NOVARTIS

Clinical Development

KJX839/Inclisiran

CKJX839A1GB01 / NCT04807400

A phase IIIb, multicentre, randomised controlled study to evaluate the implementation, preference and utility for administration of inclisiran sodium in participants with Atherosclerotic Cardiovascular Disease (ASCVD) or ASCVD-risk equivalents and elevated Low Density Lipoprotein Cholesterol (LDL-C) using a primary care models in the NHS

Statistical Analysis Plan (SAP)

Author:

Document type: SAP Documentation

Document status: Amendment v1.1

Release date: 15-May-2023

Number of pages: 37

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)
31-Mar-2023	Prior to DB lock	Creation of final version 1.0	N/A – First version	NA
15-May-2023	Prior to DB lock	Creation of amendment 1 version 1.1	• Updated number of imputations from 100 to 500	Section 2.5.2 Section 5.5.1 & 5.5.2
			• Removed text related to line plot	Section 2.5.5
			• Added clarification text about baseline imputation values in sensitivity analysis	
			• Added clarification text	Section 2.10.1 Section 5.4
			• Other minor format changes	Section 2.5.2 & 2.6.2

Table of contents

Table of contents 3
List of abbreviations 5
1 Introduction 7
1.1 Study design 7
1.2 Study objectives, endpoints and estimands 9
2 Statistical methods 11
2.1 Data analysis general information 11
2.1.1 General definitions 11
2.2 Analysis sets 12
2.2.1 Subgroup of interest 13
2.3 Patient disposition, demographics and other baseline characteristics 13
2.3.1 Patient disposition 13
2.3.2 Demographics and other baseline characteristics 13
2.3.3 Medical History 14
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 14
2.4.1 Study treatment / compliance 14
2.4.2 Prior, concomitant and post therapies 14
2.5 Analysis supporting primary objective(s) 15
2.5.1 Primary endpoint(s) 15
2.5.2 Statistical hypothesis, model, and method of analysis 16
2.5.3 Handling of intercurrent events 16
2.5.4 Handling of missing values not related to intercurrent event 17
2.5.5 Sensitivity analyses 17
2.5.6 Supplementary analyses 18
2.6 Analysis supporting secondary objectives 19
2.6.1 Secondary endpoint(s) 19
2.6.2 Statistical hypothesis, model, and method of analysis 21
2.6.3 Handling of missing values 22
2.7 Safety analyses 22
2.7.1 Adverse events (AEs) 22
2.7.2 Deaths 24
2.7.3 Laboratory data 24
2.7.4 Other safety data 24
2.8 Patient-reported outcomes 24

2.8.1 The CSQ-8 PROMs Questionnaire 24
2.8.2 The PAM PROMs Questionnaire 24
2.8.3 [redacted]
2.9 [redacted]
2.10 [redacted]
2.11 Interim analysis 26
3 Sample size calculation 26
4 Change to protocol specified analyses 26
5 Appendix 26
5.1 Imputation rules 26
5.1.1 Study drug 26
5.1.2 AE date imputation 27
5.1.3 Concomitant medication date imputation 28
5.2 AEs coding/grading 29
5.3 Search criteria for AE of special interest 29
5.4 Laboratory parameters derivations 30
5.5 Statistical models 31
5.5.1 Multiple Imputation Wash-out model 31
5.5.2 Imputation of undetectable data 33
5.6 Rule of exclusion criteria of analysis sets 34
6 Reference 36

List of tables

Table 2-1 Analysis windows for each scheduled visit 12
Table 5-1 Clinical notable criteria for selected laboratory tests 30
Table 5-2 Notable Liver function test values 30
Table 5-3 Range determination 33
Table 5-4 Protocol deviation criteria leading to exclusion from analysis sets 34

List of abbreviations

AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
CFIR	Consolidated Framework for Implementation Research
CRO	Contract Research Organization
CSQ-8	Client Satisfaction Questionnaire
CSR	Clinical Study Report
CTC	Common Terminology Criteria
DBL	Direct Bilirubin
[redacted]	[redacted]
[redacted]	[redacted]
ECG	Electrocardiogram
EMR	Electonic Medical Record
EOS	End of Study
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
eGFR	Estimated glomerular filtration rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
HbA1C	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MNAR	Missing not at random
NICE	National Institute for Health and Care Excellence
PAM	Patient Activation Measure
PT	Preferred term
PROM	Patient Reported Outcome Measure
RAN	Randomized set
REML	Restricted Maximum Likelihood
[redacted]	[redacted]
s.c.	Subcutaneous
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan

[redacted]	[redacted]
SCR	Screened set
SD	Standard deviation
SMC	Scottish Medicines Consortium
SMQ	Standardized MeDRA Query
SOC	System Organ Class
SPIRIT	Study in Primary care evaluating Inclisiran deliveRy Implementation + enhanced SupporT
TBL	Total Bilirubin
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal

1 Introduction

This document includes the analysis details of study CKJX839A1GB01. Data will be analyzed according to section 12 (data analysis and statistical methods) of CKJX839A1GB01 amended protocol v02 dated 12-Sep-2022.

The efficacy and safety analyses will be conducted after all participants have completed the Day 270 visit or discontinued prior to the Day 270 visit. There is no interim analysis planned for this study. The final analyses will be conducted when the trial has ended, and the results will be summarized in the final CSR.

The analysis of Process Evaluation Sub-study data is out of scope of this SAP.

1.1 Study design

A phase IIIb, multicentre, randomised controlled study to evaluate the implementation, preference and utility for administration of inclisiran sodium in participants on established lipid lowering medication or, have been recommended lipid lowering therapy by their healthcare provider but are unable to tolerate treatment, with elevated low density lipoprotein cholesterol (LDL-C) in a primary care population.

This study is an implementation research study that utilises implementation science methodology with the primary focus being implementation and 'transactability' – how to organise, deliver and maintain an innovative treatment for ASCVD in a primary care setting in a sustainable way.

900 eligible participants will be randomised (300 per treatment group) at up to 30 primary care centres across Greater Manchester.

