint.

All listings and tables will be presented by treatment group. Safety summaries (tables, figures) include all data from the double-blind treatment period (i.e. post-baseline assessments) and baseline data.

2.7.1 Adverse events (AEs)

A treatment-emergent adverse event (TEAE) is defined as any adverse event (AE) that started after the start of blinded investigational treatment injection or was present prior to start of double-blind treatment but increased in severity after the start of blinded investigational treatment injection. If the AE start date is the same as date of injection but time is not available for comparison, the AE will be considered to be treatment emergent.

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

The number (and percentage) of participants with TEAEs will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary SOC, PT and severity.
- by treatment, Standardized MedDRA Query (SMQ) and PT. SMQ lowest hierarchy level broad search will be presented.

Unless otherwise stated, SOCs will be sorted alphabetically and, within each SOC, the PTs will be sorted in descending order of frequency in the inclisiran column.

Separate summaries will be provided for study medication related AEs, SAEs, , AEs leading to discontinuation of study treatment, and AEs leading to discontinuation of study.

A participant with multiple AEs within a primary system organ class or preferred term is only counted once towards the total of the primary system organ class or preferred term, respectively.

2.7.2 Deaths

A separate summary by SOC and PT of death cause by treatment will be provided. Listing of all deaths will be provided.

2.7.3 Laboratory data

Laboratory data consist of hematology, clinical/limited chemistry, lipid panel and urinalysis measurements.

Notable abnormal laboratory data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities will be flagged. Shift tables based on the standard ranges for each laboratory parameter will be provided by treatment group at each visit to present incidence of transitions from a baseline high, normal or low laboratory value to a post-baseline high, normal or low value. Glucose should be measured fasting, non-fasting glucose values will be excluded from the analyses.

Number and percentages of participants with newly occurring or worsening notable liver-function, renal function and skeletal muscle laboratory values as defined in Section 5.4 will be tabulated.

2.7.4 Other safety data

2.7.4.1 Vital signs

Notable abnormal vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities will be flagged.

Number and percentages of participants notable vital sign values at screening and newly occurring or worsening notable values any time post-baseline as defined in Section 5.4 will be tabulated.

2.8 Additional analyses to assess the impact of COVID-19 pandemic

Number and percentage of participants with COVID-19 related protocol deviations will be summarized by deviation term and relationship to the COVID-19 pandemic..

To assess the impact of COVID-19 on safety, and to assess possible regional differences in reporting of AEs, the most frequent AEs will be summarized by preferred term and country.

2.9 Patient-reported outcomes

Analyses of the electronic diary and the SF-BPI are described in Section 2.6.2.3 and Section 2.6.2.4, respectively. The following questionnaires are exploratory objectives for the study:

- Short-Form health survey,
- Gastrointestinal Symptom Rating Scale,
- Treatment Satisfaction Questionnaire for Medication,
- Walking Impairment Questionnaire,
- MacNew Heart Disease Quality of Life Questionnaire.

The pre-processing of the patient-reported outcomes will be described in the following sections for each of the questionnaires.

Compliance to questionniare completion will be summarized descriptively for each questionnaire.

2.9.1 Short-Form Health Survey

The Short-Form Health Survey (SF-36) is a generic health-related quality of life instrument which comprises of 36 questions across 8 domains (see also Section 8.5.1.3 in Protocol).

The questionnaires will be preprocessed in-house by the sponsor (Novartis). Physical component summary (PCS) and Mental component summary (MCS) will be provided for further analysis for screening, baseline, Day 90, Day 210 and EOT/EOS (Day 360). All analyses will be performed by domain.

The higher the scores, the higher is the quality of life for the participant.

CCI [redacted]

2.9.2 Gastrointestinal Symptom Rating Scale

The self-administered Gastrointestinal Symptom Rating Scale (GSRS) questionnaire contains 15 items for gastrointestinal syndromes, which are composed of 5 dimensions (abdominal pain, reflux syndrome, indigestion, diarrhea and constipation) and uses a Likert scale with 7 units from 1 to 7 (no discomfort to very severe discomfort, see also Section 8.5.1.4 in Protocol)

The subscores of individual domains are calculated by averaging the scores of the associated items. The average of all subscores gives the total score, which ranges between 1 and 7. The score will be derived for each visit between baseline and EOT/EOS (Day 360).

