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Clinical Trial Protocol Title:

A 6 month randomized, double-blind, placebo-controlled study followed by a 6 month open- label extension to assess the efficacy and safety of inclisiran as monotherapy in Chinese adults with low or moderate ASCVD risk and elevated low-density lipoprotein cholesterol

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Brief Title: Efficacy and safety of inclisiran as monotherapy in Chinese adults with low or moderate ASCVD risk and elevated low-density lipoprotein cholesterol.

Study Phase: III

Sponsor Name: Novartis

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1 Protocol summary

1.1 Summary

Protocol Title:

A 6 month randomized, double-blind, placebo-controlled study followed by a 6 month open-label extension to assess the efficacy and safety of inclisiran as monotherapy in Chinese adults with low or moderate ASCVD risk and elevated low-density lipoprotein cholesterol

Brief Title:

Efficacy and safety of inclisiran as monotherapy in Chinese adults with low or moderate ASCVD risk and elevated low-density lipoprotein cholesterol.

Purpose

To evaluate the efficacy and safety of inclisiran as a monotherapy in Chinese adults with low or moderate atherosclerotic cardiovascular disease (ASCVD) risk and elevated low-density lipoprotein cholesterol (LDL-C) who are not on any lipid lowering therapy.

Study Indication /Medical Condition:

Primary hypercholesterolemia or mixed dyslipidemia

Treatment type

Drug

Study type

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of inclisiran as monotherapy, compared to placebo, on mean percentage change from baseline in LDL-C at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid lowering therapy.	Percentage change in LDL-C from baseline at Day 150
Secondary	
To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on absolute change from baseline in LDL-C at Day 150.	Absolute change in LDL-C from baseline at Day 150
To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on percentage and absolute change from baseline in Proprotein	● Percentage change from baseline at Day 150 in PCSK9

Objectives	Endpoints
Convertase Subtilisin/Kexin type 9 (PCSK9), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), apolipoprotein A-1 (ApoA-1), lipoprotein (a) (Lp(a)) and triglycerides (TG) at Day 150.	● Absolute change from baseline at Day 150 in PCSK9 ● Percentage change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG ● Absolute change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG
To evaluate the effect of inclisiran as monotherapy on percentage and absolute change in LDL-C from baseline at Day 330.	● Percentage change in LDL-C from baseline at Day 330 for inclisiran group ● Absolute change in LDL-C from baseline at Day 330 for inclisiran group
To evaluate the safety and tolerability of inclisiran as monotherapy compared to placebo during core part.	Adverse Events (AEs); vital signs and safety laboratory values
To evaluate the safety and tolerability of inclisiran as monotherapy during extension part.	Adverse Events (AEs), vital signs and safety laboratory values

Trial Design:

This study is designed as a randomized, double-blind, multi-center phase 3 trial, with a placebo-controlled treatment period and an open label treatment period, to evaluate the efficacy and safety of inclisiran sodium 300mg s.c. in participants aged 18~75 years with low or moderate ASCVD risk and fasting LDL-C value of ≥ 130 mg/dl but < 190 mg/dl who are not on any lipid lowering therapy.

The study consists of 3 parts:

- **Screening:** At screening, participants will sign the Informed Consent Form (ICF) and their eligibility will be assessed through the review of study inclusion/exclusion criteria. The screening period can be up to 14 days to allow adequate time for the eligibility evaluations.
- **Core Part:** a double-blind, placebo-controlled treatment period of 180 days in which eligible participants will be randomized 1:1 to receive either inclisiran sodium 300mg s.c. (Inclisiran Group) or matching placebo s.c. (Control Group) on Day 1 and Day 90. The end of core part (EOC) visit will be conducted on Day 180. The database lock for the core part is planned to occur after all randomized participants have completed the EOC visit (or have discontinued from the study before EOC). The primary analyses will be conducted after the database lock for the core part.
- **Extension Part:** an extended treatment period of an additional 180 days. After all "Core part" study assessments are completed on Day 180, the extension part starts. In the extension all patients randomized to inclisiran in the core part will continue on inclisiran while patients initially randomized to placebo will transit to inclisiran therapy. The extension part starts with a dose of study treatment on Day 180 (placebo in the inclisiran group and inclisiran for patients originally randomized to the control group). Thereafter, all participants will receive inclisiran sodium 300mg s.c. on Day 270. Treatment on Day 270 will be open-label. Participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (inclisiran vs placebo) throughout the study until final database lock. The EOS visit (Day 360) will be the last visit of the study.