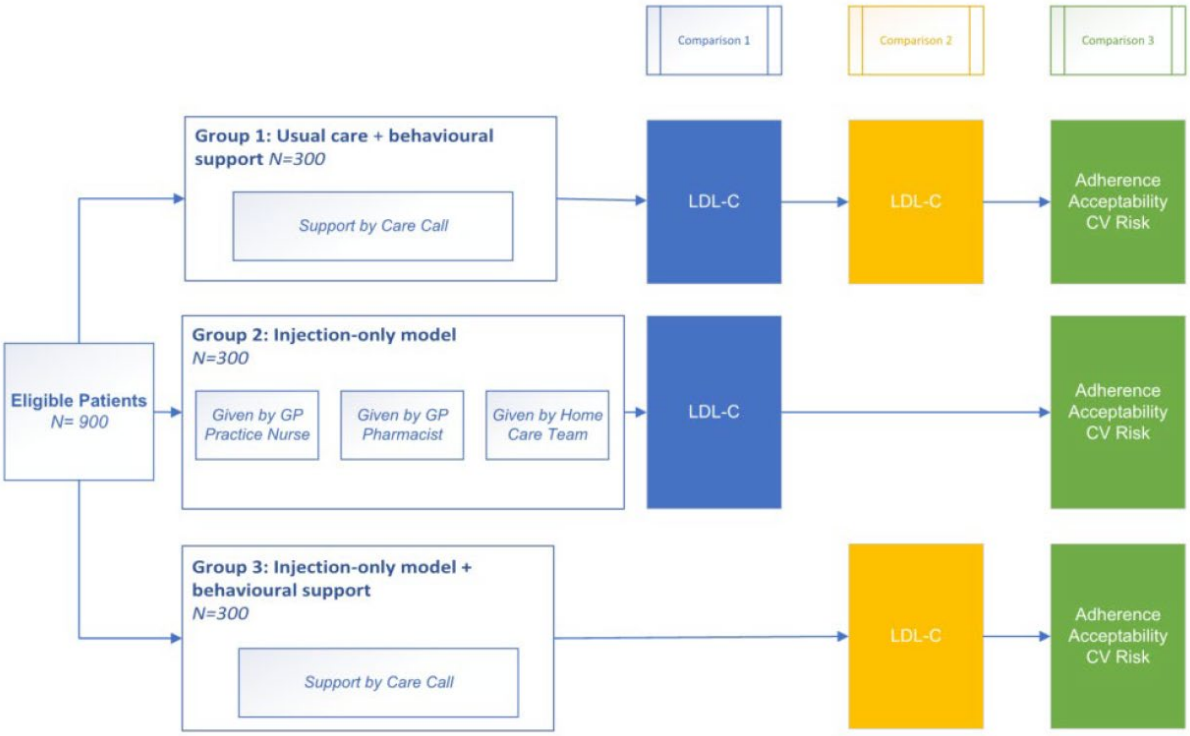
At the baseline visit/screening on receipt of a signed consent form, eligible participants will be randomised to one of the three treatment groups:

- **Group 1:** Participants will continue to receive their background lipid lowering therapy plus behavioural support
- **Group 2:** Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection (delivered in an injection-only model).
- **Group 3:** Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection, plus behavioural support.

Subjects in treatment group 1 will be referred to as the control group in this study.

The study duration will be approximately 9 months. There are no interim analyses planned for this study.

Schematic of study design

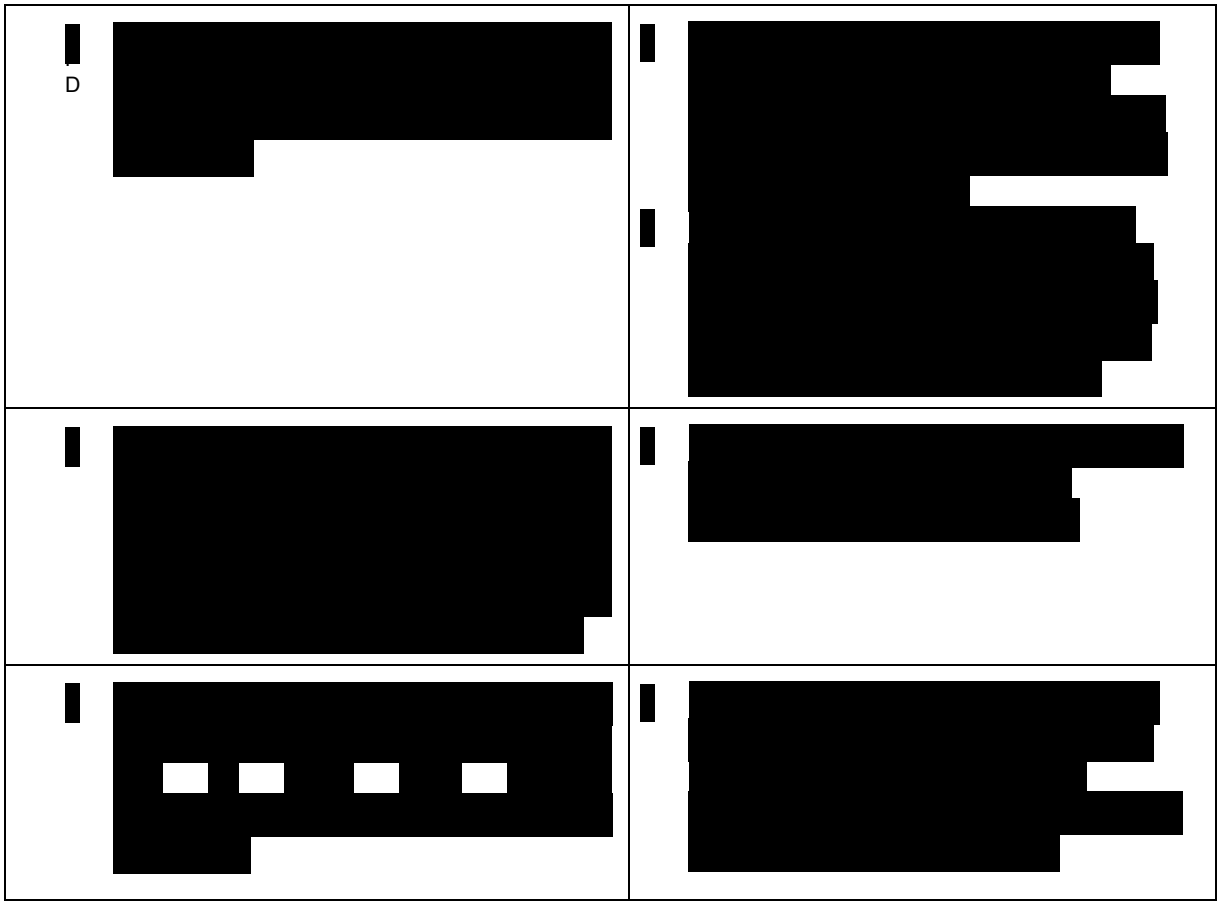


For elaborated details on study design please refer to the study design section of the protocol .