If there is missing data for a participant and the available data is more than 50% for the corresponding dimension, the missing items will be imputed using the mean score of the non-missing item scores. Else no imputation will be done and the dimension score will be excluded from the analysis (see corresponding Manual).

The lower the value, the better the gastrointestinal condition.

CCI [redacted]

2.9.3 Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM) is used to assess participant convenience and global satisfaction with treatment and consists (in version II) of eleven multiple-choice items across four domains (see also Section 8.5.1.5 in Protocol).

The items are summed up domain-wise to derive domain scores, which are then transformed to a 0 to 100 scale. A score can only be computed for a domain if no more than one item is missing from that domain. An overall score is not defined. The scores will be derived for baseline, Day 90 and EOT/EOS (Day 360). All analyses will be performed by domain.

The higher the values, the higher is the participant's satisfaction with the treatment.

CCI [redacted]

2.9.4 Walking Impairment Questionnaire

The (modified) Walking Impairment Questionnaire (WIQ) is used to assess participants walking distance, speed, and stair climbing ability and records 16 items in four categories (see also Section 8.5.1.6 in Protocol). The WIQ will only be provided to the PAD subset.

The graded scores in three of the four categories (distance, speed, stair climbing) are multiplied by a pre-specified weight for each category (see corresponding Manual), then summed up and divided by the maximal score possible to derive the final category-specific scores ranging from 0 to 100 % for baseline, Day 90 and EOT/EOS (Day 360). An overall score and a score for the fourth category (pain) is not defined. All analyses will be performed by domain score.

If there is missing data for a participant and the available data is more than 50% for the corresponding category, the maximal score possible will be adapted for this category. No imputation will be done. If less than 50% of the items are non-missing the category-specific score will be excluded from the analysis.

The higher the values, the better is the participant's condition.

CCI [redacted]

2.9.5 MacNew Heart Disease Quality of Life Questionnaire

The MacNew Heart Disease Quality of Life Questionnaire (MacNew) is used to assess the quality of life of participants with cardiovascular diseases and covers the query period of the

past 14 days (see also Section 8.5.1.7 in Protocol). It consists of 27 items across three overlapping domains. The MacNew will only be provided to the AP subset.

The scores of the three domains (physical limitations, emotional and social function) are calculated by averaging the point values in the associated items. The average value of all 27 items gives the global total score. The score will be derived for baseline, Day 90 and EOT/EOS (Day 360). If not specified otherwise all analyses will be performed for total and domain scores.

Missing responses do not contribute to the score - also no imputation will be done. If less than 50% of the items for the corresponding domain is missing, the domain score will be excluded from the analysis (see corresponding Manual).

The higher the score(s), the better ist the participant's quality of life.

CCI

2.9.6 CCI

CCI

2.9.7 CCI

CCI

2.10 Biomarkers

Summary statistics will be provided by treatment and visit/time for Lp(a) and Apo B. PCSK9 levels will remain blinded until unblinding.

2.11 Other Exploratory analyses

2.11.1 CCI

2.11.2 CCI

CCI

2.11.3 CCI

CCI

2.12 Interim analysis

Not applicable.

3 Sample size calculation

3.1 Primary endpoint(s)

The assumption for the occurrence of LDL-C target attainment on day 90 in the inclisiran-arm is based on the ORION study data set. In CCI of participants achieved an LDL-C level CCI mg/dL target at day 90 CCI (Ray et al., 2020). In CCI of participants achieved an LDL-C level CCI mg/dL at day 90 CCI (Ray et al., 2020). Assuming CCI , approx. CCI of participants achieve their individual LDL-C target at day 90. For the assumption of LDL-C target attainment at day 90 in the placebo arm, the EXPLORER trial reports response rates for CCI (Ballantyne et al., 2007): CCI of participants achieved an LDL-C level CCI mg/dL at day CCI . Mean LDL-C level at day CCI was CCI , so it can be estimated that approx. CCI of participants may have reached the CCI target. Based on the study population and treatment regime herein, day CCI of EXPLORER trial likely relates to day 90 of the present study. With the above stated assumption of a CCI among the participant population, CCI of participants are considered to reach their LDL-C target at day 90. Considering the high LDL-C levels at baseline in the EXPLORER trial compared to ORION trials, herein, a slightly higher goal attainment rate of approx. CCI at day 90 for participants in the comparator arm is assumed. Under these assumptions, CCI participants per arm are required based on a chi-squared test of proportions to achieve 90% power on a two-sided, 5% significance level. In order to compensate for missing values and other protocol deviations, approximately 880 participants per arm (approximately 1760 participants in total) should be enrolled/randomized into this trial.

