NOVARTIS

Novartis Research and Development

KJX839/Inclisiran

Clinical Trial Protocol MDCO-PCS-17-02 (CKJX839A12302) / NCT03851705

A two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy of Inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH)

ORION-5

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EUDRACT number:	2018-000893-31
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Protocol Synopsis

Name of Sponsor/Company: Novartis
Name of Finished Product: Inclisiran for Injection (also referred to as KJX839)
Name of Active Ingredient: inclisiran sodium
Title of Study: A two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH).
Phase of Development: III
Study Centers: Multicenter study
Central Facilities: This list is maintained by the Sponsor
Number of Subjects: At least 45 subjects; subjects randomized 2:1 to inclisiran: placebo.
Principal Investigator: Prof. [redacted] South Africa:
Study Period: The estimated study period will be approximately 30 months from first subject enrolled in the study to last subject completed. This two-part study will include a 6-month double-blind placebo-controlled period to assess the safety, tolerability, and efficacy followed by an 18-month open-label single arm follow-up period.
Objectives: **Primary** The primary objective is to evaluate the effect of inclisiran treatment on: • Low-density lipoprotein cholesterol (LDL-C) levels at Day 150 **Secondary** The secondary objectives are to evaluate the effect of inclisiran on: • LDL-C levels over time • Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels over time • Other lipids, lipoproteins, and apolipoproteins • Individual responsiveness of subjects to inclisiran including proportion of subjects achieving prespecified global lipid guidelines for their indication • Proportion of subjects with at least 30% LDL-C reduction from Day 1 over time and to assess the • Safety and tolerability profile of inclisiran [redacted]
Methodology: **Hypotheses:** The primary hypothesis is that inclisiran, when used in combination with maximally tolerated statin therapy with or without ezetimibe, will be well-tolerated, will suppress PCSK9 synthesis assessed by the reduction in circulating PCSK9 >50% and will result in reduction of LDL-C, defined as mean percent change of >20% from Day 1 to Day 150 in subjects with HoFH.

Study Design: This study will be a Phase III, two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy in subjects with HoFH. This study has two sequential parts:

- Part 1: 6-month double-blind period in which subjects will be randomized to receive either inclisiran or placebo
- Part 2: 18-month open-label follow-up period; placebo-treated subjects from Part 1 will be transitioned to inclisiran and all subjects will participate in an open-label follow-up period of inclisiran only

Informed consent will be obtained from subjects before the initiation of any study-specific procedures.

Subjects who meet study inclusion/exclusion criteria will be instructed to continue to follow a National Cholesterol Education Program Adult Treatment Panel III (or comparable) diet and be required to maintain their current lipid lowering drug therapy for the duration of the study.

In this study, at least 45 subjects will be enrolled and randomized 2:1 to receive either inclisiran 300 mg SC or placebo on Day 1. Inclisiran and placebo will both be administered by a health care provider. Subjects will be observed in the clinic for at least 30 minutes post injection before being discharged. A second dose of inclisiran or placebo will be given at Day 90. After completion of Part 1, the inclisiran-treated subjects from Part 1 will receive a third dose of inclisiran administered on Day 270 and subsequent doses on Day 450 and Day 630. The placebo-treated subjects from Part 1 will be transitioned to inclisiran starting on Day 180 and the study will then transition to an open-label, single arm follow-up period of inclisiran only (Part 2). Placebo-treated subjects will receive their first dose of inclisiran on Day 180 and then subsequently receive a dose of inclisiran on Day 270, Day 450 and Day 630.

Subjects on a documented regimen of LDL or plasma apheresis will be allowed to continue their same regimen during the study using approximately the same frequency/timing as done at baseline. When apheresis is performed during a study visit (Dosing or Non-Dosing), blood samples for measurement of LDL-C, other lipids and laboratory assessments must be collected before the apheresis. When apheresis is performed during a Dosing Visit, dosing must occur just after completion of the apheresis. The next scheduled apheresis must not occur within 72 hours of injection of inclisiran. The subsequent study visit must occur at least 2 weeks after an apheresis was performed to ensure LDL-C levels measured during a study visit are not confounded by the apheresis (see Figure 3-2 for details).

Safety results including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and clinical laboratory parameters will be assessed at specified visits through to the end of study (EOS) visit. All AEs must be reported. Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/Investigator and/or returns to baseline values. Other safety related information that should be reported as AEs include injection site reactions, neurological and psychiatric events, potential anaphylactic/hypersensitivity reactions, new onset of diabetes, and worsening of glycemic control.

Samples to detect formation of ADA (including binding and neutralizing antibodies) will be collected on Day 1 (prior to the injection) and at Day 90, Day 330, and Day 720.

The primary endpoint will be measured at Day 150 after which placebo-treated subjects will be transitioned to inclisiran on Day 180. All subjects will be enrolled in a long-term open-label follow-up period through Day 720 (EOS).

Efficacy (pharmacodynamic) assessments will include measurement of the effects of inclisiran on levels of LDL-C, other lipoproteins including total cholesterol (TC), triglycerides, high density lipoprotein cholesterol (HDL-C), non-HDL-C, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], and PCSK9. LDL-C is analyzed by beta-quantification (BQ) on Day 1, Day 150 and Day 720, and calculated using the Friedewald method on all visit days.

The safety and tolerability data from the double blind and open label part of the study will be reviewed by an Independent Data Monitoring Committee IDMC) at pre-defined frequency. A recommendation will be made to continue, stop, or amend the study at any of these reviews.

[redacted]

Diagnosis and Main Criteria for Selection:

Subjects may be included if they meet all of the following inclusion criteria:

1. Males and females, ≥18 years of age with a diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents (see Appendix A)
2. Stable on a low-fat diet
3. Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF) (see Appendix B)
4. Subjects not receiving statins must have documented evidence of intolerance to at least two different statins (see Appendix B)
5. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation
6. Fasting central laboratory LDL-C concentration ≥130 mg/dL (3.4 mmol/L)
7. Triglyceride concentration <400 mg/dL (4.5 mmol/L)
8. No current or planned renal dialysis or renal transplantation
9. Subjects on a documented regimen of LDL or plasma apheresis will be allowed to continue the apheresis during the study, if needed. The apheresis schedule should be maintained as deemed necessary and dosing should be scheduled to be done after apheresis. Administration of study drug should always occur at least 2 days following apheresis. Note: after implementation of protocol amendment 1, administration of study drug must either occur right after apheresis on the day of the study visit or at least 2 weeks following the last apheresis (see Figure 3-2).
10. Subjects must be willing and able to give written informed consent before initiation of any study-related procedures. The subject should be willing to comply with all required study procedures
11. Willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws, and compliance with study treatment regimens

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

1. Use of Mipomersen or Lomitapide therapy within 5 months of screening
2. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9
3. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%
4. Major adverse cardiovascular event within 3 months prior to randomization
5. Planned cardiac surgery or revascularization
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy
7. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >3x ULN, or total bilirubin >2x upper limit of normal (ULN) at screening confirmed by a repeat measurement at least 1 week apart
8. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than the duration of the trial
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or commencement of systemic therapy as treatment during the 3 years prior to randomization
10. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least one acceptable effective method of contraception (eg, oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions from this criterion:

a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age

b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of enrolment

c. Women who are surgically sterilized at least 3 months prior to enrolment

11. Known history of alcohol and/or drug abuse within 5 years

12. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:

a. Subjects who are unable to communicate or to cooperate with the investigator.

b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency)

c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study)

d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study

e. Persons directly involved in the conduct of the study

13. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate] judgment) if he/she participates in the clinical study

14. Any underlying known disease, or surgical, physical, or medical condition that, in the opinion of the Investigator (or delegate), might interfere with the interpretation of clinical study results

15. Treatment with other investigational medicinal products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer

16. Previous participation in the study

17. Hypersensitivity to any of the ingredients of inclisiran

Test Product, Dose and Mode of Administration: Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) will be administered as a single SC injection (1.5 mL) on Day 1, Day 90, and then every 180 days (Day 270, Day 450, and Day 630).

Duration of Treatment: The expected duration of the subjects' participation in the study will be approximately 734 days which includes screening, investigational product administration, and the EOS period to Day 720.

- Screening: Day -28 to -1
- Randomization, initiation of investigational product: Day 1
- Treatment Phase:
  - Dosing: Day 1 (inclisiran or placebo), Day 90 (inclisiran or placebo), Day 180 (placebo subjects switch to inclisiran), Day 270 (inclisiran), Day 450 (inclisiran), and Day 630 (inclisiran; final dose)
  - Additional clinic visits: Day 150, Day 180 (non-dosing visit for subjects randomized to the inclisiran arm), Day 330, Day 510, and Day 690
- EOS visit: Day 720 (90 days after final dose)

Reference Therapy, Dose, and Mode of Administration: Placebo will be administered as a single SC injection (1.5 mL) on Day 1 and Day 90. On Day 180, placebo-treated subjects will transition to receive inclisiran.

Criteria for Evaluation:

Efficacy:

The following endpoints will be examined:

Primary Endpoints:

Percent change in LDL-C from baseline to Day 150

Key Secondary Endpoint(s):

- Absolute change in LDL-C from baseline to Day 150
- Percentage change in Apo-B from baseline to Day 150.
- Percentage change in non-HDL-C from baseline to Day 150.
- Percentage change in total cholesterol from baseline to Day 150.
- Proportion of subjects in each group with ≥30% LDL-C reduction from baseline at Day 150.

Other Secondary Endpoint(s):

- Percentage change and absolute change in LDL-C from baseline to each assessment time up to Day 720 (i.e., Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720)
- Percentage change and absolute change from baseline to Days 90, 150, 180, 330, 510, 690, and 720 in PCSK9
- Percentage change and absolute change from baseline to Days 150, 180, 330, 510, 690, and 720 in total cholesterol, Apo-B, and non-HDL-C for subjects receiving inclisiran
- Individual responsiveness of subjects defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 150, 180, 330, 510, 690, and 720 including proportion of subjects in each group who attain global lipid targets for their indication
- Proportion of subjects in each group with ≥ 20% or ≥30% LDL-C reduction from baseline at Days 150, 180, 330, 510, 690, and 720
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 720

[redacted]

Safety: AEs, SAEs, ECGs, vital signs, clinical laboratory values (hematology, glycated hemoglobin A1C [HbA1C], coagulation testing, chemistry, high sensitivity C-reactive protein (hsCRP), and urinalysis), formation and subsequent characterization of anti-drug antibodies (ADA), and results of neurological examinations will be collected at specified visits through to the EOS visit. Collection of AEs/SAEs will occur throughout the study at each study visit and all AEs must be reported. Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/Investigator and/or returns to baseline values. Other safety related information that should be reported as AEs include injection site reactions, neurological and psychiatric events, potential anaphylactic/hypersensitivity reactions, new onset of diabetes, and worsening of glycemic control.

Samples to detect formation of ADA (including binding and neutralizing antibodies) will be collected on Day 1 (prior to the injection) and at Day 90, Day 330, and Day 720.

Statistical Methods:

Sample Size and Power:

The sample size calculation was performed with the hypothesis that the difference of mean percent change from baseline to Day 150 between inclisiran and placebo will be >20% (20% standard deviation) in subjects with HoFH when treated with inclisiran. The sample size of at least 45 subjects (randomized 2:1 to inclisiran : placebo), with at least 30 subjects in the inclisiran arm, will provide >80% power to detect a 20% reduction of LDL-C levels from baseline in the inclisiran group compared to that in the placebo at one-sided significance level of 0.025 based on two-sample t-test.

Study Population:

Intent-to-Treat (ITT) population - All subjects randomized into the study will comprise the ITT population. Treatment classification will be based on the randomized treatment.

Safety Population – All subjects who received at least one dose of investigational product. Treatment classification will be based on the actual treatment received.

Modified Intent-to-Treat (mITT) Population – All randomized subjects who receive at least one dose of investigational product and have both the baseline and the 150 day follow-up LDL-C assessment will comprise the mITT population. Treatment classification will be based on the randomized treatment.

Unless specified otherwise, the ITT will be the primary analysis population for efficacy analysis and Safety population will be the primary population for safety analysis in this study. mITT population will be used to confirm the efficacy.

Statistical Analysis:

Statistical comparisons will only be performed for the Part 1 of the study. The statistical analysis for study Part 2 is descriptive.

Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum and maximum. For categorical variables, the frequency and percentage will be given.

The primary endpoint is the percent change from baseline in LDL-C following 150 days of treatment.

The primary analysis will be conducted using ANCOVA model based on the multiply imputed datasets (100 total) - Washout based approach. The ANCOVA model will include the fixed effect of treatment group (Inclisiran or placebo) and baseline LDL-C as a covariate. Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's method. The difference between treatment groups in mean change from baseline to Day 150 in LDL-C and corresponding two-sided 95% confidence interval will be provided. The p value for testing equal mean change from baseline to Day 150 in LDL-C will also be provided. For the key secondary endpoints, the efficacy analyses will be similar to the primary analysis of the primary efficacy endpoint, the ANCOVA model will be used on the multiply imputed datasets (100 total) - Washout based approach. Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's method.

Additionally sensitivity analysis including MMRM on imputed data using PMM and without imputation will be performed for both primary and key secondary endpoints except for the endpoint of ≥ 30% LDL-C reduction from baseline to Day 150, which will be analyzed using the logistic regression model with treatment as the effect.

This study is sufficiently powered for the hypothesis testing in the primary and key secondary endpoints, all other endpoints are supportive hence no adjustment for multiplicity is planned.

Safety summaries will include the incidence of AEs, summaries of laboratory parameters, vital signs, and ECGs.