1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective of this study is to demonstrate superiority of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting, in terms of the percentage change in LDL-C from baseline to Day 270 in adults with elevated LDL-C.	• Percentage change in LDL-C from baseline to Day 270.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
The secondary objectives of this study are to evaluate the implementation of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting using the following assessments:	
• Measures of patient satisfaction using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.	• Mean difference in total score using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.
• Measures of patient activation and empowerment using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.	• Mean difference in total score using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.
• Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period.	• The frequency and percentages of subjects in the four levels of the PAM scores (below) will be summarized. Highly activated patients (level 3 and level 4) are more likely to adhere to cardiovascular self-management and thus medication adherence. Level 1: Disengaged and overwhelmed Level 2: Become aware but still struggling Level 3: Taking action

	Level 4: Maintaining behaviors and pushinng further.
• A process evaluation conducted using the Consolidated Framework for Implementation Research (CFIR) which will explore inclisiran delivery at three levels: 1. **Level 1:** Feasibility and acceptability of delivery models for inclisiran to patients 2. **Level 2:** Feasibility and acceptability of delivery models for inclisiran to providers (inner setting) 3. **Level 3:** Wider 'transactability' of the proposed delivery models (outer setting) 4. The service costs of each delivery model 5. The acceptability and perceived sustainability of patient identification and referral routes Data from the process evaluation will initially analysed blind to trial outcomes (this analysis will then be used to compare and explain any differences in outcomes between intervention arms).	This SAP does not intend to describe methodology adopted for the Process Evaluation Sub-study data analysis. This study objective is listed for completeness only. For further detail on the process evaluation and planned analyses, please refer to section 4.3 of the Protocol. The analysis results will be reported in final CSR.
• Serious adverse event profile	• Incidence, severity and relationship to the study drug of treatment emergent adverse events, serious adverse events and adverse events leading to treatment discontinuation. • Incidence of on-treatment and post-treatment deaths.
[redacted]	[redacted]
[redacted]	



2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis or a designated CRO. The most recent version of SAS available in the statistical programming environment of Novartis or the designated CRO will be used for the analysis.

Final analysis will be conducted after all participants either complete the study or discontinued early. Final analyses will be reported in Final CSR.

Additional analysis may be conducted to evaluate the impact of COVID-19 pandemic, if required.

2.1.1 General definitions

Study day:

Study day will be defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment will be defined as Day 1 and the day before the first dose of study treatment will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

For dates on or after the first date of study treatment,

Study day = Assessment date – Date of first dose of study treatment + 1;

For dates prior to the first date of study treatment,

Study day = Assessment date – Date of first dose of study treatment.

In case, participant has been randomized but has not received study treatment then randomization visit day will be considered as Day 1.

Baseline definition:

The baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) collected before the first dose of study treatment (Day 1) or randomization visit day, if no study treatment has been received.

Post-baseline measurement:

Post-baseline values are defined as those measurements that were collected after the first dose of study treatment or randomization visit if no study treatment has been received.

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:

Change from baseline = post-baseline value – baseline value.

Percent change from baseline = (change from baseline / baseline value)*100.

Visit windows:

If there is more than one observation in a specific window, then the one closest to the target day will be used for analysis. If there are two or more observations that are equally distant to the target day and within the analysis window, the first of these observations will be selected for analysis. Observations that are out of the analysis window below will be classified as unscheduled visits and will not be included in the primary and key secondary efficacy analysis. However, all data will be included in the subject data listings.

As shown in the table below, all visit will apply a window of ± 14 days.

Table 2-1 Analysis windows for each scheduled visit

Visit Name	Target day	Analysis window
Screening/Baseline	-1	Day -14 to -1
Visit 1	1	Day 1 to 14
Visit 2	90	Day 76 to 104
End of Study	270	Day 256 to 284

*Day 1 is defined as day of initiation of study drug administration or randomization visit day if no study treatment has been received.

2.2 Analysis sets

Screened Set (SCR) will include all participants who provided study informed consent.

Randomized set (RAN) will consist of all participants who received a randomization number, regardless of whether study treatment received or not.

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

Safety Set (SAF) will consist of all participants who received at least one dose of study treatment. Participants will be analysed according to the study treatment received. This will be the primary population for the safety analyses.

2.2.1 Subgroup of interest

No subgroup analysis is planned.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The overall number of participants who entered, completed, and discontinued the study will be summarized and listed, including the reasons for discontinuation. Duration on study is defined as: date of last known visit on study – date of first dose of treatment/ randomization visit, if no study treatment has been received.

The duration on study will be summarized by treatment group. The screening disposition will be based on SCR. The FAS will be used for the summary and listing of patient disposition. The number of participants in the FAS will be summarized by treatment group. Number of participants with protocol deviations will be tabulated by category (e.g., selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other), deviation using FAS. Listing of participants with protocol deviation will be provided.

The number of participants included in each analysis set will be tabulated using RAN. Participants exclusion from analysis sets will be summarized for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations) and corresponding listing will be provided.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including age, race, gender, baseline characteristics such as body height, [redacted] smoking history, Dietary advice status, Exercise status; baseline disease characteristics like LDL-C, baseline use of other lipid-lowering therapies (yes, no), statin intolerance history(yes, no), baseline diabetes status determined by the fasting glucose (≥ 7.0 mmol/L) or random glucose (≥ 11.1 mmol/L) or HbA1C (≥ 6.5% or 48 mmol/mol) or medical history, baseline measurements [redacted] will be summarized descriptively by treatment group for FAS. Listings will also be provided.

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

No inferential statistics will be provided for baseline comparability among the treatment groups.