3.2 Secondary endpoint(s)

For the secondary endpoint "Proportion of participants experiencing at least one muscle-related AE as defined in the SMQ rhabdomyolysis / myopathy from day 1 to day 360", the following deliberations apply: Due to the potent LDL-C lowering effect of inclisiran and the CCI

CCI in both treatment-arms depending on the achievement of the individual LDL-C target of the participant, it is expected that the mean and the median statin doses will be CCI . Based on the CCI of action of inclisiran, it is estimated that the CCI of participants in the CCI will require CCI rosuvastatin CCI in the treatment period. Thus, most participants in the CCI will remain on the lower doses of rosuvastatin throughout the trial. In contrast, in the CCI , most participants will require CCI of rosuvastatin CCI to sufficiently lower the LDL-C.

Various studies have shown that statins at high dosages are associated with CCI ranging between CCI for atorvastatin 80 mg/day (Parker et al., 2013) to CCI for various statins (Bruckert et al., 2005), while there is evidence from double-blind clinical trials that CCI statins are not associated with a CCI than placebo with an overall incidence of CCI (Gupta et al., 2017). For the sample size calculation, we assume a rather conservative approach of an occurrence of CCI in the CCI and CCI in the CCI . Pain can be of different CCI . Assuming CCI are CCI in a conservative approach, according to the methodology defined CCI to CCI AEs will only be CCI , if the CCI interval of the risk ratio stays below the threshold of CCI . A sample size of CCI participants per arm will result in 90% power to obtain a confidence interval of the risk ratio fulfilling this condition. For a considerable additional benefit, the respective threshold is defined by the CCI . Under the assumptions above, the power to meet this condition as well would be CCI . The power calculations were performed with SAS Software by simulating and analyzing 1000 studies with the assumed AE rates.

4 Change to protocol specified analyses

Null hypothesis for primary and secondary endpoints will be rejected as described in the testing strategy in SAP section 2.6.2.5 and protocol section 12.5.1. There is contradictory information given for the respective endpoints in protocol section 12.5.2 with regard to p-values and alpha level. This contradictory information will not be considered for the analyses and control of familywise type I error rate will be followed.

Analysis of adverse events will be done for TEAEs. Protocol section 12.5.3 describes that additionally, all summary tables for AEs will be repeated for on-treatment AEs only (TEAEs). This repetition will not be done.

First dose of double-blind treatment (Day 1) will be considered for the analyses, even if protocol mentions time of randomization. Day 1 and randomization date of some participants may not be the same, therefore Day 1 is considered for consistency of the analyses.

There will not be a separate table for exclusions from the analyses set, as there are no PDs defined excluding participants from an analysis set and exclusions are covered by the definition of the analyses set. Therefore, analysis would be redundant with other tables.

Region and country will not be summarized for the randomized set, countries are summarized on the FAS.

Supplementary analyses presenting relative risk and risk difference will be presented using CMH with Mantel-Haenszel estimators for both measures and will not be based on score statistics.

Descriptive summary of all vital signs data will not be provided, number and percentages of participants with notable abnormal vital signs will be provided instead. Listing of vital signs will be limited to the notable abnormal vital signs.

5 Appendix

5.1 Imputation rules

Any date incompletely reported is split into its day, month, and year components. In SAS, a numerical date value can only be defined if all these date components are known; incomplete dates are to be handled as text strings (character-type variables); as such, they could not be easily processed. An imputation rule for incomplete dates will be performed.

5.1.1 Blinded investigational treatment

The blinded investigational treatment administration date should be complete since it is injected at the study site. In case of missing or partial missing dates, the visit date will be used as the blinded investigational treatment administration date.