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List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
Apo-A1	apolipoprotein A1
Apo-B	apolipoprotein B
aPTT	activated partial thromboplastin
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	Beta human chorionic gonadotropin
BQ	Beta-quantification
BUN	total protein urea (blood urea nitrogen)
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CrCl	creatinine clearance
CV	Cardiovascular
CVD	cerebrovascular disease
dL	deciliter(s)
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
FUP	follow-up
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GPV	Global Pharmacovigilance
HbA1C	glycated hemoglobin A1C

HDL-C	high density lipoprotein cholesterol
HoFH	homozygous familial hypercholesterolemia
HR	heart rate
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
IDMC	Independent Data Monitoring Committee
IFN-γ	interferon-gamma
IL6	interleukin 6
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	Intravenous
L	Liter(s)
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
Lp(a)	lipoprotein(a)
[redacted]	[redacted]
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	myocardial infarction
mITT	Modified intent-to-treat
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	Millimole
MMRM	mixed-effect models for repeated measures
mRNA	messenger ribonucleic acid
NYHA	New York Heart Association
PCS	potentially clinical significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PEF	peak expiratory flow
PK	pharmacokinetic
PMM	Pattern-Mixture Model

PT	prothrombin time
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
siRNA	small interfering ribonucleic acid
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TBIL	total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse event
TNF-α	tumor necrosis factor-alpha
TTR	target transthyretin
ULN	upper limit of normal
US	United States
VLDL-C	very low density lipoprotein cholesterol
WHO	World Health Organization

Amendment 1 (08-Oct-2020)

Amendment rationale

The first subject for this trial was randomized in Feb 2019 and enrollment was completed in Sep 2019 (with 56 subjects enrolled). Part 1 (double-blind phase) of the trial was completed on 02-Mar-2020, when the last subject completed the Day 180 visit and treatment allocation was unblinded. At time of this amendment, 51 subjects are still on study treatment.

This amendment is written to address the change in sponsorship from The Medicines Company to Novartis after acquisition of The Medicines Company by Novartis in January 2020. Administrative changes were made to the title page, the footer and headers and throughout the protocol to reflect the change in sponsorship and adding the Novartis study and IMP numbers. Additional other changes are made to improve study conduct and interpretation of results, incorporate Novartis processes, language and change in sponsor contacts, allow for some flexibility during the COVID-19 pandemic and to remove the option for subjects to receive study treatment beyond Day 720 because other alternative treatments are available.

Finally, the main statistical analysis model of the primary endpoint was updated as per FDA agreement. The key secondary endpoints have been aligned with the Statistical Analysis Plan (SAP) submitted to FDA on 09-Mar-2020.

Changes to the protocol

The following table specifies each major protocol amendment change section-by-section in the order written in the protocol.

Section	Original protocol	Amendment	Rationale for change
Title page	MDCO Title page including MDCO contact information	Novartis protocol title page	To reflect change in sponsorship, add Novartis protocol number and IMP code, remove MDCO personnel
Procedures in case of an Emergency	MDCO template to provide emergency contacts in protocol	Removed	Emergency Contact information will be shared with sites outside of the protocol
Protocol Synopsis	Synopsis of original protocol	Synopsis of protocol amendment	Updated to reflect all changes made to original protocol; addition of principal investigators Prof. [redacted] and Prof. [redacted] of the trial
List of Abbreviations	For original protocol	For protocol amendment	Updated to include additional abbreviations introduced with protocol amendment
Amendment 1	n/a	Added	Section to provide amendment rationale, protocol changes and impact on IRB/IEC added

Section	Original protocol	Amendment	Rationale for change
Throughout protocol	Inclisiran, MDCO	Updated: Inclisiran sodium 300mg (equivalent to 284 mg inclisiran); Inclisiran Novartis IMP name KJX839 Novartis trial numbers; change in sponsor	To reflect change in sponsorship, (change MDCO to Novartis and/or Sponsor), to add Novartis protocol numbers and IMP code, and to clarify amount of inclisiran sodium vs inclisiran administered
Section 1.2.1	Last sentence: Additional nonclinical studies are ongoing or planned.	Removed	Updated to reflect that there are no ongoing or planned nonclinical studies at this time. The results from all completed nonclinical studies are available in the latest Investigator Brochure.
Section 1.2.2.1	Last sentence: Additional clinical pharmacology studies are ongoing or planned.	Removed	Updated to reflect that there are no ongoing or planned clinical pharmacology studies at this time. The results from all completed clinical pharmacology studies are available in latest Investigator Brochure.
Section 1.2.2.2.3	Study ORION-2	Updated study results, and added MDCO and Novartis protocol numbers	ORION-2 has been completed; updated study results to reflect this status
Section 1.2.2.2.4	Study ORION-7	Updated study results, and added MDCO and Novartis protocol numbers	ORION-7 has been completed; updated study results to reflect this status
Section 1.3 Known potential risks and benefits	referred to IB version 10	Referred to current version of IB;	Ensures that investigators reviews information from most current version of Investigator's Brochure
Section 2.2 Secondary objectives	• Proportion of subjects with at least 20% LDL-C reduction from Day 1 over time	• Proportion of subjects with at least 30% LDL-C reduction from Day 1 over time	To align with secondary endpoints as described in the Statistical Analysis Plan (SAP) submitted to FDA on 9-Mar-2020.

Section	Original protocol	Amendment	Rationale for change
Section 3.1 Type/Design of Study; Section 3.2	The apheresis schedule should be maintained as deemed necessary and dosing and subsequent assessments for LDL-C and other lipids should be scheduled to be done after apheresis, using the same frequency/timing as done at baseline. For example, if baseline LDL-C was drawn 2 days after apheresis, subsequent measurement of LDL-C and other lipids should be taken 2 days after a subsequent apheresis. Administration of study drug should always occur at least 2 days following apheresis.	Removed and replaced by: The apheresis schedule should be maintained as deemed necessary, using approximately the same frequency/timing as done at baseline. When apheresis is performed during a study visit (Dosing or Non-Dosing), blood samples for measurement of LDL-C, other lipids and laboratory assessments must be collected before the apheresis. When apheresis is performed during a Dosing Visit, dosing should occur just after completion of the apheresis. The next scheduled apheresis must not occur within 72 hours of injection of inclisiran. The subsequent study visit must occur at least 2 weeks after an apheresis was performed to ensure LDL-C levels measured during a study visit are not confounded by the apheresis (see Figure 3-2 for details). Figure 3-2 – added to Section 3.2	To ensure that LDL-C measurements are not confounded by apheresis, specific time windows and new timing between sample collection, apheresis and study drug administration were introduced.
Section 3.1 Type/Design of Study	Subjects who have completed the study to Day 720 will be given the opportunity to enroll into an open-label extension trial.	removed	As other alternative treatment options are available and there is no need to provide patients with additional open-label inclisiran.

Section	Original protocol	Amendment	Rationale for change
Section 3.4 Secondary Endpoints		Added additional secondary endpoints: • Percentage change in Apo-B from baseline to Day 150. •Percentage change in non-HDL-C from baseline to Day 150. •Percentage change in total cholesterol from baseline to Day 150. •Proportion of subjects in each group with ≥30% LDL-C reduction from baseline at Day 150.	To align with the Statistical Analysis Plan (SAP) submitted to FDA on 9-Mar-2020.
[redacted]			
Section 4.2 Inclusion Criteria		Inclusion 9 Note: After implementation of protocol amendment 1, administration of study drug must either occur right after apheresis on the same day of the study visit or at least 2 weeks following the last apheresis (see Figure 3-2).	Added additional clarification on proposed new timing of apheresis after implementation of the protocol amendment to ensure that apheresis is not impacting drug levels and/or LDL-C measurements.
Section 4.4 Withdrawal Criteria	It is imperative to obtain complete follow-up data for all subjects whether or not they receive their assigned treatment or have discontinued investigational product.	All subjects discontinuing participation in this trial should be encouraged to complete the EOS except for those subjects who specifically withdrew consent	Section updated to indicate that EOS visit should be encouraged for all patients discontinuing participation from trial.

Section	Original protocol	Amendment	Rationale for change
Section 4.4.1 Withdrawal from Study Medication	The Independent Data Monitoring Committee (IDMC) will be notified.	n/a	Removed. Reasons for withdrawals will be presented to the IDMC at the regular meetings.
	It is imperative to obtain complete follow-up data (through Day 720 procedures) for all randomized subjects whether or not they receive their assigned treatment or have discontinued investigational product.	n/a	Removed to indicate that EOS should be performed within 90 days from last dose (as indicated in Assessment Schedule) and no additional follow-up data need to be collected.
Section 5.1.6 Product Complaints		Change of section title to Product Deficiencies (Complaints) Reporting	Updated section to remove MDCO contact information
Section 5.2.1 Prohibited Concomitant Medications	The following medications/treatments are not permitted to be added during the study:	Background lipid-lowering treatment should remain stable throughout the study duration. As a result, the following medications/treatments are not permitted to be added or changed during the study:	Clarification that background lipid-lowering treatment should remain stable throughout the study duration not to confound study results.
Section 5.2.2 Permitted Concomitant Medication	Lipid-lower medications; subjects already on a stable (≥30 days before screening) lipid-lower medications (such as statins and/or ezetimibe) should remain on the dose that they have received during participation in the original protocol unless clinically indicated	Lipid-lowering medications; subjects already on a stable (≥30 days before screening) lipid-lowering medications (such as statins and/or ezetimibe) should remain on the dose that they have received at time of study entry	Clarification and correction of typos, Removal of 'unless clinically indicated' as changes in the background medication can confound the efficacy endpoint of the study.
Section 5.3.2 Pregnancy		Follow-up evaluation of fetus and newborn should also be performed up to 12 months after birth.	Added to adhere to Novartis reporting guidelines

Section	Original protocol	Amendment	Rationale for change
Section 6.1 Schedule of Assessments		Added: If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or virtual contacts (e.g. teleconsult) can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. Given the long lasting efficacy and infrequent dosing regimen of inclisiran, it is possible to introduce a more variable dosing schedule of +/- 2 months during this pandemic, which still allows subjects to receive inclisiran. If the two-month window is utilized for the next dose, the subsequent dose may be administered up to a maximum of 8 months' time from the next dose (if the next dose is given early) or within a minimum of 4 months' time (if the next dose is given late). If a dose is not given within this two-month window, then the subject should be considered to have had a missed dose and should return as per the schedule in the protocol for the subsequent dose. Schedule of assessments also updated.	Added COVID-19 related language regarding allowing for a more flexible visit and dosing schedule of +/- 2 months during COVID-19 pandemic.

Section	Original protocol	Amendment	Rationale for change
Section 6.3 Screening period (Days -28 to -1)	The following procedures will be performed within 14 days prior to randomization Demographics and medical history [redacted]	The following procedures will be performed within 28 days prior to randomization Demographics and medical history including disease history (prior history related to the disease and prior use of disease related medication, e.g. monoclonal antibodies to PCSK9) [redacted]	Correction of typo to clarify screening period is 28 days as per administrative memo issued on 6-Mar-2019. Additional clarification to information collected for disease history [redacted] sample in this study. These data are needed to allow for better interpretation of study results.
Section 6.4 Randomization	If a local reaction around the injection site occurs that requires the patient to be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site should be obtained at first presentation and at each of the follow-up visits until the injection site reaction resolves, if possible.	If a local reaction around the injection site occurs that requires the subject to be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site may be obtained if deemed necessary.	As we have now accumulated more safety data on type and extent of injection site reactions, the determination as to if and when to take photographs is left to the investigator.
Section 6.6 Additional Dosing Visits		Added: Note: For subjects randomized to the inclisiran arm this will be a non-dosing visit but the same assessments as described below will be performed.	Added clarification that Day 180 is only a dosing visit for subjects randomized to the placebo group. For subjects randomized to the inclisiran group this is a non-dosing visit, all assessments except for dosing are performed as described in this section.
Section 6.7 Additional Non-Dosing Visits		Note: for subjects randomized to the inclisiran group the Non-dosing visit on Day 180 is described in Section 6.6.	To add clarification that subjects randomized to the inclisiran group, will have a non-dosing visit on Day 180 with the same assessments described in Section 6.6 (except for study drug administration)

Section	Original protocol	Amendment	Rationale for change
Section 7.1.7 Clinical samples & Section 7.1.7.7. Lipids		Added: If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and prior to the administration of study drug (on dosing visits).	Added clarification that samples should be collected prior to start of apheresis to not confound LDL-C measurements
Section 7.2.1 Change from Day 1 in LDL-C	At baseline, Day 150, and Day 720 LDL-C will be analyzed BQ; at other visits, samples will be stored for measurement via calculated LDL-C.	Reworded: For all study visits LDL-C will be calculated (using the Friedewald method), in addition at baseline (Day 1), Day 150 and Day 720 LDL-C will be analyzed by BQ.	To clarify that results for LDL-C using beta-quantification (BQ) will be available for 3 study visits, and calculated LDL-C results will be available for all visits during which a blood sample is collected.
[redacted]			
Section 8.4.3.2 Pregnancy		Added: The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Newborns should be followed for 12 months.	Added to further describe the pregnancy and newborn follow-up.
Section 8.6.1	Similar review will be performed by the Safety Review Committee (SRC) during the open label part of the study.	Removed	Safety Review Committee and Data Monitoring Committee have been merged to one Independent Data Monitoring Committee, which will review the double-blind and open-label part of the study
Section 10.4.3 Efficacy Analysis	Primary analysis using MMRM	Primary analysis using ANCOVA Missing data imputation by Wash-out model.	Main statistical analysis model of the primary endpoint was updated as per FDA agreement.

Section	Original protocol	Amendment	Rationale for change
Section 10.5.1 Interim Safety Review	Following Day 180 the unblinded data will be reviewed by the Safety Review Committee (SRC)	Following Day 180 the unblinded data will be reviewed by the IDMC.	Safety Review Committee and Data Monitoring Committee have been merged to one Independent Data Monitoring Committee, which will review the double-blind and open-label part of the study
Section 12.3 Protocol Deviations	The following Protocol Deviations will require additional information in the eCRF explaining why the deviation occurred and what will be done to prevent it from re-occurring:	Removed first two paragraphs. Reworded third paragraph: Deviations from the protocol identified during the conduct of the trial will be recorded in the e-CRF, as applicable, and will be reviewed periodically. These include, but are not limited to the following: Added sentence at the end of the section: Additional protocol deviations and associated actions depending on the nature and impact of the protocol deviation will be defined and periodically reviewed by standard automated and/or manual checks by the clinical team or monitors.	Updated to align with Novartis process of recording protocol deviations and actions involved. Reworded third paragraph and added last paragraph to allow for recording and periodic review of all deviations observed during study conduct in the eCRF, as applicable, including those listed in the original protocol.