In addition, the following categorizations of continuous variables will be done:

- Age groups < 65, ≥ 65 and < 75, ≥ 75
- [redacted]
- LDL-C subcategories Category 1: ≤ 2.6 mmol/L, > 2.6 mmol/L; Category 2: ≤ 2.1 mmol/L, > 2.1 - ≤ 2.6 mmol/L, > 2.6 - ≤ 3.3 mmol/L and > 3.3 mmol/L
- [redacted]

2.3.3 Medical History

Relevant medical histories and current medical conditions at baseline will be summarised separately by system organ class and preferred term, by treatment group. Histories of statin intolerance will be summarised by treatment group. FAS will be used for the analysis.

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

All summaries of treatments will be performed on the Safety Set, unless otherwise specified.

2.4.1 Study treatment / compliance

The number of study doses administered, duration of exposure, patient year of exposure will be summarized by treatment group. Listings will be provided.

The number of participants dosed will also be summarized by study visit and treatment group.

Duration of exposure for inclisiran arms will be calculated as: minimum of (Date of last dose of treatment – Date of first dose of treatment + 180, Date of last known visit – Date of first dose of treatment).

Duration of exposure for lipid lowering therapies will be calculated as: minimum of (Date of last dose of lipid lowering therapy – Date of first dose of lipid lowering therapy, Date of last known visit – Date of first dose of lipid lowering therapy).

Patient-year of exposure will be calculated as duration of exposure/365.25.

2.4.2 Prior, concomitant and post therapies

Medications are collected through EMR and in this system medication end date is not available.

Lipid-lowering therapy use at screening and baseline/randomization visit (Day 1) will be summarized by treatment group. Lipid-lowering therapy newly added or changed after randomization will be summarized by treatment group.

Other medications will be listed and summarized according to the anatomical therapeutic chemical (ATC) classification system and preferred term, by treatment group.

2.5 Analysis supporting primary objective(s)

The primary objective of this study is to demonstrate superiority of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting, in adults with elevated LDL-C. Standard of care + behavioural support will be considered as control group as mentioned in section 1.1.

2.5.1 Primary endpoint(s)

The primary endpoint is the percentage change in LDL-C from baseline to Day 270.

The primary estimand is defined as follows. The primary effectiveness question of interest is: What is the effect of the test treatment inclisiran versus control on change in LDL-C after 270 days of treatment in adults on established lipid lowering medication or who have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid lowering therapy.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of changes in additional medication(s) used for lipid lowering, if they occur, in a primary care setting.

The primary estimand is described by the following attributes:

Population	Adults with elevated LDL-C on established lipid lowering medication or, have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment.
Variable	Percentage change in LDL-C from baseline to Day 270
Treatment	The randomised treatment (inclisiran alone or inclisiran with behavioural support) as add-on to the control treatment of lipid-lowering background therapy plus behavioural support, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid lowering therapy and regardless of use of prohibited medications.
Summary measure	Difference between treatments in mean percentage change in LDL-C from baseline to Day 270.
Intercurrent events	1. Study treatment discontinuation 2. Deviation in background treatment 3. Use of prohibited medications

Patients who took extra dose of inclisiran (who are identified through EMR) during the study period will be excluded and additional analysis will be provided.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary effectiveness objective of this study is to demonstrate superiority of each inclisiran arm compared to control in terms of the percentage change from baseline in LDL-C to Day 270 in adults with elevated LDL-C. The statistical hypotheses that will be tested for each inclisiran arm are as follows:

- H_0: The difference between participants treated with inclisiran and control in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C= 0
- H_a: The difference between participants treated with inclisiran and control in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C < 0

The primary objective will be achieved if null hypothesis (H_0) rejected at the one-sided significance level of 0.025.

The primary analysis will use an analysis of covariance (ANCOVA) model on the percent change in LDL-C from baseline to Day 270 to test the superiority of inclisiran over control after missing data imputation.

Due to probable heterogeneity of variances between treatment groups, ANCOVA model which assumes unequal variances for treatment group will be used. The model will include the fixed effects of treatment group with baseline LDL-C as a covariate.

Multiple imputation will be used to impute missing data using a washout model specified in Appendix 5.5.1. A total of 500 imputed datasets will be created. The ANCOVA model will be fitted to each imputed dataset, and results will be combined using Rubin's combination rules. The estimate and corresponding 2-sided 95% confidence intervals of mean difference between treatment groups will be calculated. p-value for hypothesis test for mean difference will also be provided. The FAS will be used for this analysis. The family-wise error rate for comparisons of the two inclisiran arms with the lipid-lowering background therapy plus behavioural support arm will be controlled using the Holm procedure.

2.5.3 Handling of intercurrent events

The approach of accounting for intercurrent events is as follows:

Primary estimand:

Intercurrent events (ICEs)	**Strategy and justification of handling ICEs**	**Missing value imputation**
Study treatment discontinuation	Here interest is in effect of treatment regardless of treatment discontinuations due to any reasons other than intercurrent event. This event will be handled using **a treatment policy strategy**.	The LDL-C data collected post discontinuation of study treatment will be included in the analysis. If there is no off-treatment data available, then missing data on Day 270 or after treatment discontinuation will be imputed using missing not at random (MNAR) for inclisiran arms and using missing at random (MAR)

Intercurrent events (ICEs)	Strategy and justification of handling ICEs	Missing value imputation
		approach for placebo arm participants.
Deviation in background treatment	Interest is in effect of treatment regardless of substantial changes to background therapy during study treatment. This will be handled with a **treatment policy strategy**.	The LDL-C data collected after deviation in background treatment will be included in the analysis. Missing values will be imputed in same way as mentioned in Appendix 5.5.1
Use of prohibited medications	Interest is in effect of treatment regardless of changes in concomitant lipid lowering medication during study treatment. This will be handled with a **treatment policy strategy**.	The LDL-C data collected after deviation in background treatment will be included in the analysis. Missing values will be imputed in same way as mentioned in Appendix 5.5.1

2.5.4 Handling of missing values not related to intercurrent event

The point of care device is used to measure lipid profile data at each visit. Any undetectable calculated LDL-C data due to device sensitivity for a lipid parameter will be considered as missing for the primary analysis.

Undetectable data will be imputed separately as per Appendix 5.5.1 and used in a sensitivity analysis.