At Day 1 (Baseline), all participants will be instructed to comply with lifestyle adjustment according to clinical guidelines, including but not limited to diet and regular exercise. These instructions will be reinforced at every visit throughout the study.

Participants who discontinue from study treatment should continue to attend the rest of the scheduled visits as indicated in Section 1.3.

Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit contains the same assessments of the EOS visit, and is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable. No data beyond Early Exit visit will be collected in the electronic Case Report Form (eCRF).

Investigators, site staff, participants, and the study team should be blinded to on-treatment lipid measurement results throughout the core part after randomization. Investigators, site staff and participants should continue to remain blinded to the **on-treatment** lipid measurement results **and original randomized treatment group assignment (inclisiran vs placebo)** throughout the study until final database lock..

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of inclisiran sodium 300mg s.c. , in reducing LDL-C in participants with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid lowering treatment

- The overall study duration is approximately 374 days but can vary depending on individual screening and the visit window.
- Participants will receive inclisiran/placebo subcutaneous injections on Day 1, Day 90, Day 180. And all participants will receive inclisiran treatment on Day 270.
- Visits will be on Day 1, Day 30, Day 90, Day 150 (primary endpoint), Day 180 (end of core part, EOC), Day 210, Day 270, Day 330 and Day 360 (EOS).

Treatment of interest

For primary estimand, the treatment of interest is inclisiran sodium 300 mg s.c. at Day 1 and Day 90 as monotherapy (no other lipid lowering therapy) comparing to matching placebo s.c. at Day 1 and Day 90 as monotherapy, regardless of study treatment discontinuation.

Number of Participants:

Approximately 200 participants will be randomized 1:1 to inclisiran and placebo .

Key Inclusion criteria

- Written informed consent must be obtained before any assessment is performed
- Adults ≥ 18 and ≤ 75 years of age
- Fasting LDL-C value of ≥ 130 mg/dL but <190mg/dL at screening
- Triglycerides ≤ 400 mg/dL at screening

- Categorized as low or moderate ASCVD risk by the 2016 Chinese guideline for the management of dyslipidemia in adults at screening
- No plan of introducing other lipid lowering therapy during the study participation

Key Exclusion criteria

- Use of any lipid-lowering therapy within 90 days prior to screening visit
- Previous exposure to inclisiran or any non-mAb PCSK9-targeted therapy, either as an investigational or marketed drug within 2 years prior to screening visit
- History of ASCVD
- Diabetes mellitus or fasting plasma glucose at screening ≥ 7.0 mmol/L or glycated hemoglobin (hemoglobin A1c) (HbA1c) ≥ 6.5%
- Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening

Treatment Groups:

At Day 1 (Baseline), all participants will be randomized 1:1 to one of the two treatment groups:

- **Inclisiran Group:** 100 participants. Treated with inclisiran sodium 300mg s.c. on Day 1, Day 90 and Day 270, and with matching placebo s.c. on Day 180.
- **Control Group:** 100 participants. Treated with matching placebo s.c. on Day 1 and Day 90, and with inclisiran sodium 300mg s.c. on Day 180 and Day 270.

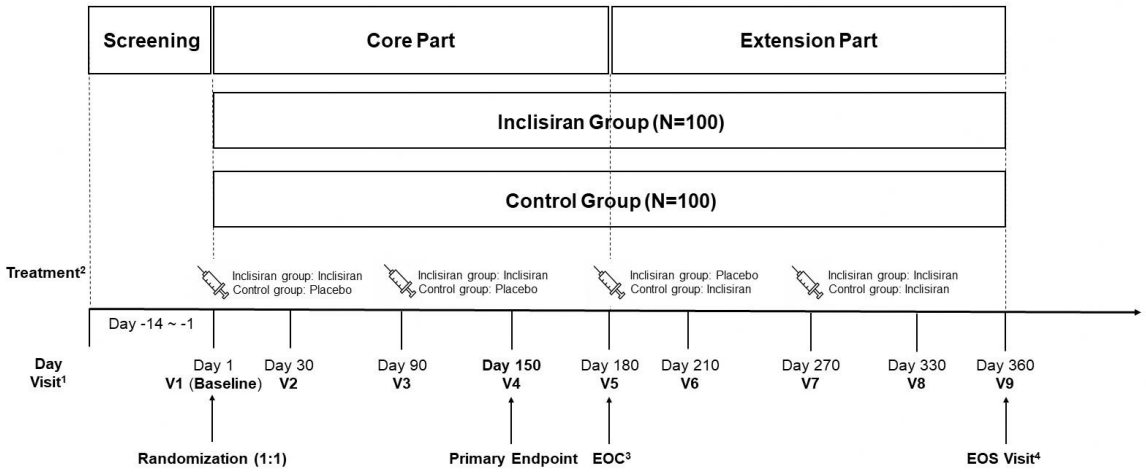
Steering Committee: *Yes (see Section 10.1.4 Committees Structure)*