Additional minor changes to correct typos and provide clarifications were only incorporated directly into the protocol and are not specifically listed in the above summary of changes.

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

IRBs/IECs

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

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Introduction

Inclisiran (also referred to as KJX839) is a novel synthetic ribonucleic acid (RNA) interference (RNAi) therapeutic for injection (subcutaneous [SC] use) and used for the treatment of hypercholesterolemia. This protocol describes a study to evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 150 in subjects with homozygous familial hypercholesterolemia (HoFH). This study is sponsored by Novartis and will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1 Background

1.1.1 Disease Overview

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death worldwide, resulting in over 17 million deaths annually (WHO 2016). Eighty percent of all CVD deaths are due to coronary heart disease (CHD) or strokes. Elevated low-density lipoprotein associated cholesterol (LDL-C) is a major risk factor for the development of CVD (Grundy et al 2004; Go et al 2014). Lowering LDL-C has been shown to reduce the risk of death or heart attack and within the range of effects achieved so far, the clinical risk reduction is linearly proportional to the absolute LDL-C reduction (Baigent et al 2005).

Approximately 100 million people worldwide are treated with lipid lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death nonfatal myocardial infarction (MI) and nonfatal stroke or associated events (Decision Resources Group 2015). Yet residual risk for cardiovascular (CV) events remains and statins are associated with well-known limitations. First, not all patients reach LDL-C levels associated with optimal protection against clinical events (Davidson et al 2005; Foley et al 2003; CTT Collaborators et al 2008; Foody et al 2010; Baigent et al 2005). Second, not all patients tolerate statins or are able to take statins at sufficiently intensive doses. And third, observational studies have demonstrated that >50% of patients do not adhere to statin therapy for more than 6 months (Mann et al 2010; Poluzzi et al 2008).

There is an unmet need for additional treatment options beyond currently available treatments for lowering of the LDL-C level to reduce cardiovascular risk.

Despite statins alone or in combination with other lipid lowering medications, current therapies for the management of elevated LDL-C remain insufficient in some patients (Fitzgerald et al 2017; Barkas et al 2015; Jameson et al 2014; Jones et al 2012). This is particularly true in patients with pre-existing CHD and/or diabetes or a history of familial hypercholesterolemia (Appendix A), who are at the highest risk and require the most intensive management (Davidson et al 2005).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in controlling the levels of low-density lipoprotein receptors (LDLR) on the surface of hepatocytes (Khorova 2017). PCSK9 is expressed and secreted

into the bloodstream predominantly by the liver, binds LDLR both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, (Lakoski et al 2009; Mousavi et al 2009) thereby increasing the circulating LDL-C levels. Loss of function mutations in PCSK9 have been found to lead to increased LDLR in liver, reduced serum LDL-C, and a lower risk for CHD (Berge et al 2006; Cohen et al 2006; Kotowski et al 2006; Zhao et al 2006) with no apparent negative health consequences. (Zhao et al 2006; Hooper et al 2007; Horton et al 2009).

Recently developed and approved PCSK9-blocking monoclonal antibodies reduce circulating PCSK9 levels and lower LDL-C levels. Results from the first completed large CV outcomes trial (FOURIER) were reported in March 2017. Repatha® (evolocumab) significantly reduced the risk of cardiovascular events. The study in approximately 27,000 patients with clinically evident atherosclerotic cardiovascular disease met its primary composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, nonfatal MI or nonfatal stroke) (Sabatine et al 2015).

The data from PCSK9 blocking antibodies such as Repatha® (evolocumab) and Praluent® (arilocumab) are very encouraging. However, these products are dosed SC every 2 to 4 weeks necessitating up to 26 injections per year (Hooper et al 2005; Navarese et al 2015; Zhang et al 2015). In contrast, one injection of inclisiran is anticipated to be given three times in the first year and every 6 months thereafter.

1.1.2 PCSK9 Biology and Target Rationale

PCSK9 is a member of the subtilisin serine protease family. Proprotein convertase subtilisin kexin type 9 is predominantly expressed by the liver and is critical for the down regulation of hepatocyte LDLR expression (Mousavi et al 2009). LDL-C levels in plasma are markedly elevated in humans with gain of function mutations in PCSK9, classifying them as having severe familial hypercholesterolemia (Abifadel et al 2003). Data from genetic association studies have identified loss of function alleles in human PCSK9 that result in lower PCSK9 protein levels and lower LDL-C levels (Zhao et al 2006; Hooper et al 2007; Horton et al 2009). In one published study, heterozygous individuals (carrying a single copy of a loss of function PCSK9 mutation) had significantly lower LDL-C with median levels of approximately 70 mg/dL (1.81 mmol/L) (Cohen et al 2006). Over a 15-year period of retrospective data analysis, this sustained lowering in LDL-C levels translated to an 88% lower risk of risk for CHD. Follow-up publications describe two adult individuals that are compound heterozygous for loss of function alleles of PCSK9. These individuals lack detectable plasma PCSK9 protein, have LDL-C levels ≤20 mg/dL, and yet are otherwise healthy (Zhao et al 2006; Hooper et al 2007). Additionally, recent human clinical trials with PCSK9 blocking antibodies have shown significant lowering of LDL-C in healthy volunteers and across a range of high cardiovascular (CV)-risk populations and with elevated LDL-C both with and without statins (Banerjee et al 2012; Dias et al 2012; Milazzo et al 2012; Raal et al 2012; Roth et al 2012; Stein et al 2012; Sullivan et al 2012;

Hooper et al 2013). Two monoclonal agents to inhibit PCSK9 are currently approved in Europe and North America. Recent cardiovascular outcomes trials have further confirmed that PCSK9 is a validated drug target whose inhibition results in LDL-C lowering and significant outcomes benefit without otherwise negatively impacting overall health (Ridker et al 2017; Sabatine et al 2017).

1.1.3 Mechanism of RNA Interference

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering RNAs (siRNAs). Typically, synthetic siRNAs are 19-base to 25-base pair double-stranded oligonucleotides in a staggered duplex with a two- to four-nucleotide overhang at one or both of the 3' ends. Such siRNAs can be designed to target an endogenous messenger RNA (mRNA) transcript of a given gene. When introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-Induced Silencing Complex (RISC). This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the target mRNA and the suppression of the target protein encoded by the mRNA (Elbashir et al 2001).

Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration (Soutschek et al 2004), various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo, in animal models (including in rodents and nonhuman primates) and humans employs intravenous delivery of siRNA in lipid nanoparticle formulations (Soutschek et al 2004; Morrissey et al 2005; Geisbert et al 2006; Judge et al 2006; Zimmermann et al 2006; Coelho et al 2013; Tabernero et al 2013). Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a N-acetylgalactosamine (GalNAc) carbohydrate ligand (Ashwell and Morell 1974). Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor (ASGPR), resulting in engagement of the RNAi pathway and down regulation of hepatic proteins. Single and multiple doses of subcutaneously administered siRNA-GalNAc conjugates have been used to target transthyretin (TTR) mRNA for the treatment of TTR-mediated amyloidosis. ALN-TTRCSC has been found to be generally safe and well tolerated in Phase I and Phase II clinical trials in over 40 healthy volunteers and 18 subjects with familial amyloidotic cardiomyopathy and senile systemic amyloidosis (ALN-TTRSC-001; EudraCT 2012-004203-12 and ALN-TTRSC-002; EudraCT 2013 002856 33).

1.2 Inclisiran, an siRNA Therapeutic for Hypercholesterolemia

Inclisiran sodium is a chemically synthesized small interfering RNA (siRNA) double-stranded oligonucleotide, covalently linked to a ligand containing three GalNAc residues.

Inclisiran is a long-acting, subcutaneously delivered, synthetic siRNA directed against PCSK9 that is conjugated to triantennary GalNAc carbohydrates. These carbohydrates bind to abundant liver-expressed ASGPR, leading to inclisiran uptake specifically into hepatocytes.

When introduced into the hepatocyte, inclisiran engages the natural pathway of RNAi by binding intracellularly to the RISC, enabling it to cleave messenger RNA (mRNA) molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein. A single siRNA-bound RISC is catalytic and cleaves many transcripts and the duration of action is anticipated to be longer than other mechanisms.

1.2.1 Nonclinical Studies

Inclisiran was specifically designed with molecular and biochemical characteristics to minimize untoward side effects which are reflected by the absence of dose limiting toxicities in preclinical models. For example, GalNAc ligands were added to the RNA strands in order to target inclisiran to receptors on hepatocytes, thereby greatly reducing uptake by heterologous tissue. This is highlighted by tissue distribution studies in rats showing that compared to liver, inclisiran exposure in other tissues was 36- to 1076-fold lower than liver. In addition, once inclisiran is inside the cell, there is a low likelihood of off-target binding because inclisiran is sequestered within RISC and guided to its complementary PCSK9 mRNA sequence which is highly conserved across diverse ethnic and geographical populations. The specificity of the active antisense strand of inclisiran was determined by performing a comprehensive search against the human transcriptome using an exhaustive "brute-force" algorithm implemented in the python script 'BruteForce.py'. The search revealed 20 possible off-target transcripts, two of which are not normally expressed in liver cells. The other 18 transcripts were subsequently assayed in an in vitro study to experimentally assess their response to inclisiran. The 18 gene transcripts were transfected into liver cells along with inclisiran and expression analysis indicated a ≥45-fold difference between the "on target" suppression of PCSK9 and the suppression of any of the "off-target" transcripts.

Inclisiran was well tolerated in all studies. The most common findings were related to the expected pharmacological effects of inclisiran on lipid profiles and histopathological findings of vacuolation in hepatocytes of rats and lymph node macrophages of monkeys and the presence of basophilic granules in hepatocytes of monkeys and kidneys of rats. These microscopic findings are not considered adverse because they are not associated with changes in clinical pathology parameters. Liver function enzymes were only minimally to mildly increased, and were reversible following treatment-free periods, and there were no changes in urinalysis or urine chemistry parameters.

1.2.2 Clinical Studies

1.2.2.1 Clinical pharmacology

Inclisiran is inactive in plasma and acts directly in the hepatocytes leading to inhibition of PCSK9 protein synthesis. After SC administration of inclisiran, peak plasma concentrations were observed by 4 hours and became undetectable in plasma in 24 to 48 hours with a fast elimination half-life ($t_{1/2}$) of 7.3 hours and dose-proportional increase in exposure parameters of maximum plasma concentration (C_{max}) and area under the curve (AUC). There was no accumulation of inclisiran plasma concentrations following multiple weekly, biweekly or monthly dosing. Mean fraction excreted unchanged in the urine was around 25%. In vitro studies using hepatic P450 metabolic enzymes showed that inclisiran neither inhibited nor induced common hepatic metabolic pathways.

In ORION-7 (CKJX839A12103) (Section 1.2.2.2.4), a single 300 mg SC dose of inclisiran sodium was observed to increase C_{max} and AUC up to approximately two-fold in subjects with mild and moderate renal impairment, and increased C_{max} up to four-fold and AUC up to three-fold in subjects with severe renal impairment compared to subjects with normal renal function. However, by 48 hours plasma levels of inclisiran were below the level of quantification in all groups.

Despite the differences observed in pharmacokinetic (PK) parameters over the first 48 hours following injection of inclisiran, there were generally no relevant differences between the groups with respect to PCSK9 reduction and LDL-C reduction. In addition, there was no difference in the overall safety profile between subjects with normal renal function and those with mild, moderate, or severe renal impairment.

This finding is consistent with that observed in the previous Phase I (ALN-PCSSC-001, CKJX839A12101) study (Section 1.2.2.2.1) where doses above 300 mg led to a dose related increase in PK parameters. A single 500 mg dose increased AUC 2-3 fold and C_{max} 4-5 fold compared to a single 300 mg dose, which is similar to the increase observed in subjects with severe renal impairment compared to those with normal renal function in this study. In both the Phase I (ALN-PCSSC-001, CKJX839A12101) and Phase II (ORION-1, CKJX839A12201) studies single doses above 300 mg did not lead to greater reductions in PCSK9 or LDL-C levels over time or differences in the safety profile.

These data support the administration of inclisiran to subjects with mild, moderate, or severe renal impairment in future and ongoing clinical studies with inclisiran.

1.2.2.2 Clinical

Results are presented from 4 clinical trials:

1.2.2.2.1 Study ALN-PCSSC-001 (CKJX839A12101)

ALN-PCSSC-001 (CKJX839A12101, completed) was a Phase I study in which single (25 mg, 100 mg, 300 mg, 500 mg and 800 mg) and multiple (125 mg once weekly (four doses),

250 mg every 2 weeks (two doses), 300 mg every 4 weeks (two doses) and 500 mg every four weeks (two doses) doses of inclisiran sodium were evaluated. Subjects in this study were followed until their LDL-C levels returned to ≥80% of the baseline value or until 180 days after the last dose was given, whichever occurred first. At cumulative doses of 100 mg or greater, the majority of subjects reached 180 days of follow-up after the last dose, confirming the extended duration of action of inclisiran. No further follow-up occurred beyond this time point in this Phase I study. All adverse events (AEs) were mild or moderate (Grade 1 or 2) in severity with no differences relative to placebo other than skin reactions which were infrequent, mild and reversible following inclisiran.

The Phase I study demonstrated that the 300 mg dose of inclisiran sodium administered as a single or multiple dose is the lowest dose to achieve near-maximal reductions in PCSK9 and LDL-C levels. Two 300 mg doses of inclisiran sodium given 30 days apart achieved an additional 10% LDL-C reduction compared to a single 300 mg dose. PK parameters of inclisiran demonstrated a short plasma half-life (t1/2 = ~6 hours) and did not correlate with the observed pharmacodynamic (PD) effects of inclisiran.