LDL-C data will be calculated using Friedwald's formula as mentioned below:

LDL-C = Total cholesterol – HDL – Triglycerides/2.2

Friedewald's formula valid only when Triglycerides < 4.52 mmol/L

[redacted]

Other missing data are expected to be intermittent missing data and will be assumed to be missing at random. The post-death missing values will be treated in same way as other missing data. Imputation details for data missing at random in the washout model has been provided in Appendix 5.5.1.

2.5.5 Sensitivity analyses

The following sensitivity analyses will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis on the FAS only:

- Linear mixed-effect model for repeated measures (MMRM) analysis without multiple imputation

Analyses using the MMRM will include fixed effects for treatment, visits, interaction between treatment and visits, baseline LDL-C and interaction between baseline LDL-C and visit. Day 90 and 270 will be included as visit. The Restricted Maximum Likelihood (REML) estimation approach will be used with covariance structure set as "Unstructured". If the model does not converge with unstructured covariance matrix, the compound symmetry covariance matrix will be used in the mixed model.

As a sensitivity analysis, the imputation algorithm will be changed from a regression approach to a multivariate normal model to include in the imputation information that is provided by undetectable LDL-C values. An LDL-C value is undetectable when either [redacted] are outside of the limit of detection. Based on the limit of detection and through Friedewald's formula, a range for an LDL-C value can be calculated. In this sensitivity analysis, the LDL-C range is considered in the imputation model. As for the primary analysis, undetectable LDL-C values for either study arm are imputed under a MAR assumption, missing values in the placebo arm are imputed under a MAR assumption, and missing data on Day 270 or after treatment discontinuation in the inclisiran arm are imputed using a wash-out model (i.e., using a jump-to-reference approach).

In the sensitivity analysis, imputed baseline values will be restricted to ≥ 0.1 to avoid imputed values close to zero which can lead to numerical instabilities in the analysis of percentage LDL-C change from baseline.

The imputation will be carriedout using in SAS/R as mentioned in Appendix 5.5.2.

The analysis will be carried out using ANCOVA procedure as mentioned in section 2.5.2.

2.5.6 Supplementary analyses

Supplementary analysis of LDL-C change from baseline to Day 270 will be performed using linear mixed-effect model for repeated measures (MMRM) analysis with multiple imputation as specified in section 2.5.5. This supplementary analysis will be performed by assessing supplementary estimand as mentioned below.

Intercurrent events (Study treatment discontinuation and Deviation in background treatment) will be handled similarly as mentioned in primary endpoint (Refer section 2.5.3) and additionally below mentioned strategy will be used for "Use of prohibited medications".

ICE	Strategy and justification of handling ICEs	Missing value imputation
Use of prohibited medications	Interest is in effect of treatment regardless of changes in concomitant lipid lowering medication during study treatment. Use of prohibited medications (includes treatments which are	LDL-C data after this event will be set to missing. Missing data after this event will be imputed in same way as mentioned in Appendix 5.5.1.

ICE	Strategy and justification of handling ICEs	Missing value imputation
	added to existing background therapy during the study) will not be allowed in the study and will lead to study treatment discontinuation. The LDL-C data collected after the use of any prohibited medication will not be included in the analysis. **Hypothetical strategy** with the hypothetical scenario 'as if patients would have not received any prohibited medication.	

2.6 Analysis supporting secondary objectives

The secondary objectives of this study are to evaluate the implementation of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting using the following assessments that will be reported based on this SAP are:

- Measures of patient satisfaction using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.
- Measures of patient activation and empowerment using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.
- Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period.
- Serious adverse event profile and adverse events leading to treatment discontinuation.

The following secondary endpoint will be analysed by Manchester University and are not covered by this SAP:

- A process evaluation conducted using the Consolidated Framework for Implementation Research (CFIR) which will explore inclisiran delivery at three levels:
  - Feasibility and acceptability of delivery models for inclisiran to patients
  - Feasibility and acceptability of delivery models for inclisiran to providers (inner setting)
  - Wider 'transactability' of the proposed delivery models (outer setting)
  - The service costs of each delivery model
  - The acceptability and perceived sustainability of patient identification and referral routes

2.6.1 Secondary endpoint(s)

The following are key secondary efficacy endpoints:

- Mean difference in total score using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.
- Mean difference in total score using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.
- Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period.

All the analyses on above endpoints will be based on observed data only.

2.6.1.1 The CSQ-8 PROMs Questionnaire

The Client Satisfaction Questionnaire© (CSQ) is a portfolio of measurement instruments (CSQScales®) designed to assess consumer satisfaction with health and human services, including governmental and public benefit programs and services.

Each scale measures the recipients' direct satisfaction with specific services offered and received within a particular time frame from a specific provider or service setting.

The CSQ-8 has 8 items and no subscales. and It reports a single score measuring a single dimension of overall satisfaction.

A total score is produced by summing all item responses, with a higher scores indicating higher satisfaction. The outcome is the mean difference in total score between treatment groups. For the CSQ-8 version, scores range from 8 to 32, with higher values indicating higher satisfaction. Scoring for other versions is similar after extrapolating for number of items.

The following endpoint will be analyzed with CSQ-8 PROMs Questionnaire data.

Endpoint: Mean difference in total score using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90. **Summary measure:** Mean difference in total scores between treatment groups.

2.6.1.2 The PAM PROMs Questionnaire

This study will use the 13-point PAM questionnaire, which will be complimented by data on medication adherence to Inclisiran or standard of care recorded during the trial. The 13 item PAM consists of 13 statements relating to patients beliefs about health care, confidence in their management of health related tasks, and self-assessed knowledge of their condition.

For each statement patients are required to say how much they either agree or disagree on a response scale of 1–4, where 1 represents "strongly disagree" and 4 represents "strongly agree". Patients may also answer "non-applicable" which is scored as 0. A total score is created by summing the scores for the 13 statements and multiplying by 13/(13-n) where n is the number of statements answered as "non-applicable" or missing. The total is rounded to the nearest integer. The total score in the range [13,52] is then converted to a score in the range [0,100] using a calibration table. Note that if n>3, the calibrated score defaults to 51.

The continuous PAM scores are then categorized into four levels for descriptive purposes: according to the materials supplied by Insignia, scores less than 47.1 are level 1, scores between

47.1 and 53.2 are level 2, scores between 53.3 and 70.2 are level 3, and scores above 70.2 are level 4.