Key words

Inclisiran, LDL-C, monotherapy

1.2 Schema

Figure 1-1 Study Design



1. Participants who discontinue from study treatment should continue to attend the rest of the scheduled visits.
2. Participants randomized to Inclisiran Group will be treated with inclisiran sodium 300mg s.c. on Day 1 and Day 90 and Day 270, and with matching placebo s.c. on Day 180. Participants randomized to Control Group will be treated with matching placebo s.c. on Day 1 and Day 90, and with inclisiran sodium 300mg on Day 180 and Day 270.
3. The end of core part visit. The database lock for the core part is planned to occur after all randomized participants have completed the EOC visit (or have discontinued from the study before EOC). The primary endpoint analysis will be conducted after the database lock for the core part.
4. Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable.

1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes when a study assessment is to be performed and results recorded in the clinical database or received electronically from a vendor. The "S" in the table also denotes when certain study assessment is to be performed. While in this case the result is only captured in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. A window of +/- 7 days from the scheduled day is acceptable for visits after Visit 1 (Day 1 or Baseline). Missed or rescheduled visits should not lead to automatic discontinuation.

If it is a visit with treatment (Day 1, Day 90, Day 180 and Day 270), all assessments should be performed before study treatment administration. Participants who discontinue from study treatment should continue to attend the following visits as indicated in the SoA. Every effort

should be made to encourage participants who discontinue from study treatment to remain in the study for follow up. Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit contains the same assessments of the EOS visit, and is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on the CRF.

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

- Fasted for at least 10 hours for all visits to obtain fasting lipids and/or glucose blood samples. If the participant is not fasting at the time of Informed Consent signature, he/she will have to return for a blood draw in a fasting state.
- Must refrain from unaccustomed strenuous physical activity for 48 hours prior to any study visit.

As per Section 4.5, during a public health emergency as declared by local authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls or virtual contacts (e.g. tele consultation) can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 1-2 Assessment Schedule

Period	**Screening**	**Core Part**[1]					**Extension Part**[1]			
Visit Name	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5/EOC**	**V6**	**V7**	**V8**	**V9/EOS**[2]
Days	**-14 to -1**	**1**	**30 ±7**	**90 ±7**	**150 ±7**	**180 ±7**	**210 ±7**	**270 ±7**	**330 ±7**	**360 ±7**
Informed consent	X									
Inclusion / Exclusion criteria	X	X[3]								
Demography	X									
Smoking and alcohol history	X									
Medical history/current medical conditions	X									
Prior or concomitant medication[4]	X	X	X	X	X	X	X	X	X	X
Surgical/medical procedures[4]	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S		S		S		S		S
Body Height/Weight	X									
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Lifestyle instructions		S	S	S	S	S	S	S	S	S
Pregnancy Test (serum)[6,7]	X									
Pregnancy Test (urine)[8]		S	S	S	S	S	S	S	S	S
Follicle stimulating hormone (FSH) [7,9]	X									
Fasting Lipid Profile[10]	X	X	X	X	X	X	X	X	X	X
Fasting Lp(a)[11]		X			X	X			X	X
PCSK9[11]		X	X	X	X	X	X	X	X	X
Clinical Chemistry[7]	X									
Limited Chemistry[7]		X	X	X	X	X	X	X	X	X