1.2.2.2.2 Study ORION-1 (MDCO-PCS-15-01, CKJX839A12201)

ORION-1 (MDCO-PCS-15-01, CKJX839A12201; completed) was a Phase II placebo controlled, dose-finding trial performed in 501 subjects with atherosclerotic cardiovascular disease which showed dose-dependent PD effects of inclisiran. The 300 mg dose provided near maximal PCSK9 and LDL-C reductions. The 500 mg dose did not provide a meaningful further increase in PD effect.

The loading dose regimen of 300 mg given on Day 1 and on Day 90 led to reduced mean PCSK9 and LDL-C levels by 69% and 53%, respectively, at Day 180. This regimen also produced a time-adjusted average LDL-C reduction of 51% for the 6-month period following the second (Day 90) loading dose. Return of LDL-C from nadir levels was observed at a linear rate of 2 to 3% per month. At Day 270 (6 months after the second 300 mg dose), LDL-C reduction was similar to that observed on Day 90. There were no clinically significant safety observations other than mild-moderate, short-lived skin reactions at injection site in approximately 5% of subjects. Local injection site reactions were not dose-related.

1.2.2.2.3 Study ORION-2 (MDCO-PCS-16-02, CKJX839A12202)

ORION-2 (MDCO-PCS-16-02, CKJX839A12202; completed) was a Phase II, open label, single arm, multicenter pilot study in subjects with homozygous familial hypercholesterolemia. Four subjects were randomized and received open-label inclisiran sodium 300 mg SC on Day 1. The subsequent dosing interval was determined by PCSK9 level at Day 60 or 90 or rate of change of PCSK9 between Days 60 and 90. Three subjects received a second injection because mean serum PCSK9 levels were not suppressed by >70% at Day 60 or 90, as compared to baseline.

Inclisiran treatment resulted in robust and durable reductions in PCSK9 levels in all four subjects treated at a dose of 300 mg SC. Three of the four subjects also had significantly reduced levels of LDL-C. One subject had a significant reduction in PCSK9 but not a concomitant reduction in LDL-C. The mean percentage LDL-C reduction from baseline was 12.3% and 21.0% at Day 90 and Day 180, respectively. The maximum reductions in LDL-C were at Day 120 for two subjects and at Day 150 for a third subject. Therefore, the second dose achieved a greater reduction in LDL-C than after the first dose.

The mean percentage PCSK9 reduction from baseline was 59.0% and 62.9% at Day 90 and Day 180, respectively. Decreases in other lipids, lipoproteins, and apolipoproteins were commensurate with the decreases in LDL-C.

No safety observations were noted and inclisiran was generally well tolerated. Three of the four subjects reported adverse events. There were no deaths and one SAE (unstable angina, which was not considered related to study drug). No subjects withdrew due to an adverse event and no adverse events at the injection site were reported.

A number of notable elevations chemistry parameters were observed. One subject with an elevated total bilirubin (>1x ULN) at screening experienced a single elevation of total bilirubin >2x ULN on Day 120. There were no ALT or AST elevations >3 x ULN or CK elevations >5x ULN. None of the subjects developed anti-drug antibodies.

The results from this pilot study support the 300mg dose and dose regimen for the ongoing Phase III ORION-5 study in HoFH.

1.2.2.2.4 Study ORION-7 (MDCO-PCS-16-03, CKJX839A12103)

ORION-7 (MDCO-PCS-16-03, CKJX839A12103; completed) was a Phase I, single-dose, open-label trial to evaluate the safety, PK, and PD of a single dose of inclisiran sodium 300 mg SC injection. Subjects were classified into one of four renal function groups (normal, mild, moderate, and severe), as defined by creatinine clearance (CrCl) which was calculated using the Cockcroft and Gault estimation from a spot serum creatinine level (Table 1-1).

Table 1-1 Renal Function Categories by Estimated CrCl Ranges

Group	Description	Estimated CrCl (mL/min)
1	Normal renal function	≥ 90
2	Mild renal impairment	60 to 89
3	Moderate renal impairment	30 to 59
4	Severe renal impairment	15 to 29

CrCl=creatinine clearance

The subjects in the normal renal function group (Group 1) were dosed following completion of dosing of the subjects in the three renal impairment groups. These subjects were matched for age (+/- 10 years), body weight (+/- 20%), and proportional race and

gender in order to ensure that the normal renal function group was comparable to the renal impairment groups for average demographics.

Thirty-one subjects were randomized into the study, eight subjects in each of the normal renal function and the mild and moderate renal impairment groups and seven in the severe renal impairment group. All subjects completed the study (EOS visit, Day 60), and additional follow-up visit (Day 120 or Day 180).

At Day 60, PCSK9 levels were reduced by 68.1%, 74.2%, 79.7%, and 67.9% in the normal, mild, moderate, and severe renal impairment groups respectively. There were no observed differences in PCSK9 reduction in subjects with normal renal function compared with those with mild, moderate, or severe renal impairment. At Day 60, LDL-C was reduced by 57.6%, 35.1%, 53.1%, and 49.2%, in the normal renal function group and the mild, moderate, and severe renal impairment groups respectively. Mean LDL-C reduction was less in the mild renal impairment group compared to the other three groups. Overall, LDL-C reduction was generally similar between groups with no impact of renal function on LDL-C response.

A single injection of 300 mg inclisiran sodium was generally well tolerated in all study groups with no clinically significant safety findings. There was no difference in the overall safety profile between subjects with normal renal function and those with mild, moderate, or severe renal impairment.

1.3 Known and Potential Risks and Benefits

Subjects taking part in this clinical study will receive guideline recommended standard of care as background therapy (including maximally-tolerated statin therapy and/or other LDL-C lowering therapies) when administered inclisiran or placebo. Reduction of LDL-C has been associated with reduced CV risk both by epidemiology and in controlled clinical trials. Local reaction at injection site is the only event known to be attributed to inclisiran treatment. The safety profile of inclisiran observed to date is considered acceptable for this clinical trial.

An expanded risk-benefit summary is provided in the current version of the Investigator's Brochure (IB).

1.4 Study Rationale

1.4.1 Study Rationale

The overall safety data from inclisiran nonclinical studies and clinical data from the Phase I and Phase II study (ORION-1, CKJX839A12201), and the results from multiple PCSK9 antibody studies demonstrated that potent lowering of PCSK9 is well tolerated in human subjects and support the dose and dosing schedule proposed in this Phase III study.

In addition, a pilot study (ORION-2, CKJX83912202) in which a 300 mg dose of inclisiran sodium was administered to subjects with HoFH resulted in robust and prolonged reductions in PCSK9 and LDL-C levels in plasma.

This study is being conducted in subjects with a genetic or clinical diagnosis of HoFH; Orphan designation for this disease has been received from the US Food and Drug Administration (FDA).

1.4.2 Dose Rationale

Previous studies have shown that a 300 mg dose of inclisiran sodium is well tolerated and provides maximum efficacy (ie, doses higher than 300 mg did not provide additional efficacy in LDL-C lowering). In this study, the 300 mg dose of inclisiran sodium will be administered on Days 1, 90, 270 and 450 to subjects with HoFH. Modelling and simulation has demonstrated that this regimen will allow for the necessary robust and sustained reduction in PCSK9 (and LDL-C) and has the potential to tackle the lack of adherence generally seen in the chronic management of subjects with hypercholesterolemia. The 300 mg dose of inclisiran sodium will be used for the entire duration of this study for subjects receiving inclisiran.

In addition, a pilot study (ORION-2, CKJX839A12202) in which a 300 mg dose of inclisiran sodium was administered to subjects with HoFH resulted in robust and prolonged reductions in PCSK9 and LDL-C levels in plasma.

1.5 Study Population

This study will include male and female subjects ≥18 years of age with a genetic or clinical diagnosis of HoFH.

2 Study Objectives and Purpose

2.1 Primary Objective

The primary objective is to evaluate the effect of inclisiran treatment on:

- Low-density lipoprotein cholesterol (LDL-C) levels at Day 150

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect of inclisiran on:

- LDL-C levels over time
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels over time
- Other lipids, lipoproteins, and apolipoproteins
- Individual responsiveness of subjects to inclisiran including proportion of subjects achieving prespecified global lipid guidelines for their indication

- Proportion of subjects with at least 30% LDL-C reduction from Day 1 over time

And to assess the:

- Safety and tolerability profile of inclisiran

3 Study Design

3.1 Type/Design of Study

This study will be a Phase III two-part (double-blind placebo-controlled/open-label) multicenter study in subjects with HoFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the safety, tolerability, and efficacy of subcutaneous inclisiran injection(s). This study has two sequential parts:

- Part 1: 6-month double-blind period in which subjects will be randomized to receive either inclisiran or placebo
- Part 2: 18-month open-label follow-up period; placebo-treated subjects from Part 1 will be transitioned to inclisiran and all subjects will participate in an open-label follow-up period of inclisiran only

Informed consent will be obtained from subjects before the initiation of any study-specific procedures. Subjects who meet study inclusion/exclusion criteria will be instructed to continue to follow a National Cholesterol Education Program Adult Treatment Panel III (or comparable) diet and be required to maintain their current lipid lowering drug therapy for the duration of the study.

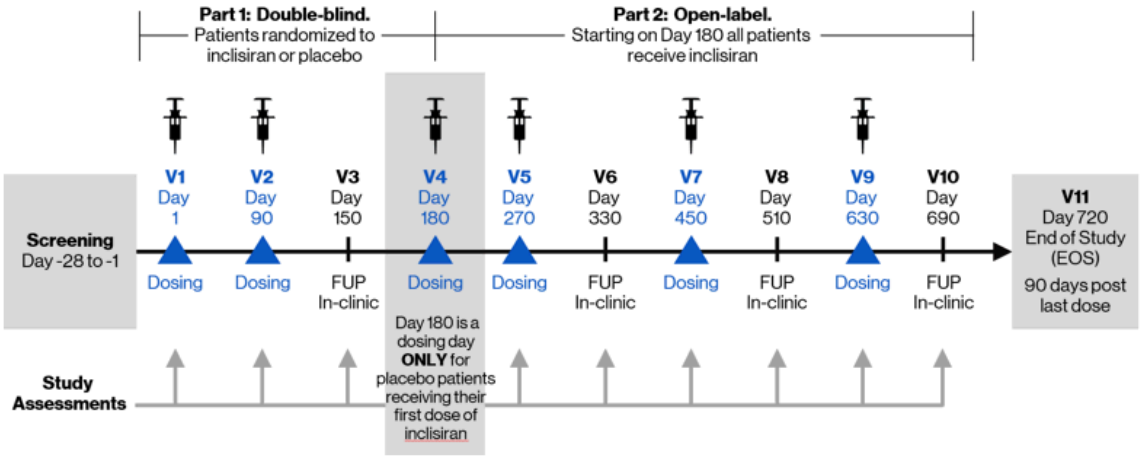
In this study, at least 45 subjects will be enrolled and randomized 2:1 to receive either inclisiran sodium 300 mg SC or placebo on Day 1. Inclisiran and placebo will both be administered by a health care provider. Subjects will be observed in the clinic for at least 30 minutes post injection before being discharged. A second dose of inclisiran or placebo will be given at Day 90.

After completion of Part 1, the inclisiran-treated subjects from Part 1 will receive a third dose of inclisiran administered on Day 270 and subsequent doses on Day 450 and Day 630. The placebo-treated subjects from Part 1 will be transitioned to inclisiran on Day 180, the start of the open-label, single arm follow-up period of inclisiran only (Part 2). Placebo-treated subjects will receive their first dose of inclisiran on Day 180 and then subsequently receive a dose of inclisiran on Day 270, Day 450, and Day 630.

Subjects on a documented regimen of LDL or plasma apheresis will be allowed to continue their same regimen during the study using approximately the same frequency/timing as done at baseline. When apheresis is performed on a study visit (Dosing or Non-Dosing), blood samples for measurement of LDL-C, other lipids and laboratory assessments must be collected before the apheresis. When apheresis is performed on a Dosing Visit, dosing must occur just after completion of the apheresis. The next scheduled apheresis must not occur within 72 hours of injection of inclisiran. The subsequent study visit must occur at least 2 weeks after an apheresis was performed to ensure LDL-C levels measured during a study visit are not confounded by the apheresis (see Figure 3-2 for details).

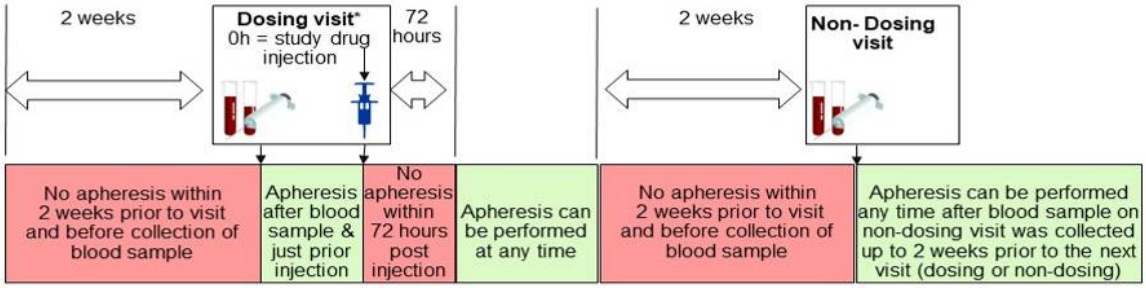
3.2 Schematic Diagram of Study Design

Figure 3-1 Schematic Diagram of Study Design



FUP=follow-up; V=visit

Figure 3-2 Timing of blood sample collection, apheresis and dosing



* **On Dosing visits**, blood sample collection, apheresis and dosing should be performed on the same day. Apheresis should only start after the blood sample was collected and should end just before study drug administration.