The following endpoints will be analyzed with PAM PROMs Questionnaire data.

- **Endpoint:** Mean difference in total score using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90. **Summary measure:** Difference between treatment groups in mean change in total scores from baseline to Day 90.
- **Endpoint:** Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period. **Summary measure:** The frequency and percentages of subjects in the four levels of the PAM scores (below) will be summarized. Note that highly activated patients (level 3 and level 4) are more likely to adhere to cardiovascular self-management and thus medication adherence.

  Level 1: Disengaged and overwhelmed
  Level 2: Become aware but still struggling
  Level 3: Taking action
  Level 4: Maintaining behaviors and pushinng further

2.6.2 Statistical hypothesis, model, and method of analysis

The key secondary variables will be analyzed as follows:

- Mean difference in total score using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90 between the groups will be analyzed using ANOVA. The test statistics, mean difference, 95% confidence interval and the p-value obtained using the ANOVA will be presented.
- The comparison between inclisiran and inclisiran + behavioural support also will be done and presented as mentioned above. Inclisiran arm will be considered as control for this analysis.
- The descriptive statistics for the total CSQ score will be provided for each treatment group.

- Mean difference in total score using the validated Patient Activation Measure (PAM) questionnaire administered after treatment from baseline today 90 will be analyzed using ANCOVA model. ANCOVA model which assumes unequal variances for treatment group will be used. The model will include the fixed effects of treatment group with baseline total scores as a covariate. The estimate and corresponding 2-sided 95% confidence intervals of mean difference between treatment groups will be calculated. p-value for hypothesis test for mean difference will also be provided. The FAS will be used for this analysis.
- The comparison between inclisiran and inclisiran + behavioural support also will be done and presented as mentioned above. Inclisiran arm will be considered as control for this analysis.

- Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period will be summarized by providing the frequency and percentages of subjects in the four levels of the PAM scores (below) by visit and treatment. Note, highly activated patients (level 3 and level 4) are more likely to adhere to cardiovascular self-management and thus medication adherence.

  Level 1: Disengaged and overwhelmed
  Level 2: Become aware but still struggling
  Level 3: Taking action
  Level 4: Maintaining behaviors and pushinng further

- Also frequecncy and percentage of subjects completed each item of PAM questionnaire will be summarized by visit and treatement.

2.6.3 Handling of missing values

No imputation will be applied if the scores are missing at a visit in any the questionnaire. The proportion of missing data will be included in summaries to aid interpretation.

2.7 Safety analyses

For all safety analyses, the safety set will be used.

Safety summaries (tables, figures) will include only treatment emergent adverse events (i.e. adverse events started after the first dose of study treatment or adverse events that were present prior to start of study treatment but increased in severity during the course of the study). Listings will include all data.

Vital signs values that have complete data and time values will be allocated to pre- or post-dose assessment (as per protocol) based on the actual date/time. For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by visit/time point summary.

2.7.1 Adverse events (AEs)

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

- By treatment, primary system organ class (SOC) and preferred term (PT).
- By treatment, primary system organ class (SOC), PT and maximum severity.
- By treatment, Standardized MeDRA query (SMQ) and PT.

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

Unless otherwise specified, SOCs will be sorted alphabetically and, within each SOC, the PTs will be sorted in descending order of frequency in the total column. A participant with multiple

adverse events within the same PT, the AE will be counted only once. 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. In case of summary by severity or relationship to study drug, summary will be done using the most severe or related occurrence respectively. Listing of all AEs and SAEs will be provided.

AE reporting for CT.gov and EudraCT: For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events, on 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 ≤ 1 day gap between the end date of the preceding AE and the start date 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 has to be checked in a block e.g., among AE's in a ≤ 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 event of special interest (AESI): The number and percentage of participants who reported TEAEs of special interest will be summarized by PT, treatment group. PTs will be sorted in descending order of frequency in the total column. If a participant reported more than one adverse event with the same PT, the AE will be counted only once. If a participant reported more than one AE within the same AESI, the participant will be counted only once at that AESI. Listing of participants with adverse event of special interest will be provided.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest.

Adverse event of special interest will include the following:

- Hepatotoxicity (Hepatic events)
- New onset or worsening of diabetis mellitus

For search criteria of AE of special interest, refer to Appendix 5.3.

The most recent list of adverse events of special interest at the time of database lock will be used. CRS listing will be provided.

2.7.2 Deaths

Please refer section 2.7.1.

2.7.3 Laboratory data

There are no regular laboratory tests required by this protocol. All blood tests will be performed locally by clinical pathology laboratories, in common with usual practice. Methods for sampling, handling and analysis will be the same as usually applied in routine care.

Abnormal laboratory findings, that are detected during the study or are present at baseline and significantly worsen following study drug administration, and are deemed as clinically significant by the investigator will be recorded as AEs if they lead to treatment discontinuation.

2.7.4 Other safety data

2.7.4.1 Vital signs

Absolute values, change from baseline and percentage change from baseline will be summarized for vital sign parameters by visit, time point and treatment group using overall data. Baseline and change from baseline in height, [redacted] will be summarized by visit, treatment group using overall data.

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

2.8 Patient-reported outcomes

2.8.1 The CSQ-8 PROMs Questionnaire

The details about Client Satisfaction Questionnaire (CSQ) and the endpoints were mentioned in section 2.6.1.1. For more details on the questionnaire, please refer to the study protocol.

2.8.2 The PAM PROMs Questionnaire

The details about Patient Activation Measure (PAM) Questionnaire and the endpoints were mentioned in section 2.6.1.2. For more details on the questionnaire, please refer to the study protocol.

2.8.3 [redacted]

[redacted]

2.9 [redacted]

[redacted]

2.10 [redacted]

[redacted]

2.10.1 Other efficacy data

A capillary blood sample will be taken for immediate analysis of the participants lipid profile[redacted] for assessment of efficacy. This will be performed at screening/baseline visit, day 90 visit and EOS (day 270) visit in the following:

- [redacted]
- Non-HDL (calculated)
- LDL-C calculated using Friedwald

Descriptive summaries by treatment group will be presented. [redacted]

Line-Plot displaying mean and SE of change from baseline will be provided for all parameters using all available visits.