5.1.2 AE and hospitalization date imputation

The partially missing AE and hospitalization start/end date will be imputed. Completely missing start and end dates will not be imputed. If imputed date is after the EOS/EOT date, EOS/EOT date will be used instead. If imputed date is after the date of death, date of death will be used instead. Details will be provided in the study Programming Dataset Specification (PDS).

5.1.3 Concomitant medication date imputation

The partially missing concomitant medication start/end date will be imputed. Completely missing start and end dates will not be imputed. If the imputed date is after the EOS/EOT date, EOS/EOT date will be used instead. If imputed date is after the date of death, date of death will be used instead. Details will be provided in the study PDS.

5.1.4 Other missing dates

If other dates (e.g. medical history, procedures) are partially missing, details for imputation will be provided in the study PDS.

5.2 Stratification

The stratification factor is given by the CV risk group as defined in the following:

- Very high risk participants with at least one the following:
  1. Documented ASCVD
     - ACS: Unstable angina or myocardial infarction

- Stable angina
- Coronary revascularization
- Unequivocally documented ASCVD
- Stroke and TIA
- PAD

2. Diabetes mellitus (DM) with target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), or at least ≥ 3 major risk factors, or early onset of Type 1 DM of long duration (< 20 years)
3. A calculated SCORE ≥ 10% for 10-year risk of fatal CVD
4. Pre-existing diagnosis of heterozygous familial hypercholesterolemia (HeFH) with ASCVD or with another major risk factor.

- High risk participants with at least one of the following:
  1. Markedly elevated single risk factors, in particular triglycerides > 8 mmol/L (>310 mg/dL), LDL-C > 4.9 mmol/L (> 190 mg/dL), or blood pressure ≥ 180/110 mmHg
  2. Pre-existing diagnosis of HeFH without other major risk factors
  3. DM without target organ damage (defined as microalbuminuria, retinopathy, or neuropathy), with DM duration ≥ 10 years or other additional risk factor
  4. Moderate chronic kidney disease (eGFR 30-59 mL/min/1.73m^2)
  5. A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD as defined by the cardiovascular risk categories in the 2019 ESC/EAS guideline (Mach et al 2020).

5.3 AEs coding/grading

Adverse events (AEs) are to be coded with the MedDRA dictionary based on the latest version available at the time of the analyses (version 25 or above) gives preferred term (PT) and primary system organ class (SOC) information.

5.4 Laboratory parameters derivations

Table 5-1, 5-2, 5-3 and 5-4 show the criteria for clinically notable liver test values, renal function, skeletal muscle function and vital signs, respectively.

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur on the same assessment. A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

For additional safety monitoring see Section 10.2.2 and 10.2.3 of Protocol.

Table 5-1 Notable liver function test values

Criterion
ALT ≥ 3 x the upper limit of normal range (ULN)
ALT ≥ 5 x ULN
AST ≥ 3 x ULN
AST ≥ 5 x ULN
ALT or AST ≥ 3 x ULN
ALT or AST ≥ 5 x ULN
Total bilirubin ≥ 2 x ULN
ALP ≥ 2 x ULN
ALT or AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

Table 5-2 Notable renal function

Criterion	
eGFR ≥ 30 and ≤ 60 ml/min /1.73m^2	Moderate renal impairment
eGFR < 30 ml/min/1.73m^2	Severe renal impairment

eGFR = Estimated glomerular filtration rate

Table 5-3 Notable skeletal muscle values

Criterion
CK > 5 x the upper limit of normal range (ULN)

CK = Creatine kinase

Table 5-4 Notable Criteria for Vital Signs

Vital sign		Notable abnormalities
Pulse (bpm)		<40 or >180
BP (mmHg)	Systolic (SBP)	<40 or >180 for Screening Visit <40 or >220 for Other Visits
	Diastolic (DBP)	<40 or >110 for Screening Visit <30 or >130 for Other Visits

5.5 Statistical models

5.5.1 Analysis supporting primary objective(s)

5.5.1.1 (Binary) Logistic regression

The primary endpoint will be analyzed using a binary logistic regression of the following form:

$$logit\ (LDL\ \leq LDL\ target) = treatment + CV\ risk\ category.$$

In SAS the PROC LOGISTIC procedure will be therefore used. The ODDSRATIO statement will be used to estimate the odds ratio. The E option will be used to obtain a table of coefficients of the linear combination of parameters that define the log odds for each treatment group. Odds

ratios will be presented with associated two-sided 95% confidence interval for treatment comparison.