3.3 Primary Endpoints

The primary endpoint of this study is:

- Percent change in LDL-C from baseline to Day 150 (Part 1 of study)

3.4 Secondary Endpoints

The key secondary endpoints of this study are:

- Absolute change in LDL-C from baseline to Day 150
- Percentage change in Apo-B from baseline to Day 150.
- Percentage change in non-HDL-C from baseline to Day 150.
- Percentage change in total cholesterol from baseline to Day 150.
- Proportion of subjects in each group with ≥30% LDL-C reduction from baseline at Day 150.

The other secondary endpoints of this study are:

- Percentage change and absolute change in LDL-C from baseline to each assessment time up to Day 720 (ie, Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720)
- Percentage change and absolute change from baseline to Days 90, 150, 180, 330, 510, 690, and 720 in PCSK9
- Percentage change and absolute change from baseline to Days 150, 180, 330, 510, 690, and 720 in total cholesterol, Apo-B, and non-HDL-C for subjects receiving inclisiran
- Individual responsiveness of subjects defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 150, 180, 330, 510, 690, and 720 including proportion of subjects in each group who attain global lipid targets for their indication
- Proportion of subjects in each group with greater or equal to 30% LDL-C reduction from baseline at Days 150, 180, 330, 510, 690, and 720

- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 720
- Safety and tolerability profile of inclisiran as measured by AEs, SAEs, vital signs, clinical laboratory values, ECG measurements and formation and subsequent characterization of anti-drug antibodies (ADA)

3.6 Measures to Minimize/Avoid Bias

3.6.1 Blinded Study

Part 1 of this study will employ double-blind technique with a placebo control. Randomization via automated interactive response technology (IRT) will be used to assign subject to blinded investigational product kits. In addition, investigational product will be dispensed and administered in a blinded syringe. Blinding will minimize bias based on subject selection, baseline characteristics, clinical endpoint and AE reporting. Specifics on how the blind for the investigational product is maintained are provided in Section 5.5.

4 Subject Population

This will be a multicenter, international study in subjects with HoFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies.

4.1 Number of Subjects

At least 45 subjects will be randomized 2:1 to inclisiran or placebo.

4.2 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Males and females, ≥18 years of age with a diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents (see Appendix°A).
2. Stable on a low-fat diet
3. Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF) (see Appendix B)
4. Subjects not receiving statins must have documented evidence of intolerance to at least two different statins (see Appendix B)
5. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation
6. Fasting central laboratory LDL-C concentration ≥130 mg/dL (3.4 mmol/L)
7. Triglyceride concentration <400 mg/dL (4.5 mmol/L)
8. No current or planned renal dialysis or renal transplantation
9. Subjects on a documented regimen of LDL or plasma apheresis will be allowed to continue the apheresis during the study, if needed. The apheresis schedule should be maintained as deemed necessary and dosing should be scheduled to be done after apheresis. Administration of study drug should always occur at least 2 days following apheresis. Note: after implementation of protocol amendment 1, administration of study drug must occur right after apheresis on the same day of the study visit or at least 2 weeks following the last apheresis (see Figure 3-2).
10. Subjects must be willing and able to give written informed consent before initiation of any study-related procedures. The subject should be willing to comply with all required study procedures
11. Willing to follow all study procedures including adherence to dietary guidelines, study visits, fasting blood draws, and compliance with study treatment regimens

4.3 Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

1. Use of Mipomersen or Lomitapide therapy within 5 months of screening
2. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9
3. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%
4. Major adverse cardiovascular event within 3 months prior to randomization
5. Planned cardiac surgery or revascularization
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy
7. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >3x ULN, or total bilirubin >2x upper limit of normal (ULN) at screening confirmed by a repeat measurement at least 1 week apart
8. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than the duration of the trial
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or commencement of systemic therapy as treatment during the 3 years prior to randomization
10. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least one acceptable effective method of contraception (eg, oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device) for the entire duration of the study. Exemptions from this criterion:
    a. Women >2 years postmenopausal (defined as 1 year or longer since their last menstrual period) AND more than 55 years of age
    b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of enrolment
    c. Women who are surgically sterilized at least 3 months prior to enrolment
11. Known history of alcohol and/or drug abuse within 5 years
12. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    a. Subjects who are unable to communicate or to cooperate with the investigator.
    b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency)

c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study)
d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study
e. Persons directly involved in the conduct of the study

13. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate] judgment) if he/she participates in the clinical study
14. Any underlying known disease, or surgical, physical, or medical condition that, in the opinion of the Investigator (or delegate), might interfere with the interpretation of clinical study results
15. Treatment with other investigational medicinal products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer
16. Previous participation in the study
17. Hypersensitivity to any of the ingredients of inclisiran

Subjects excluded for any of the above reasons may not be re-screened for participation at any time even if the exclusion characteristic has changed.

4.4 Withdrawal Criteria

All subjects have the right to withdraw from the study at any point during treatment without prejudice. The investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completed the clinical study. If study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. The reasons a subject may discontinue their participation in the study could be from one of the following:

- AE
- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up
- Initiation of protocol-prohibited lipid-lowering therapy (eg, an approved PCSK9 inhibitor)

The applicable reason above will be recorded in the eCRF. All data collected up until the time of subject withdrawal is to be entered into the eCRF. All subjects discontinuing participation in this trial should be encouraged to complete the EOS visit except for those subjects who specifically withdrew consent.

Participating study sites will be trained on the importance of completing study follow-up procedures, and collecting the documentation required for missing data values. Any withdrawn subjects will not be replaced in this study.

4.4.1 Withdrawal from Study Medication

In the event a subject withdraws or is withdrawn from the study medication (eg, receives first injection and not second injection), the investigator will inform the Medical Monitor and the Sponsor immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator for protocol-specified safety follow up procedures.

4.5 Stopping Criteria

4.5.1 Individual Subject Dosing Stopping Criteria

During the study subjects will have clinic visits at regular intervals. Dosing with study medication (inclisiran and/or matching placebo) should be temporarily discontinued or stopped in subjects with:

1. Intolerable adverse events, or if the Investigator believes that continuing dosing will be detrimental to the subject's mental or physical health. This includes severe or serious reactions at the injection site and any anaphylactic type reactions.
2. Unexplained increases in transaminases (ALT or AST) or total bilirubin as follows:
   a. ALT or AST >8xULN
   b. ALT or AST >5xULN for more than 2 weeks
   c. ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5)
   d. ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The investigator should evaluate to see if other causes for the laboratory abnormalities are immediately apparent, such as obstructive gall bladder or bile duct disease, viral or alcoholic hepatitis, malignancy involving the liver, congestive hepatopathy, other hepatotoxins or heritable disorders.

3. Unexplained creatine kinase (CK) values >5 x ULN confirmed by repeat test when the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction.

In the case that study medication is permanently discontinued the subject will be asked to complete the remainder of the scheduled visits without receiving study medication (inclisiran or placebo).

All trial subjects should be followed until all abnormalities return to normal or to the baseline state.

5 Treatment of Subjects

5.1 Study Medications

5.1.1 Inclisiran (also referred to as KJX839)

Investigational product (inclisiran) information is described in Table 5-1.

Table 5-1 Investigational Product

Product Name:	Inclisiran for injection
Active ingredient	Inclisiran sodium
Dosage Form:	Solution for Injection
Unit Dose	Inclisiran sodium 300 mg/1.5 mL (equivalent to 284 mg inclisiran)
Route of Administration	SC use
Physical Description	Clear, colorless to pale yellow solution essentially free of particulates
Manufacturer	[redacted]

Investigational product preparation: The procedure for preparing investigational product is provided in the Pharmacy Manual.

Investigational product administration: Subjects will be administered a single SC injection of 300 mg Inclisiran for Injection at predefined time points as described in the Schedule of Assessments (Table 6-1). Investigational product injection will be administered by qualified clinical study site staff under the supervision of the investigator or designee. The site of injection is the abdomen, alternating sides for each injection. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

5.1.2 Placebo

For Part 1, placebo will be supplied by the Sponsor to clinical study site as sterile normal saline (0.9% sodium chloride in water for injection) for SC injection. The placebo will be blinded and look identical to the inclisiran investigational product. Placebo will be administered as a single SC injection in an amount matched to the doses within the active inclisiran arm (Table 5-1).

5.1.3 Packaging and Labeling

Investigational product (Inclisiran for Injection and matching placebo) will be provided by the sponsor in a blinded fashion. All inclisiran and placebo investigational product will look identical to each other. Medication labels will comply with regulatory requirements.

The storage conditions for each medication provided will be described on the medication label.

All inclisiran and placebo investigational product will have a yellow shroud to maintain the blind.

5.1.4 Storage

Investigational product will be stored at controlled room temperature (20°C to 25°C [68°F to 77°F], with allowable excursions between 15°C and 30°C [59°F to 86°F]) as specified in the Pharmacy Manual. Access should be strictly limited to the investigator, pharmacists, and their designees. No special procedures are required for the safe handling of Inclisiran for Injection.

5.1.5 Accountability

The investigator or designee must maintain an inventory record of investigational product (inclisiran/placebo) received and all administered to assure the regulatory authorities and the Sponsor that the new investigational product will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Investigational product accountability forms and/or specific instructions can be found in the Pharmacy Manual.

The investigational product supplied for use in this study is to be prescribed only by the Principal Investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

During the study, all used investigational product containers will be kept until the monitor has reviewed the accountability records.

All unused investigational product will be destroyed on site (or returned to the packaging and labeling facility for destruction) once the investigational product has been inventoried and the monitor has reviewed the accountability records. In the event that investigational product needs to be returned for any other reason, the site will receive a written request listing the investigational product lot number(s) to be returned and the reason for the return request.

5.1.6 Product Deficiencies (Complaints) Reporting

Sites are required to report any product deficiencies (complaints) observed to the Sponsor immediately but no later than 24 hours from the time of awareness.

Product Deficiencies reporting: deficiencies related to the identity, durability, reliability, quality, safety, effectiveness or performance of a product, after it is released for distribution (European Union [EU] DIR 2001/83/EC). (Derived from Ref United States [US] 21 CFR 211.198).

Product Technical Complaint: is defined as any verbal or written expression of dissatisfaction with a Novartis product after it is released for distribution, in its identity, quality, stability, durability, usability, reliability, safety, effectiveness or performance Examples include:

- An indication that there is an unexpected physical change in the drug product such as discoloration, change in shape of the drug product, presence of particulates or any other physical change that might indicate contamination, a manufacturing defect or any other event that might indicate a compromise in product quality.
- An indication that the content does not meet its labeled volume, count, etc.
- An indication that there is an unexpected physical change in any part of the container (this includes the vial/container, any part of the seal, the cap or the label).
- An indication that the product is mislabeled.
- An indication that there is an unexpected physical change of the product or container once the product is diluted or reconstituted (the container includes the unit dose, bag, intravenous line, syringe or any other item that is in contact with the product).
- An indication that the product is falsified, tampered with, or adulterated.

5.2 Concomitant Medications

5.2.1 Prohibited Concomitant Medications

Background lipid-lowering treatment should remain stable throughout the study duration. As a result, the following medications/treatments are not permitted to be added or changed during the study:

- Additional medications prescribed to lower LDL-C after study entry (eg, statins, ezetimibe, lomitapide, mipomersen, niacin, colesevelam, bile acid absorption inhibitors)
- Monoclonal antibodies directed towards PCSK9
- Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies.

5.2.2 Permitted Concomitant Medications

The following medications/treatments are permitted during the study:

- Hormone replacement therapy
- Lipid-lowering medications; subjects already on a stable (≥30 days before screening) lipid-lowering medications (such as statins and/or ezetimibe) should remain on the dose that they have received at time of study entry
- Prescription medications prescribed to treat preexisting medical conditions such as diabetes and hypertension

- Prescription or nonprescription medications, when necessary to treat an AE, and at the discretion of the investigator

5.3 Medical Management Guidelines

5.3.1 Adverse events

Adverse events or abnormal test findings must be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/Investigator and/or returns to baseline values.

5.3.2 Pregnancy

Pregnant women are excluded from the study. If a subject becomes pregnant during the course of the study, the investigational product administration must be discontinued and the pregnancy should be followed through to outcome. Follow-up evaluation of fetus and newborn should also be performed up to 12 months after birth. Reporting of pregnancy and any associated AEs are specified in Section 8.4.3.2.

5.4 Restrictions

Subjects will have to comply with the following restrictions during the study:

- Fasted for at least 8 hours for all visits for fasting lipids and glucose blood samples
- Blood donation will not be allowed at any time during the study
- Must refrain from unaccustomed strenuous physical exercise for 48 hours before the screening and any study visit until the follow-up has been completed

5.5 Blinding

5.5.1 Blinding of study medications

Part 1 of this study will be conducted under a double-blind placebo-control. Study medication will be blinded prior to distribution to the site. Each unit dose of investigational product will contain a yellow shroud to maintain the blind.

Randomization via an automated IRT will be used to assign subjects to blinded investigational product. The clinical study site pharmacist will maintain the double blind according to site-specific procedures and the Pharmacy Manual. It should be noted that inclisiran may be visually distinguishable from placebo; therefore, blinded syringes will be provided to all study sites and used to maintain the blind.

5.5.2 Method and Maintenance of Blinding

Investigational product will be blinded prior to distribution to sites. All unit doses of investigational product (inclisiran/placebo) will contain a yellow shroud to maintain the blind.

5.6 Unblinding

The unblinding of investigational product during the study can only be performed via the IRT. The Principal Investigators/designee will have authorization to unblind a subject via the IRT.

During Part 1 of the study, in the event of a suspected unexpected serious adverse reaction (SUSAR), The Medicines Company Global Pharmacovigilance (MDCO GPV) Department may be required to unblind a subject to meet reporting requirements per country specific regulations. In this case, a designated member will have authorization to unblind via the IRT.

5.6.1 In the Event of an Emergency: Unblinding a Code

In Part 1, unblinding by request of an Investigator should occur only in the event of an emergency or AE for which it is necessary to know the investigational product to determine an appropriate course of therapy for the subject. If the Investigator must identify the treatment assignment to an individual subject, an Investigator or qualified designee should request the medication information from the IRT. The documentation received from the IRT indicating the code break must be retained with the subject's source documents in a secure manner so as not to unblind the treatment assignment to other site or Sponsor personnel. The Investigator is also advised not to reveal the study treatment assignment to other site or Sponsor personnel.