[redacted]

Descriptive summaries by treatment group will be presented.

Listing of all above endpoints for all available visits will be provided.

The threshold analysis on LDL-C data will be performed. Frequency and percentage of patients with secondary prevention who achieved following threshold targets at day 270 will be provided.

- <1.8 mmol/L (<70 mg/dL)
- <1.4 mmol/L (<55 mg/dL)

2.10.2 [redacted]

[redacted]

[redacted]

2.10.3 [redacted]

[redacted]

2.11 Interim analysis

There are no interim analyses planned for this study.

3 Sample size calculation

The primary effectiveness endpoint of the study is percent change of LDL-C from baseline. However, the sample size is driven by patient experience (CSQ-8) and patient activation (PAM); two key secondary outcomes in this trial.

The trial has been powered to detect differences equivalent to a Cohen's effect size of 0.3, approximating a 'small-to-medium' effect in conventional terms

A sample size of 300 patients per arm would be able to detect this effect size with 90% power using a one-sided significance level of 0.025 (this includes a 20% allowance for drop-out in this primary care setting).

This sample size could also detect a reduction of at least 10% change of LDL-C from baseline in the inclisiran group compared to the control group (assuming a standard deviation of 30% in the control group and 20% in the inclisiran group based on observed results from previous inclisiran studies).

The total sample size for the study will be 900 participants.

4 Change to protocol specified analyses

- [redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing/partial start date or end date of treatment will not be imputed.

5.1.2 AE date imputation

5.1.2.1 AE start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < study drug start date then AE start reference date = min(informed consent date, earliest visit date).
- Else AE start reference date = study drug start date

Impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the study drug start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the study drug start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the study drug start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the study drug start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2.2 AE end date imputaion

For the purpose of date imputation the treatment follow-up period date is defined as the last available visit date.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.
4. If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.3 Concomitant medication date imputation

5.1.3.1 CM start date imputation

The following table explains the notation used in the logic matrix.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a)	(3.b)	(3.b)	(3.b)

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the investigational study treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid –year point (01JULYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the investigational study treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the investigational study treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Search criteria for AE of special interest

The Adverse events of special interest (AESIs) based on MedDRA terms are defined in the Case Retrieval Strategy (eCRS). To select the corresponding records from SAS dataset ECRS in Novartis computing environment, use

- Compound name (DRGNAM)=” KJX839”,
- Compound indication (DRGINDC)=” Hypercholesterolemia”,
- Records with MDRAVER = 25.0

Safety topics flagged in the eCRS using the safety flag (PSURFL =YES) will be filtered and further safety topics mentioned in section 2.7.1.1 will be considered for analyses.

5.4 Laboratory parameters derivations

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined:

Table 5-1 Clinical notable criteria for selected laboratory tests

Test	Notable post-baseline criteria
Glucose, fasting	≥ 5.5 to < 7.0 mmol/L ≥ 7.0 mmol/L
HbA1c	≥ 5.7 % to < 6.5 % (≥ 39 mmol/mol to < 48 mmol/mol) ≥ 6.5 % (≥ 48 mmol/mol)

Table 5-2 Notable Liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
AST > 3 x ULN AST > 5 x ULN AST > 8 x ULN AST > 10 x ULN AST > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin > 2 x ULN
TBL >2xULN & DBL >ULN TBL >2xULN & DBL >2xULN
ALP > 2 x ULN
ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, DBL = Direct bilirubin

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window.

The liver function tests are not required as per the assessment schedule of the protocol. This data collected from EMR based on the availability. Whatever data collected will be presented.

Normal ranges provided by medical team will be considered for this analysis since reference ranges are not collected in source data.

5.5 Statistical models

5.5.1 Multiple Imputation Wash-out model

A multiple imputation washout model will be utilized for the primary efficacy analysis of the percentage change in LDL-C from baseline to Day 270 endpoint. The washout model can be thought of as a control-based PMM that will be used to explore the possibility of missing data being MNAR for subjects who discontinued the study early. For subjects who discontinued the study early, their missing values will be imputed under the assumption that their outcome would be similar to those in the control group with similar background characteristics. For subjects in the inclisiran groups only missing Day 270 values will be imputed.

For subjects whose LDL-C values are undetectable i.e., both baseline and post-baseline due to device sensitivity for a lipid parameter in inclisiran groups will be considered as missing and imputed under MAR assumption.

For subjects in the control group, their missing values over all visits after early termination as well as undetectable values including both baseline and post-baseline due to device sensitivity for a lipid parameter will be imputed based on the missing at random (MAR) assumption.

Multiple imputation will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method. Further details are provided below.

For the control group the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MAR:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 90 (continuous)
- Observed value of efficacy measurement at Day 270 (continuous)

For the subjects in the inclisiran group who completed the doses and with intermittent missing as well as undetectable data, the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MAR:

- Baseline value of efficacy measurement (continuous)
- Observed value of efficacy measurement at Day 90 (continuous)
- Observed value of efficacy measurement at Day 270 from the inclisiran group (continuous)

For the subjects in the inclisiran groups and with missing data at Day 270 which does not includes undetectable data, the following variables will be included in a multiple imputation procedure (SAS PROC MI), this assumes missing data are MNAR:

- Baseline value of efficacy measurement (continuous)

- Observed value of efficacy measurement at Day 270 from the control group (continuous)

[redacted]

[redacted]

5.5.2 Imputation of undetectable data

For each undetectable LDL-C value, a range is determined based on Friedewald's formula. Below table will provide example range calculation when [redacted] are distributed in different categories.

Table 5-3 Range determination

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

As a next step, the undetectable LDL-C values are baseline are imputed to create 500 complete sets of baseline LDL-C values. The imputation is performed by fitting a normal distribution to all available baseline LDL-C values including the LDL-C ranges. The imputed values are obtained by sampling from the posterior predictive distribution. As prior distribution for mean and the standard deviation a normal distribution (mean=0, sd=10) and a half-t-distribution (df=3, scale=2.5) are chosen.

To create 500 complete data sets of baseline and post-baseline LDL-C data sets, the following approach is performed for each of the 500 data sets with complete baseline LDL-C data.