5.5.2 Analysis supporting secondary objective(s)

5.5.2.1 Mixed Model for Repeated Measures (MMRM)

The first secondary endpoint (change in LDL-C) will be analyzed via a mixed model for repeated measures (MMRM) with an unstructured covariance matrix (representing the within-participants correlation). Study visit will be included as a repeated factor nested within participant:

$$\Delta LDL = treatment + CV\ risk\ category + scheduled\ visit + scheduled\ visit * treatment + LDL_{baseline} + LDL_{baseline} * visit$$

with $LDL_{baseline}$ as the concentration of LDL-C at baseline.

The MMRM will also be used for the fourth secondary endpoint (change in SF-BPI) as described above with the only exception, that additional visits will be included into the model as per schedule of assessments, which leads to the following model:

$$\Delta SFBPI = treatment + CV\ risk\ category + scheduled\ visit + scheduled\ visit * treatment + SF_{BPI_{baseline}} + SF_{BPI_{baseline}} * visit.$$

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997).

If the model fails to converge with unstructured covariance matrix, either a compound symmetry (first choice) or first order autoregressive (AR1) (second choice) covariance structure will be applied.

In SAS the PROC MIXED procedure will be used. To fit the model, the REPEATED statement is used to specify the repeated measures factor, the unstructured covariance matrix will be specified using the TYPE eq UN optional parameter. Results will be presented with LSM and standard error (SE) for treatment effects. Any missing data are considered MAR (missing [conditionally] at random) and handled as such in the MMRM.

5.5.2.2 Logistic regression

To analyze the number of muscle-related adverse events the same method as for the primary endpoint is used (see Section 5.5.1.1) with the adaptation that the model is given by:

$$logit(\#AE \geq 1) = treatment + CV\ risk\ category$$

5.5.2.3 Negative binomial model

The third secondary endpoint will be analyzed using a generalized linear model of the following form assuming a negative binomial distribution:

$$\#pain\ days = treatment + CV\ risk\ category + \log(time[y]).$$

CCI

In SAS the PROC GENMOD procedure is used with the DIST equal to NB statement to choose the negative binomial distribution and LINK equal to LOG as link function. The offset will be defined in the OFFSET option (eq LOGRISK).

If the model fails to converge a quasi-Poisson model will be fitted instead, with the exception of subgroup analyses.

5.5.2.4 Analysis of Covariance (ANCOVA)

The changes from baseline for different traits will be analyzed by an linear analysis of covariance of the following form:

$$\Delta trait = treatment + trait_{baseline} + CV\ risk\ category.$$

In SAS the PROC MIXED procedure will be used to run the different ANCOVAs. Results will be presented with LSM and standard error (SE) for treatment effects.

5.5.2.5 Time to event analysis

For the sensitivity analysis a Cox proportional hazards regression model will be applied in time-to-event analyses to test the null-hypothesis $H_0 = \frac{\lambda_{inclisiran}(t)}{\lambda_{placebo}(t)} = 1$, where λ(t) is the hazard function for the event time of participants treated with Inclisiran and Placebo, respectively. The event time is thereby defined as the time to first experience of at least one muscle-related AE ((SMQ) rhabdomyolysis / myopathy). The Cox regression model will include terms for treatment and CV risk category.

The SAS procedure PROC PHREG will be used for analysis. Results will be presented with adjusted hazard ratios for treatment group comparisons and associated 95% confidence intervals. One-sided p-value from Z-test will be presented.

5.5.3 Multiple imputation

If not stated otherwise, imputation for primary and secondary analyses will be done by the following rules: For missing data, target day of the visit is considerd to assess if missing is related or not related to intercurrent event. Absolute values are imputed corresponding endpoint variables are derived on imputed data.