6 Schedule and sequence of procedures

The Schedule of Assessments (Table 6-1) summarizes the study assessments by time point. This study consists of four periods: Screening, Randomization, Treatment, and End of Study.

- **Screening period (Days -28 to -1)**: occurs prior to randomization and consists of confirming eligibility and collecting baseline assessments.
- **Randomization (Day 1)**: occurs on the day of initial administration of investigational product (inclisiran or placebo).
- **Treatment period (Day 1 through Day 690)**: occurs from the start of investigational product administration through the final clinic visit.
  - Dosing: Day 1 (inclisiran or placebo), Day 90 (inclisiran or placebo), Day 180 (inclisiran for placebo subjects switching to inclisiran), Day 270 (inclisiran), Day 450 (inclisiran), and Day 630 (inclisiran; final dose)
  - Additional clinic visits: Day 150, Day 180 (non-dosing visit for subjects randomized to the inclisiran arm), Day 330, Day 510, and Day 690
- **End of study (EOS) visit:** Day 720 (90 days after final dose)

The expected duration of a subject's participation in this study is approximately 734 days which includes screening, investigational product administration, and the EOS period to Day 720.

6.1 Schedule of Assessments

The schedule of assessments is provided in (Table 6-1).

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or virtual contacts (e.g. teleconsult) can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. Given the long lasting efficacy and infrequent dosing regimen of inclisiran, it is possible to introduce a more variable dosing schedule of +/- 2 months during this pandemic, which still allows subjects to receive inclisiran. If the two-month window is utilized for the next dose, the subsequent dose may be administered up to a maximum of 8 months' time from the next dose (if the next dose is given early) or within a minimum of 4 months' time (if the next dose is given late).

If a dose is not given within this two-month window, then the subject should be considered to have had a missed dose and should return as per the schedule in the protocol for the subsequent dose.

Table 6-1 Schedule of Assessments

	Screening	Randomization and Treatment	Treatment									EOS[13]
Visit		**V1 (baseline)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 (90 days post last dose)**
Timelines	**Day -28 to -1**	**Day 1**	**Day 90**	**Day 150**	**Day 180**	**Day 270**	**Day 330**	**Day 450**	**Day 510**	**Day 630**	**Day 690**	**Day 720**
Visit windows (+/-weeks)		1	3	3	3*	3*	3*	3*	3*	3*	3*	3*
Informed Consent	X											
Medical history and prior meds	X											
Assessment of eligibility[1]	X	X										
β-HCG pregnancy test [2]	X	X	X	X	X	X	X	X		X	X	X
Study drug administration (inclisiran)		X	X			X		X		X		
Study drug administration (placebo; switch to inclisiran at Day 180)		X	X		X	X		X		X		
Physical examination [3]	X											X
Neurological examination[4]		X		X			X					X
Weight/Height/Waist circumference [5]	X			X	X		X					X
Vital signs[6]	X	X	X	X	X	X		X		X		X
12-lead ECG	X											X
Fasted lipid profile/biomarkers[7]	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Screening	Randomization and Treatment	Treatment									EOS[13]
		V1 (baseline)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (90 days post last dose)
Timelines	**Day -28 to -1**	**Day 1**	**Day 90**	**Day 150**	**Day 180**	**Day 270**	**Day 330**	**Day 450**	**Day 510**	**Day 630**	**Day 690**	**Day 720**
Full serum chemistry [8]		X										X
Limited serum chemistry[9]	X		X	X	X	X	X	X	X	X	X	
Hematology and coagulation[10]	X	X		X								X
Urinalysis (local) [11]	X	X										X
[redacted]												
ADA assessment		X	X	X			X					X
Previous/concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

β-HCG=beta-human chorionic gonadotrophic hormone; ADA=anti-drug antibodies; BP=blood pressure; CPK=creatine phosphokinase; CV=cardiovascular; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOS=end of study; HbA1C=glycated hemoglobin A1C; HDL-C=high density lipoprotein cholesterol; HR=heart rate; LDL-C=low density lipoprotein cholesterol; SC=subcutaneous; V=visit

*: The visit window is extended to +/- 2 months during the COVID-19 pandemic, to allow on-site visits (rather than remote visits) to occur as much as possible

1. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
2. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test).
3. Physical examination is the responsibility of the principal investigator or medically qualified designee.
4. Full neurological examination will be performed as described in Appendix°C.
5. Height will be measured at baseline only and used to calculate body mass index.

Visit	Screening	Randomization and Treatment	Treatment									EOS[13]
		V1 (baseline)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (90 days post last dose)
Timelines	**Day -28 to -1**	**Day 1**	**Day 90**	**Day 150**	**Day 180**	**Day 270**	**Day 330**	**Day 450**	**Day 510**	**Day 630**	**Day 690**	**Day 720**

6. On dosing days, vital signs will be measured prior to injection. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit
7. See Section 7.2 for details of specific tests to be analyzed
8. See Section 7.1.7.3 for details of specific tests to be analyzed
9. See Section 7.1.7.3 for details of specific tests to be analyzed
10. See Section 7.1.7.1 and Section 7.1.7.2 for details of specific tests to be analyzed
11. Performed locally using the central laboratory kit supplies

[redacted]

13. For subjects prematurely and permanently discontinued from study treatment, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

6.2 General Conduct of the Study

Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all subjects before the performance of any protocol-specific procedure.

Please see the Schedule of Assessments (Table 6-1) for a detailed schedule and Section 7 for details of all tests required in each panel.

6.3 Screening Period (Days -28 to -1)

All screening laboratory tests will be collected and shipped to the Central Laboratory, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using the testing materials provided by the Central Laboratory. The results of all screening laboratory tests should be reviewed prior to enrollment. If results do not confirm subject eligibility or suggest any contraindication to treatment with inclisiran, and/or other required ancillary medication(s), the subject must not be enrolled.

The following procedures will be performed within 28 days prior to randomization:

- Informed consent
- Assessment of inclusion and exclusion criteria
- Demographics and medical history including disease history (prior history related to the disease and prior use of disease related medication, e.g. monoclonal antibodies to PCSK9)
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only)
- Physical examination (including height, weight, and waist circumference)
- Vital signs (blood pressure and heart rate) (Section 7.1.3)
- 12-lead ECG
- Fasting lipid profile/biomarkers (Section 7.2)
- Central clinical laboratory (limited serum chemistry, hematology and coagulation) (Section 7.1.7)
- Urinalysis (performed locally, using central laboratory supplies)
- Previous and concomitant medications
- [redacted]

Central laboratory blood draws should be performed after all other screening tests have been confirmed. Results must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria (Section 4.2 and Section 4.3). Please refer to Section 7.1.7 and Section 7.2 for details of laboratory tests performed during the screening period.

6.4 Randomization (Day 1)

Randomization should only occur once subject eligibility is confirmed and will be conducted via an automated IRT to assign subjects to investigational product. All treatment groups will be studied concurrently. At least 45 subjects are planned to be randomized 2:1 (inclisiran: placebo) for inclusion in the study.

The following procedures will be performed prior to the injection:

- Assessment of inclusion and exclusion criteria
- Pregnancy test (performed locally, prior to any dosing, using central laboratory supplies) (women of childbearing potential only)
- Randomization
- Neurological examination (Appendix°C)
- Vital signs: blood pressure and heart rate (Section 7.1.3)
- Fasting lipid profile/biomarkers (Section 7.2)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 7.1.7)
- Urinalysis (performed locally, using central laboratory supplies)
- Assessment of ADA (Section 7.1.7.8)

The following procedures will be performed after the injection:

- Concomitant medications
- AE/SAE reporting

Investigational product (inclisiran or placebo) administration will occur at this visit for all subjects as per Section 5.1.1 and the Pharmacy Manual.

Subjects must be observed in the clinic for at least 30 minutes after injection.

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

If a local reaction around the injection site occurs that requires the subject to be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site may be obtained if deemed necessary. Photographs should be submitted to the study inbox.

Detailed instructions for investigational product administration are found in the Pharmacy Manual.

6.5 Primary Efficacy Visit (Day 150)

The following assessments will be completed during this visit:

- Pregnancy test (performed locally, prior to any dosing, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Weight and waist circumference
- Fasting lipid profile/biomarkers (Section 7.2)

- Assessment of ADA (Section 7.1.7.8)
- Vital signs: blood pressure and heart rate (Section 7.1.3)
- Central clinical laboratory (limited serum chemistry, hematology, and coagulation) (Section 7.1.7)
- Neurological examination (Appendix°C)
- Concomitant medications
- AE/SAE reporting

6.6 Additional Dosing Visits (Days 90, 180, 270, 450, and 630)

Subjects will return on Day 90 for a second investigational product injection. Subsequent inclisiran injections will be administered to all subjects on Day 270, Day 450 and Day 630. In addition, on Day 180 subjects originally randomized to the placebo group will be switched to inclisiran and receive their first dose of inclisiran on Day 180.

Note: For subjects randomized to the inclisiran arm, Day 180 will be a non-dosing visit but the same assessments as described below will be performed except for investigational product administration.

The following assessments will be completed during these visits prior to investigational product administration:

- Pregnancy test (performed locally, prior to any dosing, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Vital signs: blood pressure and heart rate (Section 7.1.3)
- Fasting lipid profile/biomarkers (Section 7.2)
- Assessment of ADA (Day 90 only) (Section 7.1.7.8)
- Central clinical laboratory (limited serum chemistry) (Section 7.1.7)
- Concomitant medication
- AE/SAE reporting

Administration of the investigational product is identical to Day 1 and is per Section 5.1.1 and the Pharmacy Manual.

Subjects must be observed in the clinic for at least 30 minutes after injection.

Should a subject develop signs or symptoms of anaphylaxis on days when investigational product is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logically possible).

6.7 Additional non dosing Clinic Visits (Days 330, 510 and 690)

Subjects will return to the clinic for dosing follow-up visits on Days 330, 510, and 690. Note: for subjects randomized to the inclisiran group the Non-dosing visit on Day 180 is described in Section 6.6. The following assessments will be completed during these visits:

6.7.1 Day 330

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Weight and waist circumference
- Fasting lipid profile/biomarkers (Section 7.2)
- Assessment of ADA (Section 7.1.7.8)
- Central clinical laboratory (limited serum chemistry) (Section 7.1.7)
- Neurological examination (Appendix°C)
- Concomitant medications
- AE/SAE reporting

6.7.2 Day 510

- Fasting lipid profile/biomarkers (Section 7.2)
- Central clinical laboratory (limited serum chemistry) (Section 7.1.7)
- Concomitant medications
- AE/SAE reporting

6.7.3 Day 690

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Fasting lipid profile/biomarkers (Section 7.2)
- Central clinical laboratory (limited serum chemistry) (Section 7.1.7)
- Concomitant medications
- AE/SAE reporting

6.8 End of Study (EOS) Visit (Day 720 - 90 days post last dose)

A subject's participation in the study is complete when the final visit, 90 days after the last dose of investigational product, has occurred. The following assessments will be completed during this visit:

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Physical examination (including weight and waist circumference)
- Neurological examination (Appendix°C)
- Vital signs: blood pressure and heart rate (Section 7.1.3)
- 12-lead ECG
- Fasting lipid profile/biomarkers (Section 7.2)
- Assessment of ADA (Section 7.1.7.8)
- Central clinical laboratory (full serum chemistry, hematology and coagulation) (Section 7.1.7)

- Urinalysis (performed locally, using central laboratory supplies)
- Concomitant medication
- AE/SAE reporting
  - All ongoing AEs or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolved, stabilized at a level acceptable to the Sponsor/Investigator and/or returned to baseline values (Section 8.4.1)

7 Protocol assessments

7.1 Assessment of Safety

7.1.1 Adverse Events

Subjects will be carefully monitored for adverse events by the investigator during the designated study period (see Section 8 for details).

7.1.2 Demographics and Medical History

Baseline demographic information will be collected during screening, and will include age, sex, and race/ethnicity.

Relevant medical history includes all ongoing medical or surgical issues and any statin intolerance documentation. Remote medical and surgical history >5 years from the time of screening should only be included if considered relevant to the study.

7.1.3 Vital Signs

Vital signs include heart rate and blood pressure. When available, an automated blood pressure device is recommended for collection of blood pressure and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (heart rate, blood pressure) is required per applicable visit.

7.1.4 Electrocardiograms

Twelve lead ECGs will be collected at the time points in the Schedule of Assessments (Table 6-1) only, unless clinically indicated.

7.1.5 Physical Examination

The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, abdominal, and extremities evaluations, and recording of weight, waist circumference, and height (baseline only).

7.1.6 Neurological Evaluation

A full neurological examination (Appendix°C) will be performed as per the Schedule of Assessment (Table 6-1).

7.1.7 Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1). If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and prior to the administration of study drug (on dosing visits).

Subjects will be in a fasted state for all clinical laboratory assessments. Screening laboratory tests will be performed by the Central Laboratory, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using testing materials supplied by the Central Laboratory. Results from these screening tests related to eligibility must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual. Note: Efficacy laboratory assessments (eg, LDL-C and PCSK9) are described in Section 7.2.

7.1.7.1 Hematology

Blood draws for hematology will include:

- Hemoglobin, hematocrit, erythrocytes, reticulocytes, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count with differential.

7.1.7.2 Coagulation

Blood draws for coagulation will include:

- Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT).

7.1.7.3 Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments (Table 6-1). Analysis will vary based on visit day as follows:

- **Full serum chemistry - Baseline (Day 1) and EOS (Day 720)**
  AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, urea (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), glycated hemoglobin A1C (HbA1C), and tryptase (as required).
- **Limited serum chemistry - Screening, Days 90, 150, 180, 270, 330, 450, 510, 630, and 690**
  ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, fasting glucose, HbA1C (not at Day 150, 330, or 510), and tryptase (as required).