Period	**Screening**	**Core Part**[1]					**Extension Part**[1]			
Visit Name	**Screening**	**V1**	**V2**	**V3**	**V4**	**V5/EOC**	**V6**	**V7**	**V8**	**V9/EOS**[2]
Days	**-14 to -1**	**1**	**30 ±7**	**90 ±7**	**150 ±7**	**180 ±7**	**210 ±7**	**270 ±7**	**330 ±7**	**360 ±7**
Hematology[7]	X	X				X				X
Urinalysis[7]	X					X				X
Coagulation Panel[7]		X								
Enter participant visit in IRT	X	X		X		X		X		X
Randomization		X								
Study drug administration - s.c. inclisiran/placebo[12]		X		X		X		X		
Disposition	X					X				X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] The participant who discontinues the study treatment but continues to participate in the study should come to the regular visits per Assessment Schedule.
[2] Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable.
[3] Inclusion/exclusion criteria will only be assessed and captured once in Electronic Data Capture (EDC) system in screening period including any recheck between screening and randomization.
[4] All medications, procedures, and significant non-drug therapies used by/performed on the participant within 30 days prior to the screening visit and throughout the study must be documented in the appropriate page of the eCRF
[5] Blood pressure and pulse will be taken 3 times in sitting position.
[6] Only in women of childbearing potential.
[7] Performed by the central lab. See Table 8-1 in Section 8.4.
[8] Only in women of childbearing potential. Performed locally, urine or serum pregnancy test can be used based on local requirements.
[9] Required for any female participant who is considered as surgically sterile or post-menopausal in the absence of medical documentation confirming this reproductive/menopausal status at screening.
[10] Performed by the central lab. Fasting lipid profile includes LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, ApoA1 and Apo B. The fasting lipid profile results will not be reported to the site except the screening visit, and will be blinded for participants, investigators, site staff, persons performing the assessments, monitors and the Novartis Clinical Trial Team (CTT) until the core part database lock. After the core part database has been locked, fasting lipid profile results should remain blind to the participants, investigators and site staff throughout the study until final database lock.
[11] Performed by the central lab. The results will not be reported to the site and will be blinded for participants, investigators, site staff, persons performing the assessments, monitors and the Novartis Clinical Trial Team (CTT) until the core part database lock. After the core part database has been locked, Lp(a) and PCSK9 results should remain blind to the participants, investigators and site staff throughout the study until final database lock.
[12] Subcutaneous inclisiran/placebo will be administered by qualified personnel after all other study assessments have been completed for this visit

2 Introduction

2.1 Study rationale

Despite the availability of multiple options of lipid-lowering therapies (LLT), many Chinese low/moderate ASCVD risk patients on therapy do not reach LDL-C treatment goals. High statin non-adherence rate may be one of the most critical reasons for this high rate of substandard LDL-C reduction. Results of previous Phase 3 studies have demonstrated the ability of inclisiran to provide sufficient, sustainable LDL-C reduction with much lower treatment frequency (see below), which suggests that inclisiran monotherapy may be an alternative option for these patients. The purpose of this study is to evaluate the efficacy and safety of inclisiran sodium 300 mg s.c., administered as monotherapy to participants with low or moderate ASCVD risk and elevated LDL-C who are not on any LLT.

2.2 Background

ASCVD is the leading cause of death and disability worldwide and is expected to remain so beyond 2040 (Foreman et al 2018). A trend of increasing cardiovascular (CV) mortality has been observed in China mainland population, mainly attributed to heart attack and stroke, the two main pathologies associated with ASCVD (Zhou et al 2016).

Multiple factors contribute to the development of ASCVD, among which, elevated low density lipoprotein cholesterol (LDL-C) is one of the most well-recognized and modifiable ones (Yusuf et al 2004). Various studies have consistently shown that reductions in LDL-C levels could reduce the incidence of major adverse cardiovascular events (MACE) caused by ASCVD, regardless of baseline LDL-C or different LDL-C lowering agents (statin or non-statin) (Baigent et al 2010,Silverman et al 2016). Moreover, in a meta-analysis including 200 studies and 2 million participants with more than 20 million person-years of follow-up and over 150,000 CV events, a dose-dependent log-linear association is observed between the magnitude of exposure to LDL-C and the risk of ASCVD (Ference et al 2017). To conclude, it is well recognized, and also recommended by local and international guidelines that, the lower the LDL-C level attained – in addition to a reduction in lifetime exposure to LDL-C – the lower the CV risk (Zhao et al 2016). While in China, 26.3% of adults have elevated LDL-cholesterol level (≥ 130 mg/dL)(Zhang et al 2018).