1. Fit a Bayesian linear mixed model to all available post-baseline LDL-C data including the LDL-C ranges from Day 90 and Day 270.
    a. The model includes study arm, visit, and baseline LDL-C as well as all interactions as fixed effects.
    b. The model includes a normally distributed patient-specific random effect and a normally distributed residual error. The variance of the residual error differs by study arm and visit.

[redacted]

2. For the missing values or undetectable LDL-C values of patient i at visit j in study arm k that are imputed under the MAR assumption, the imputed value is drawn from the posterior predictive distribution of the outcome (i.e., LDL-C) of patient i at visit j in study arm k.
3. For the missing values of patient i at visit j in the inclisiran arm that are imputed under the jump-to-reference assumption, the imputed value is drawn from the posterior predictive distribution of the outcome (i.e., LDL-C) of patient i at visit j whereas the components (e.g., fixed effects and random effects) of the posterior predictive distribution that are associated with the inclisiran arm are replaced by the corresponding value from the placebo arm.

The above imputation will be carried out using R software.

Each of the 500 complete data sets is analyzed with an ANCOVA as specified for the primary analysis. The resulting point estimates will be combined using Rubin's method.

5.6 Rule of exclusion criteria of analysis sets

The protocol deviations (PD) and other criteria leading to complete exclusion from analyses sets are provided in below table, which may be updated prospectively and will be finalized before study DBL.

Table 5-4 Protocol deviation criteria leading to exclusion from analysis sets

Protocol Deviation		Excluding from Analysis set		
ID	**Desctiption**	**RAN**	**FAS**	**SAF**
INCL01A	No study informed consent prior to performing study assessments	X	X	X
INCL01B	No signed informed consent exists at site	X	X	X
INCL02	Participant's age < 18 years at screening visit			
INCL03A	Participant not on statin therapy and intolerance not documented			
INCL03B	Participant is indicated to have partial statin intolerance but not documented			
INCL04	Participant's total cholesterol not available at screening visit or is <4mmol/L (160mg/dL)			
INCL05	Participant's lipid-lowering therapy at study entry not stable for ≥ 30 days before screening visit			
EXCL01	Participant has medical or surgical history that might limit the individual's ability to take study treatments for the duration of the study and/or put the participant at significant risk			
EXCL02	Current or planned renal dialysis or transplantation			

Protocol Deviation		Excluding from Analysis set		
ID	**Desctiption**	**RAN**	**FAS**	**SAF**
EXCL03	Participant had acute coronary syndrome or stroke less than 4 weeks before the screening visit			
EXCL05	Participant is a female of child-bearing potential and NOT agreeing to either abstinence or, if sexually active, to using effective methods of contraception			
EXCL06A	Participant confirmed to be pregnant or nursing and randomized			
EXCL06B	Pregnancy test(s) not performed at screening or randomization visit			
EXCL07	Treatment with monoclonal antibodies directed towards PCSK9 initiated at any time during the course of the study			
EXCL08	Participant has previous exposure to inclisiran or participation in a randomised study of inclisiran			
EXCL09	Participants treated with other investigational medicinal products or devices within 30 days or five half lives (whichever is longer) of the screening visit			
EXCL10	Participant who plans to move away from the geographical area where the study is being conducted during the study period			
EXCL11	The participant has a triglyceride value of greater than or equal to 4.52			
COMD01	Introduction of new lipid lowering therapy (either different statin or new additional therapy) during the study			
COMD02	Treatment with monoclonal antibodies directed towards PCSK9 initiated at any time during the course of the study			
COMD03	Another investigational treatment initiated at any time during the course of the study			
OTH01	Study treatment given and/or assessment(s) performed after withdrawal of ICF			
OTH02	Subject resumes study treatment after pregnancy but continues breast feeding			
OTH03	Site closed due to GCP reason		X	
OTH04	Scheduled visit missed due to COVID-19			
OTH05	Participant discontinues from study due to COVID-19 situation			
OTH06	Assessment / procedure at visits changed due to COVID-19			
OTH07	Drug supply method changed due to COVID-19			

Protocol Deviation		Excluding from Analysis set		
ID	**Desctiption**	**RAN**	**FAS**	**SAF**
OTH08	The participant has withdrawn from the Behavioural Support calls so these calls are no longer being made			
OTH09	Patient received behavioural support calls when they had not been randomised to receive these			
OTH10	Patient did not receive behavioural support calls when they had been randomised to receive these			
OTH11	Patient visits have occurred out of visit window and/or the visit is very late			
OTH12	Other protocol deviation			
WITH01	Participant became pregnant during the course of the study but study treatment was not discontinued			
WITH02	Participant has been treated with monoclonal antibodies directed towards PCSK9 but study treatment was not discontinued or re-started			
WITH03	Participant has received other investigational treatments but study treatment was not discontinued or re-started			
WITH04	Participant had a severe and persistent (>14 days despite appropriate treatment) injection site reaction but study treatment was not discontinued			
WITH05	Participant had a confirmed anaphylactic reaction but study treatment was not discontinued			
TRT01	Participant was given wrong medication number/pack or administered with study drug that was not stored appropriately or dosed with expired medication			
TRT02	Participant was not randomized but took study drug	X	X	
TRT03	Participant received study drug between screening visit and randomization (Day 1) visit by mistake			
TRT04	Missed dosing for any reason other than participant safety or withdrawal (and non-COVID-19 related)			
TRT05	Participant did not receive study treatment due to COVID-19			
TRT06	Participant discontinues from treatment due to COVID-19 situation			

6 Reference

CKJX839A1GB01 amended protocol v02 dated 12-Sep-2022.

Attkisson, C. C. & Zwick, R. The client satisfaction questionnaire. Psychometric properties and correlations with service utilization and psychotherapy outcome. Eval. Program Plan. 5, 233–237 (1982)

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Hibbard J, Gilburt H. Supporting people to manage their health: An introduction to patient activation. 2014. The King's Fund. 25-12-0016. http:// www.kingsfund.org.uk/publications/supporting-people-manage-their-health

Hibbard J, Mahoney E, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure (PAM). Health Serv Res. 2005; 40(6):1918–30.

Hibbard J, Stockard J, Mahoney E, Tusler M. Development of the Patient Activation Measure (PAM): Conceptualizing and measuring activation in patients and consumers. Health Serv Res. 2004;39(4):1005–26.