7.1.7.4 Inflammatory markers (IL6, IFN-γ, and TNF-α, hsCRP)

High sensitivity C-reactive protein (hsCRP) testing is performed routinely for safety throughout the study and is part of the central laboratory draws.

Tryptase and other inflammatory markers such as interleukin 6 (IL6), interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) may be performed from centrally stored sample aliquots at a later date, as required. Should a subject develop anaphylaxis on days when inclisiran is injected, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logically possible).

7.1.7.5 Urinalysis

Urinalysis will be performed at the time points defined in the Schedule of Assessments (Table 6-1) and evaluated by dipstick analyses at the investigational site (a standardized dipstick test will be supplied by the Central Laboratory). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

The following parameters will be assessed:

- Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities).

7.1.7.6 Urine Pregnancy

Urine pregnancy testing will be performed locally at the visits specified in the Schedule of Assessments (Table 6-1), using the supplies provided by the Central Laboratory.

7.1.7.7 Lipids / Lipoproteins

Lipids and lipoproteins assessments are described in Section 7.2.

If an apheresis is performed on a visit day, blood samples must be collected prior to the apheresis, and, prior to the administration of the study drug (on dosing visits).

7.1.7.8 Anti-drug Antibodies

A serum sample for detection of formation of anti-drug antibodies will be collected at the time points in the Schedule of Assessments (Table 6-1). Collection will be prior to investigational product administration (injection) and then as per the Schedule of Assessments.

7.1.8 Stored samples

[redacted] Biological samples for biomarker research will be retained on behalf of the Sponsor for a maximum of 1 year following the last subject's last visit in the study. Details regarding the collection, processing, storage, and shipping will be in the Study Laboratory Manual.

7.2 Assessment of Efficacy

Subjects will be in a fasted state for all efficacy laboratory assessments of lipids/lipoproteins/biomarkers. Specimens will be obtained at the time points in the Schedule of Assessments (Table 6-1). Parameters to be assessed will include:

- Total cholesterol (TC), triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, lipoprotein (a) [Lp(a)], hsCRP, and PCSK9.

7.2.1 Change from Day 1 in LDL-C

The primary efficacy endpoint is the percent change in LDL-C from baseline to Day 150.

In addition, this study will assess:

- Absolute change in LDL-C (beta quantification [BQ]) from baseline to Day 150
- Percentage change and absolute change in LDL-C from baseline to each assessment time up to Day 720 (ie, Days 90, 150, 180, 270, 330, 450, 510, 630, 690, and 720)
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, 70 mg/dL, and <100 mg/dL at Days 150, 330, 510, 690, and 720
- Proportion of subjects in each group with greater or equal to 30% LDL-C reduction from baseline at Days 150, 180, 330, 510, 690, and 720

Blood samples for determination of LDL-C concentrations will be collected at the time points in the Schedule of Assessments (Table 6-1). For all study visits, LDL-C will be calculated (using the Friedewald method), in addition at baseline (Day 1), Day 150 and Day 720 LDL-C will be analyzed by BQ. Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

7.2.2 Change from Day 1 in Lipids/Lipoproteins

Secondary efficacy assessments will include the measure the effects of inclisiran on levels of lipids and lipoproteins including total cholesterol, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B, Lp(a), hsCRP, and PCSK9.

[redacted]

Plasma samples will be analyzed using a validated enzyme linked immunosorbent assay to determine PCSK9 protein concentration. Full details of the analytical methods used will be described in a separate bioanalytical report.

7.3 Assessment of Pharmacodynamics

Assessment of lipids/lipoproteins as discussed in Section 7.2 will cover pharmacodynamics.

[redacted]

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.1.2 Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a MI that may be considered minor could be an SAE if it prolonged hospitalization.

8.1.3 Special Situations

Information that is not necessarily considered an adverse event but which can possibly contribute to the overall knowledge concerning the safety of the investigational product.

Examples include, but are not limited to, reports of pregnancy/lactation exposures with or without any AEs related to the parent or child; medication errors - actual and potential; accidental exposure; suspected transmission via an investigational product of an infectious agent; drug interaction.

8.2 Collection and Assessment of Adverse Events

8.2.1 Pre-existing Conditions

Planned hospital admissions and/or surgical operations for an illness or disease that existed at baseline and did not aggravate during the study should not be reported as AEs.

8.2.2 Adverse Event Severity

The severity of AEs will be assessed by the Investigator using the 3-point scale below:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

8.2.3 Relationship to Investigational Product

The relationship between the AE and the investigational product will be assessed by using a binary assessment. The investigator should determine whether there is a ‘Reasonable possibility’ or ‘No reasonable possibility’ that the investigational product caused the event based on the definitions below.

Reasonable possibility - There is a reasonable possibility that the administration of the investigational product caused the AE. There is evidence to suggest a causal relationship between the investigational product and the AE.

No reasonable possibility - There is no reasonable possibility that the administration of the investigational product caused the AE. There is no temporal relationship between the investigational product and event onset, or an alternative etiology has been established.

8.3 Requirements For Additional Safety Data Collection

8.3.1 Special Situations

Special Situations designated for this study include:

- Medication errors that fall into the following categories
  - wrong investigational product
  - wrong dose (including overdose, underdose, change in dosing regimen, strength, form concentration, amount)
  - wrong route of administration
  - wrong subject (ie, not administered to the intended subject)
  - accidental exposure
- Pregnancy/lactation exposures with or without any AEs related to the parent or child
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions

8.3.2 Other safety related information

Injection-site reactions including individual signs or symptoms at the injection site following investigational product administration should be recorded on specifically designed eCRF pages. Photographs of injection-site reactions, if they were obtained during the study visits, should be forwarded to study inbox.

Other safety related information that should be reported as adverse events in accordance with the process described in Section 8.4 include:

- Abnormal neurological examination, eg, peripheral sensory and motor evaluation, an assessment of gait, pain, position, strength and reflexes (Appendix°C).
- Potential anaphylactic reactions assessed by Sampson criteria (Appendix°D). If Sampson criteria are positive, confirm by elevation of tryptase in blood plasma measured within 30 minutes of symptoms.
- Hyperglycemia-related AEs:
  - Report ‘New onset of diabetes’ in subjects with no medical history of diabetes when:
    - HbA1C becomes ≥6.5% and/or
    - Two consecutive values of fasting plasma glucose that are ≥126 mg/dL
    - If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected.
  - Report ‘Worsening of the glycemic control’ or ‘diabetic complications’ in subjects with a medical history of disease (HbA1C ≥6.5% at baseline) when:
    - HbA1C increases from baseline > 0.5% and/or
    - New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

8.4 Procedure for Adverse Event Reporting

8.4.1 Serious Adverse Events (SAEs)

All SAEs that occur during the designated study period from randomization through EOS must be reported using study specific SAE Report Form within 24 hours of awareness of the event. Each SAE must also be recorded on the source documents and on the appropriate page of the eCRF.

The Investigator should provide any follow-up information for the event to the Sponsor on an updated SAE Report Form as soon as it becomes available. The Sponsor will contact the Investigator, if necessary, to clarify any of the event information or request additional information.

If the Investigator is notified of a SAE that occurs post-study period, that he or she wishes to report to the Sponsor (eg, an event suspected to be causally related to investigational product), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the Investigator should report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority in addition to the Sponsor.

8.4.2 Nonserious AEs

All nonserious AEs that occur during the designated study period from randomization through EOS must be assessed and recorded on the source documents and eCRF, regardless of causal relationship to the investigational product.

8.4.3 Special situations

8.4.3.1 Medication Errors

Medication errors (e.g, wrong dose concentration, wrong treatment, wrong regimen, wrong injection site), with or without an associated AE, will be reported as a protocol deviation (Section 12.3). Medication errors and an associated SAE will be recorded in the eCRF and also reported to the Sponsor as described in Section 8.4.1. Medication errors and an associated non-serious AE will be recorded in the eCRF as described in Section 8.4.2.

8.4.3.2 Pregnancy

Occurrences of pregnancy/lactation exposure in a study subject from the time of Day 1 through EOS must be reported to the Sponsor within 24 hours using the Pregnancy Exposure Report Form.

In cases where a pregnancy/lactation exposure occurs with a SAE, the SAE Report Form should be used to report the SAE and the Pregnancy Exposure Report Form should be used to report the pregnancy/lactation exposure.

When a pregnancy occurs without any concurrent SAE, the Pregnancy Exposure Report Form must be submitted alone.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital

abnormalities, or maternal and/or newborn complications. Newborns should be followed for 12 months.

8.5 Expectedness

8.5.1 Expectedness Determination

Novartis Safety Department will be responsible for determining whether an AE is expected or unexpected for the purpose of SUSAR reporting. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information previously described for the investigational product in the current/approved version of the Inclisiran Investigator's Brochure.

8.6 Study Stopping Criteria

8.6.1 Independent Data Monitoring Committee (IDMC) Stopping Rules

The IDMC will use all available evidence and its collective judgment to make a recommendation to continue, stop, or amend the study at any of its reviews during the double blind and open label part of the study. Any statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise. Details will be provided in the IDMC charter.

8.6.2 Sponsor Discontinuation Stopping Criteria

The Sponsor will review data on an ongoing basis and may, on discussion with the IDMC terminate the study for any clinically significant drug related safety signal (eg. serious hypersensitivity reactions or drug induced liver injury, etc).

Premature termination of a study may also occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of inclisiran at any time.

If a study is prematurely terminated or discontinued, the Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days of the notification. Final study visits should occur within 30 days of subject contact. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

The Sponsor will inform the health authorities and the IRBs/EC that the study has been stopped and the reasons for doing so, within the locally applicable timelines.

9 Data Collection

An electronic data capture (EDC) system which is 21 CFR Part 11 compliant will be used for this study. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A UserID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site 3 days after each

visit. It is not expected that the eCRF will serve as source for any data collected in this study. If there is a reason for a site to do so, it must be approved by Sponsor and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the Investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic. After the end of the study, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification. For this study, the EOS will be defined as the last visit of the last subject.

10 Statistical Plan

This study will be a Phase III, two-part (double-blind placebo-controlled/open-label) multicenter study to evaluate safety, tolerability, and efficacy in subjects with HoFH. This study has two sequential parts:

- Part 1: 6-month double-blind period in which subjects will be randomized to receive either inclisiran or placebo
- Part 2: 18-month open-label follow-up period; placebo-treated subjects from Part 1 will be transitioned to inclisiran and all subjects will participate in an open-label follow-up period of inclisiran only

The study will be a multicenter, international study. A separate Statistical Analysis Plan (SAP) document will provide more detailed specifications in data analysis and presentation.

10.1 Sample Size

The sample size calculation was performed with the hypothesis that the difference of mean percent change from baseline to Day 150 between inclisiran and placebo will be >20% (20% standard deviation) in subjects with HoFH when treated with inclisiran. The sample size of at least 45 subjects (randomized 2:1 to inclisiran : placebo), with at least 30 subjects in the inclisiran arm, will provide >80% power to detect a 20% reduction of LDL-C levels from baseline in the inclisiran group compared to that in the placebo at one-sided significance level of 0.025 based on two-sample t-test.

10.2 Randomization

Randomization should only occur once subject eligibility is confirmed and will be conducted via an automated interactive response technology (IRT) to assign subjects to blinded investigational product at 2:1 ratio to inclisiran versus placebo. Each subject will receive SC injections of blinded inclisiran or placebo on Day 1 and Day 90. The inclisiran-treated subjects will receive a third dose of inclisiran administered on Day 270 and subsequent doses on Day 450 and Day 630. The placebo-treated subjects from Part 1 will transition to an open-label, single arm follow-up period of inclisiran only; placebo-treated subjects will receive their first dose of inclisiran on Day 180 and then subsequently receive a dose of inclisiran on Day 270, Day 450, and Day 630.

10.3 General Statistical Considerations and Definitions

10.3.1 General Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage.

10.3.2 Analysis Population

The following populations will be used for data analyses and/or presentation.

10.3.2.1 Intent-to-Treat (ITT) Population

All subjects randomized into the study will comprise the ITT population. Treatment classification will be based on the randomized treatment. The ITT population will be used as the primary population for efficacy.

10.3.2.2 Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least one dose of investigational product and have both the baseline and the 150 day follow-up LDL-C assessment will comprise the mITT population. Treatment classification will be based on the randomized treatment. This population will be used to confirm the efficacy.

10.3.2.3 Safety Population

All subjects who received at least one dose of investigational product. Treatment classification will be based on the actual treatment received. This will be primary population for the safety analyses.

10.3.3 Analysis Windows and Baseline

The observational period for the study includes the screening period (Day -28 to Day -1), the treatment period (Day 1 to Day 690), and the EOS visit (Day 720±3 weeks). Any event occurring beyond the defined observational period, even if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

Unless otherwise specified, for evaluations that are collected at multiple occasions prior to initiation of investigational product administration, the latest evaluation will be considered the "Baseline" evaluation for analysis.

10.3.4 Missing Data Handling

The sponsor will diligently follow up each subject from the beginning till end of study (Day 720±3 weeks), and make every effort to keep each subject visit within protocol specified window on all efficacy assessments of lipids/lipoproteins/biomarkers to keep missing data to the minimum

regardless of whether the subject is on study treatment, use ancillary therapies, experience an adverse event, or adhere to the protocol.

However, if a missing value indeed occurs for any efficacy parameter up to Day 180, it's going to be imputed using appropriate imputation method. The method of the imputation will be consistent with that in the other Phase III studies and the details will be in the SAP.

For all missing values after Day 180 on all efficacy parameters, for all other parameters other than efficacy, missing data will not be imputed and will be excluded from the associated analysis.

10.4 Statistical Analyses

10.4.1 Demographic and Background Characteristics

Subject demographics and baseline characteristics (including medical history) will be summarized by treatment group using the ITT or safety populations.