In order to ensure that appropriate interventions are offered to individuals at risk of ASCVD, guidelines define risk classifications which are used to guide the intensity of intervention – ranging from lifestyle modification alone, to intervention with lipid lowering agents – and target LDL-C levels which the interventions aim to enable patients to achieve. For low and moderate ASCVD risk patients, the Chinese guideline suggests starting with lifestyle adjustment, and considering moderate intensity statin therapy if not meeting lipid target (LDL-C < 130mg/dL).(Zhao et al 2016)

Despite the availability of multiple options of lipid-lowering drugs, many low/moderate ASCVD risk patients on therapy do not reach LDL-C treatment goals. A nationally representative survey of 163,641 Chinese adults reported that 18.1% of low risk patients and 45.5% of moderate risk patients failed to reach lipid-lowering target(Zhang et al 2018).

High statin non-adherent rate may be one of the most critical reasons for the high rate of substandard LDL-C reduction. According to an observational study involving 109,306 Chinese patients under statin therapy, the mean (standard deviation) proportion of days covered (PDC) was only 0.19 (0.15) in primary prevention subgroup (patients without prior ASCVD), with only 5.4% patients having PDC ≥ 0.5. (Zhao et al 2020). In addtion, as reported in another study, the statin adherence levels tend to decline over time in primary prevention patients, and a transition to levels of adherence lower than a PDC of 0.8 is associated with increased risk of CV events (Slejko et al 2014). Clearly, there is an urgent need for a new effective lipid-lowering therapy that imposes less medication administration burden and improves compliance.

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of protein convertase subtilisin/kexin type 9 (PCSK9) messenger RNA (mRNA) leading to the reduction of PCSK9 protein. PCSK9 is predominantly expressed by the liver and is critical for the down regulation of hepatocyte low density lipoprotein receptor (LDLR) expression (Mousavi et al 2009). Inclisiran mediated reduction of PCSK9 protein results in higher levels of LDLR on hepatocytes and subsequent reduction of serum LDL-C. siRNA is covalently linked to a ligand comprising N-acetylgalactosamine(GalNAc) residues that enables preferential uptake by hepatocytes through binding to liver-expressed asialoglyco protein receptors (ASGPR). In hepatocytes, the antisense strand released from inclisiran is inserted in the Ribonucleic acid-Induced Silencing Complex (RISC), which directly cleaves the mature mRNA for PCSK9, thereby inhibiting the synthesis of the PCSK9 protein. Reduced intrahepatic PCSK9 increases LDL-R on the hepatocyte cell surface, thereby increases LDL-C uptake and lowers plasma LDL-C levels (Fitzgerald et al 2017).

The efficacy and safety of inclisiran has been shown in the phase 3 studies (ORION-9, -10, and -11). Treatment with inclisiran 300 mg administered by subcutaneous injection on Day 1, Day 90 and every 6 months thereafter resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 47.9% to 52.3%, with time-adjusted average reduction of 44.3% to 53.8% in participants with ASCVD, ASCVD risk equivalent, and/or heterozygous familial hypercholesterolemia (HeFH) (Raal et al 2020, Ray et al 2020). Longer-term treatment to >3 years in ORION-3, support and extend the observation. ORION-18 is another phase 3 study with a similar study design as ORION-9, -10 and -11 but conducted in an Asian population. The observed placebo-adjusted percentage change in LDL-C from baseline was -57.2% at Day 330. The totality of evidence collected from the ORION-18 study demonstrated that the substantial benefits of inclisiran in reducing LDL-C in Asian patients is consistent with that in the global population. (Investigator's Brochure)

There were no clinically relevant differences in the safety profile of inclisiran compared with placebo in the above trials, except for a higher incidence of treatment-emergent adverse events (TEAEs) at the injection site. AEs at the injection site were localized, mild and transient in nature. Inclisiran is not associated with an increased risk for hepatic or renal dysfunction, hypersensitivity, neurologic events and neurocognitive disorders, or ophthalmological events and there's no difference from placebo in new onset or worsening of diabetes. The potential for immunogenicity of inclisiran is low.

Additional details on the efficacy and safety of inclisiran are available in the Investigator's Brochure (IB).