Select data to fit the imputation model considering strategy applied for intercurrent events:

1. For primary endpoint all observed data will be included except for data collected after intercurrent events where composite strategy is applied, e.g. data collected after PCSK-9 inhibitors will be set to missing. Note, after death no data are collected, thus no need to take any action for while alive strategy. In case of occurrence of multiple intercurrent events e.g. double-blind treatment discontinuation and later PCSK-9 use, all data RDO data up to PCSK-9 inhibitor use will be used, others will be set to missing.
2. For secondary endpoints data all observed data will be included except for data collected after intercurrent events where hypothetical strategy is applied, these will be set to missing after intercurrent event. In case of occurrence of multiple intercurrent events e.g. double-blind treatment discontinuation and later PCSK-9 use, all RDO data up to

PCSK-9 inhibitor use will be used, others will be set to missing for LDL-C analyses where hypothetical strategy is applied for PCSK-9 inhibitor use.

3. Impute missing data using MAR (missing at random):

   Select all participants, impute missing values at baseline and scheduled post-baseline visits, under assumption of missing at random (MAR), using the PROC MI procedure in SAS based on the fully conditional specification (FCS statement) method for 100 times and obtain 100 imputed datasets. Missing baseline values will be imputed using a model with treatment and CV risk category. Missing Day 30 values will be imputed using a model based on values of baseline, treatment and CV risk category. The same procedure will be repeated for subsequent visits.

   This results in 100 imputed datasets.

   For participants in the inclisiran treatment groups who discontinued double-blind treatment prematurely, set imputed values after discontinuation of double-blind treatment to missing, if not after occurrence of other intercurrent event such as PCSK-9 inhibitor, as these will be imputed using jump to reference (J2R) in step 4.

4. For intercurrent event of double-blind treatment discontinuation, in case of missing RDO data and no occurrence of other intercurrent event such as PCSK-9 inhibitor impute missing values for participants in the inclisiran treatment groups using J2R.

   Select all participants, impute missing values at scheduled post-baseline visits using the MI approach, under assumption of missing not at random (MNAR) that participants in inclisiran treatment groups will behave as participants treated with placebo, based on the fully conditional specification (FCS) method for 100 times and obtain 100 imputed datasets. Model will include same covariates as in step 1, except for treatment which is considered in the MNAR assumption.

   This results in 100 imputed datasets.

5. Merge datasets from step 3 and step 4.

   a. For participants in inclisiran treatment groups discontinuing double-blind treatment prematurely take imputed values after discontinuation of double-blind treatment from step 4 if not after occurrence of other intercurrent event such as PCSK-9 inhibitor.

   b. For all other missing (including those for placebo participants) values take imputed values from step 3.

6. Derive endpoint variable for imputed values, e.g. change from baseline/response variable/percent change from baseline.

7. For each considered endpoint the specified analysis model will be applied on every of the 100 final multiply-imputed datasets where all missing values are filled (from MI or single imputation as defined by the respective strategy).

8. The results for the treatment effect from the 100 datasets will then be combined to obtain the statistical quantities of interest using Rubin's rule. Therefore, in SAS the PROC

MIANALYZE procedure is used and generates valid statistical inferences. If models failed to converge for a subset of imputations the remaining ones are used.

5.6 Rule of exclusion criteria of analysis sets

Table 5-5 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded
SCR	Not having informed consent
RIS	No run-in phase needed, already at MTD
RAN	Not randomized
FAS	Not in RAN; Mis-randomized and no double-blind investigational treatment taken
SAF	No double-blind investigational treatment taken
AP set	Not in FAS; No diagnosis of angina pectoris at baseline
PAD set	Not in FAS; No diagnosis of peripheral artery disease at baseline

6 Reference

- Ballantyne CM, Weiss R, Moccetti T, et al (2007): Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol*; p. 673-80.
- Bruckert E, Hayem G, Dejager S, et al (2005): Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther*; p. 403-14.
- Gupta A, Thompson D, Whitehouse A, et al (2017): Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet*; p. 2473-2481.
- Kenward, M. G., & Roger, J. H. (1997): Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*, p. 983-997.
- Mach F, Baigent C, Catapano AL, et al (2020): 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*; 41:111-188.

- Parker BA, Capizzi JA, Grimaldi AS, et al (2013): Effect of statins on skeletal muscle function. *Circulation*; p. 96-103.
- Ray KK, Wright RS, Kallend D, et al (2020): Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med*; p. 1507-1519.