10.4.2 Investigational Product and Concomitant Medications

Summaries of investigational product and each prior (pre-baseline) medication and concomitant (baseline or later) medication will be provided by treatment. Separate summaries will be provided for prior medication use. Medications will be coded using the World Health Organization (WHO) drug dictionary. Subjects will be counted only once within each period by medication.

10.4.3 Efficacy Analysis

This study is sufficiently powered to show the effect in the primary and key secondary endpoints, all other secondary [redacted] endpoints are supportive hence statistical testing on all other secondary [redacted] endpoints will be performed only if the null hypothesis on primary and the key secondary endpoints are rejected. No adjustment for multiplicity is planned among the other secondary [redacted] endpoints.

The ITT population will be the primary population for the efficacy analysis. Efficacy analysis may also be performed for the mITT population as supportive analysis.

10.4.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is percent change from baseline to Day 150 in LDL-C.

The primary analysis will be conducted using ANCOVA model based on the multiply imputed datasets (100 total). The ANCOVA model will include the fixed effect of treatment group (Inclisiran or placebo) and baseline LDL-C as a covariate. Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's method. The difference between treatment groups in mean change from baseline to Day 150 in LDL-C and corresponding two-sided 95% confidence interval will be provided. The p-value for testing equal mean change from baseline to Day 150 in LDL-C will also be provided.

The missing data imputation for primary analysis will be the Washout-model-based approach. The washout model can be thought of as a modified control-based Pattern-Mixture Model (PMM) that

will be used to explore the possibility of data missing not at random (MNAR) for subjects who discontinued the study early.

Sensitivity analysis for the primary efficacy endpoint will use Wilcoxon rank-sum test, a nonparametric analysis method, as well as the two-sample t-test.

Also, we will perform sensitivity analyses to explore the dropout pattern and its possible impact on treatment comparisons in order to support the robustness of the conclusion drawn from the primary analysis using data up to Day 180. Pattern-Mixture Model (PMM) will be used to check the robustness when data missing not at random (MNAR) for subjects who discontinued study treatment. A control-based pattern-mixture model will be utilized. Multiple imputation will be used to account for uncertainty in the imputation process and results from a Mixed-effects Model for Repeated Measures (MMRM) on the imputed datasets will be combined using Rubin's method. Furthermore, a tipping point analysis will be performed to search for the tipping point that reverses the study conclusion. In addition, an analysis based on a Mixed-effects Model for Repeated Measures (MMRM) without multiple imputation will be performed.

The primary analysis and sensitivity analyses will be performed on both ITT and mITT populations.

Details of the sensitivity analysis specified above will be in the SAP.

10.4.3.2 Secondary Efficacy Endpoints

For the first four key secondary endpoints, the following efficacy analyses will be performed on the ITT and mITT populations:

- Similar to the primary analysis of the primary efficacy endpoint, the ANCOVA model will be used on the multiply imputed datasets (100 total) – Washout based approach. Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's method.
- MMRM model will be used on the multiply imputed datasets (100 total) – PPM based imputation. Treatment effects from these 100 ANCOVA analyses will then be combined using Rubin's method
- Analysis based on a Mixed-effects Model for Repeated Measures (MMRM) without multiple imputation will be performed.

For the key secondary endpoint of ≥ 30% LDL-C reduction from baseline to Day 150, a logistic regression model with treatment as the effect will be used, and the odds ratio and its 95% confidence interval will be provided. The multiply imputed datasets created from both the washout model and the control-based PMM will be utilized in this analysis.

For the other secondary endpoints specified in Section 3.4, generally descriptive and graphical summaries by treatment group will be presented for the ITT population. The two-sided 95% confidence interval may be provided for continuous variables based on the MMRM model. Odds ratio and 95% confidence interval may be provided for binary variables. Nominal p-values may be provided when applicable.Details of the analyses for the secondary endpoints are specified in the SAP.

[redacted]

[redacted]

10.4.4 Safety Analysis

The safety objectives of this study are to evaluate the safety and tolerability profile of inclisiran.

10.4.4.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified by preferred term) occurring during the investigational product treatment period will be counted as a treatment emergent AE (TEAE) either if it is not present at baseline or if it is present at baseline but increased in severity during the treatment period.

The number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to investigational product. If more than one event occurred with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to investigational product, respectively.

10.4.4.2 Laboratory Tests

Laboratory values will be summarized by treatment group, including changes and percent changes from baseline at each time point. Analyses will also be performed for each laboratory parameter by treatment group for incidence rates of potentially clinical significant (PCS) values for subjects without PCS value at baseline.

Numerical values of laboratory parameters from different local laboratories with different units and normal ranges will be converted to the conventional units and normalized to a standard set of reference/normal ranges. The normalization process will be performed and separated by each of the laboratory parameters. A shift analysis by normal range will be done which counts the number of patients with a low, normal or high value at baseline and a low, normal or high value post baseline.

10.4.4.3 Vital Signs

Change and percent change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group.

10.4.4.4 Neurological Examinations

The percentage of subjects with a treatment-emergent abnormal neurological examination and the specific abnormality reported will be summarized by treatment group.

10.4.4.5 Pharmacodynamic Parameters

Pharmacodynamic biomarker samples will be collected and stored for up to 1 year following the completion of the last subject for research purposes to identify and/or verify biomarkers that are predictive of response to inclisiran treatment (in terms of efficacy, safety and tolerability).

10.5 Interim Analysis

No formal interim analysis will be performed in this study.

10.5.1 Interim Safety Review

The Independent Data Monitoring Committee (IDMC) will review safety data 90 days after the first 20 subjects receive the first injection of inclisiran or placebo. Thereafter the IDMC will review safety data every 3 months until all patients have reached Day 180 unless requested otherwise by the IDMC. A recommendation will be made to continue, stop or amend the study at any of these reviews. Following Day 180 the unblinded data will be reviewed by the IDMC.

11 Records Retention

The US FDA regulations require all investigators participating in clinical study drug studies to maintain detailed clinical data for one of the following periods:

- At least two years following the date on which a New Drug Application is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA.

Similarly, current EU Directives / Regulations and International Conference on Harmonisation (ICH) guidelines collectively require that essential clinical study documents (including case report forms) other than patient's medical files must be retained for the following time period:

- for at least 15 years after completion or discontinuation of the study,
- or for at least two years after the granting of the last marketing authorization in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs received from the sponsor of the final data. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

12 Quality Control and Quality Assurance

12.1 Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this study. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

12.2 Auditing

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, investigational product supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must permit regulatory authority inspections.

12.3 Protocol Deviations

Deviations from the protocol identified during the conduct of the trial will be recorded in the eCRF. These include but are not limited to the following:

- Inclusion criteria violation
- Exclusion criteria violation
- Laboratory assessments not drawn at Day 1, Day 150, 510 or Day 720 (EOS) visits
- Mis-Dosing for any reason other than subject safety or withdrawal (defined as missing dose or a dose delayed by more than 30 days)*
- Subject taking any prohibited concomitant medication
- Change in baseline statin or other lipid-lowering therapy dose
- SAEs not reported to the Sponsor within 24 hours
- Informed Consent not signed prior to study entry

*If the mis-dosing was unintended, ie, a medication error, the error should be reported as per instructions in Section 8.4.3.1, Medication Errors.

Additional protocol deviations and associated actions depending on the nature and impact of the protocol deviation will be defined and periodically reviewed by standard automated and/or manual checks by the clinical team or monitors.

13 Ethics and Responsibility

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the US FDA regulations, the ICH GCP guidelines, the Declaration of Helsinki and other local regulations, as applicable.

13.1 Informed Consent

Written informed consent will be obtained from all subjects (or their guardian or legally authorized representative), and whenever possible, or as per IRB or EC guidelines before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the investigator (or designee) shall sign the IRB- or EC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2 Institutional Review Board/Ethics Committee

This protocol, the written informed consent form and any materials presented to subjects shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such nonparticipation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

14 Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

Sponsor commits to comply with all applicable data protection laws and regulations and take all appropriate measures to ensure that subjects' data is processed securely and appropriately. Sponsor adheres to the privacy principles of notice, choice, accountability for onward transfer, security, data integrity, purpose limitation, access, and enforcement regarding the collection, use, and retention of personal information from European Economic Area countries and Switzerland. In addition, Sponsor's Global Commercial General Liability with Umbrella Liability and Global Products / Clinical Trial Liability policy includes coverage for the processing of subjects' data.

15 Investigator Agreement (for Original Protocol)

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the new study drug inclisiran, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the IRB or EC responsible for such matters in the Clinical Study Facility where inclisiran will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB or EC approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for subjects screened or randomized in the study.

I agree to provide all subjects with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11 and applicable local regulations.

Principal Investigator (Signature)	Date
Principal Investigator (Printed Name)	Protocol Version
Institution Name	

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Available upon request.

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Appendix A: Simon Broome diagnostic criteria for Familial Hypercholesterolemia

Definite Familial Hypercholesterolemia:

Required laboratory = high cholesterol levels:

- Adult = Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
- Child less than 16 years of age = Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)

Plus at least one of the two:

1. Plus physical finding = tendon xanthomas, or tendon xanthomas in first or second degree relative

   OR

2. DNA-based evidence of an LDL-receptor mutation, familial defective Apo-B-100, or a PCSK9 mutation

Possible Familial Hypercholesterolemia:

Laboratory - high cholesterol levels:

- Adult = Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
- Child less than 16 years of age = Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)

Plus at least one of the two:

1. Family history of at least one of the following.
   a. Family history of myocardial infarction at:
      i. Age 60 years or younger in first-degree relative
      ii. Age 50 years or younger in second-degree relative

   OR

2. Family history of elevated total cholesterol
   a. Greater than 290 mg/dL (7.5 mmol/L) in adult first- or second-degree relative
   b. Greater than 260 mg/dL (6.7 mmol/L) in child, brother or sister aged younger than 16 years

Source: Austin, et al, 2004.

Appendix B: Requirements for background lipid lowering treatment

There should be no plans at the time of screening and randomization to modify the dose of statin or other lipid lowering medication such as ezetimibe for the duration of the trial. Unless the background lipid lowering treatment exceptions described below are met, subjects must have been treated with one of the following highly effective statins at the specified daily doses and at a stable dose, preferably for 6 weeks but for at least 30 days, prior to screening for the study:

1. atorvastatin, 40 or 80 milligrams (mg) once a day;
2. rosuvastatin, 20 or 40 mg, once a day;
3. simvastatin 40 mg, once a day or, if a subject has been on that dose for >1 year, 80 mg, once a day.

Combination medications that contain atorvastatin, rosuvastatin, or simvastatin components described at the aforementioned doses will be permitted.

Background lipid lowering treatment exceptions

The following background lipid lowering treatment exceptions are permitted:

1. Lower doses of statins due to partial statin intolerance:

Subjects may be on a lower dose of one of the highly effective statins described above if there is documented intolerance to any one of them (atorvastatin, rosuvastatin, or simvastatin) at the aforementioned doses. Intolerance to any dose of any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and eCRF.

2. Regulatory limitations:

Subjects may be on a lower dose of one of the highly effective statins described above if the highest locally approved dose for one of the stated statins is lower than those doses shown above (eg, in some countries, atorvastatin 20 mg, once a day, is the highest locally approved dose).

3. Alternative statins:

Subjects may be treated with other statins (pravastatin, fluvastatin, pitavastatin, or lovastatin), different from the highly effective statins listed above, if there is documented intolerance to any two different highly effective statins (atorvastatin, rosuvastatin, simvastatin) at the lowest available daily dose for at least one of those highly effective statins. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and eCRF.

4. No background statin therapy:

Subjects may be enrolled who are only on nonstatin lipid lowering therapy, if complete statin intolerance has been documented. Subjects with complete statin intolerance must be unable to tolerate at least two statins: one statin at the lowest available daily dose AND another statin at any dose. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and eCRF. The sole exception, for which a subject may participate in the study with documentation of intolerance to only one statin, is a documented history of rhabdomyolysis attributed to that statin.

Appendix C: Recommended Neurological Examination

Motor Function

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

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

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

Assessment of a Conscious Patient

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

Grade Strength

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

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

Lower Extremities

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

Upper Extremities

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

Assessment of an Unconscious Patient

Upper Extremities

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

Lower Extremities

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

Sensory Function

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

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

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

Sensory Tests:

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

- **Stereognosis**: The ability to recognize an object by feel. Place a common object in the persons hand and ask them to identify the object.

- **Graphesthesis:** "Draw" a number in the palm of the person's hand and ask them to identify the number.
- **Two-Point Discrimination:** Simultaneously apply two pin pricks to the skin surface. Continually repeat the test while bringing the two pins closer together, until the individual can no longer identify two separate stimuli. The finger tips are the most sensitive location for recognizing two point differences while the upper arms, thighs and back are the least sensitive.
- **Extinction:** Touch the same spot on both sides of the body at the same time (eg, the left and right forearms. Ask the individual to describe how many spots are being touched. Normally, both sides are felt; with sensory lesions the individual will sense only one.
- **Point Locations:** Touch the surface of the skin and remove the stimulus quickly. Ask the individual to touch the spot where the sensation was felt. Sensory lesions can impair accurate identification, even if they retain their sensation of light touch.

Tone and Reflexes

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

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

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

Reflex responses:

0	No response
1+	Diminished, low normal
2+	Average, normal
3+	Brisker than normal
4+	Very brisk, hyperactive

Lower motor neuron disease is associated with 0 or 1+, upper motor neuron disease is associated with 3+ or 4+.

Biceps Reflex (C5 – C6):

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

Triceps Reflex (C7-C8):

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

Brachioradialis Reflex (C5-C6):

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

Quadriceps Reflex (Knee jerk) L2 - L4:

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

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

Achilles Reflex (ankle jerks) L5 - S2:

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

Heel Lift:

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

Babinski Response:

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

Cerebellar Function

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

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

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

Appendix D: Sampson Criteria for Diagnosing Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, painful abdominal cramps, vomiting)
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure*
   b. Adults: systolic blood pressure <90 millimeters of mercury (mmHg) or >30% decrease from that person's Day 1 reading

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

Source: Sampson et al, 2005; Sampson et al, 2006.