2.3 Benefit/Risk assessment

In general, the risk of participation in this trial may be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring of safety parameters. The risk is further reduced by a minimal duration of placebo-controlled period (core part) of only approximately 6 months. In particular any concern about the theoretical risk to participants randomized to Control Group not being on any LLT during the core part of the study is mitigated by the following: 1) The study population is limited to patients with only low and moderate ASCVD risk, who had not been treated with prior LLT and for whom the investigator had not planned to start LLT in the next 6 months. 2) Lifestyle modification is the first line treatment recommended to these patients in the Chinese Lipid Guidelines, with consideration to add lipid lowering therapy (eg. moderate intensity statin) only if patients can not reach lipid targets with 3~6 months of lifestyle adjustment (Zhao et al 2016). While in this study, participants randomized to Control Group will only receive placebo treatment for 6 months. 3) Instruction on lifestyle modification is provided to all participants in the study according to clinical guidelines throughout the study participation. 4) Additionally, all participants will receive inclisiran treatment in the extension part. In addition to the potential reduction in LDL-C, the benefit a participant may have by participating in this study is the close monitoring of their condition, the opportunity to learn more about primary hypercholesterolemia and how to reduce future progression to clinical ASCVD and prevention of ASCVD events. In case of new onset of ASCVD events (eg. myocardial infarction, ischemic stroke), which is expected to be very rare in these low/moderate risk patients, investigators and treating physician are encouraged to take any action deemed necessary for the safety of the participants based on clinical standard of care.

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

In non-clinical toxicity studies, inclisiran was not carcinogenic or genotoxic. There was no effect on paternal performance, spermatogenesis, estrous cycle, and uterine or ovarian parameters. Inclisiran did not show evidence of embryo lethality, fetotoxicity, or teratogenicity. In addition, there were no effects of inclisiran on the development of the F1 generation, including survival, growth, physical and reflexological development, behavior and reproductive performance.

The overall clinical experience with inclisiran includes the following completed studies:

- Four completed Phase I studies: ALN-OCSSC-001 in participants with elevated LDL-C, ORION-6 in participants with mild to moderate hepatic impairment, ORION-7 in participants with renal impairment (mild, moderate, severe), and ORION-14 in Chinese patients with elevated LDL-C
- Two completed Phase II studies: ORION-1 in participants with ASCVD or ASCVD risk equivalent, and ORION-2 in participants with homozygous familial hypercholesterolemia

- Four completed Phase III studies: ORION-9, -10, and -11 in participants with HeFH, ASCVD or ASCVD risk equivalents, and ORION-18 in Asian participants with ASCVD or High ASCVD risk.

The safety profile of inclisiran in clinical studies is well characterized and based on data obtained from 3 large pivotal trials (ORION-9, -10,-11) that include 1,833 participants treated with inclisiran for up to 18 months and was generally comparable to placebo. The only inclisiran-related adverse drug reaction (ADR) identified in clinical studies was a higher incidence of TEAEs at the injection site, including injection site erythema, injection site hypersensitivity, injection site pruritus, injection site rash, and injection site reaction. All TEAEs at injection site were localized, mild or occasionally moderate, transient and resolved without sequelae. The impact of this side effect is further mitigated by the infrequent dosing regimen of inclisiran.

In Phase 3 studies (ORION-9, -10 and -11) in participants with HeFH, ASCVD or ASCVD risk equivalents, inclisiran administered on Day 1, Day 90 and every 6 months thereafter lowered LDL-C by approximately 50% or more versus placebo in participants on maximally tolerated statin therapy with or without other LLT.

Results of the Phase 3 study ORION-18 further demonstrated that the efficacy and safety of inclisiran in reducing LDL-C in Asian patients is consistent with that in global patients.

It is widely recognized that LDL-C plays a major role in the initiation and progression of ASCVD, and accumulated exposure of elevated LDL-C is causally related to the development of ASCVD. As the degree and duration of exposure to elevated LDL-C levels increases the atherosclerotic burden, early treatment of hypercholesterolemia in primary prevention is essential to the prevention of ASCVD events.

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate the superiority of inclisiran as monotherapy, compared to placebo, on mean percentage change from baseline in LDL-C at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid lowering therapy.	● Percentage change in LDL-C from baseline at Day 150
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on absolute change from baseline in LDL-C at Day 150.	● Absolute change in LDL-C from baseline at Day 150
● To demonstrate the efficacy of inclisiran as monotherapy, compared to placebo on percentage and absolute change from baseline in PCSK9, total cholesterol (TC), high-density lipoprotein (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), apolipoprotein A-1 (ApoA-1), lipoprotein (a) (Lp(a)) and triglycerides (TG) at Day 150.	● Percentage change from baseline at Day 150 in PCSK9 ● Absolute change from baseline at Day 150 in PCSK9 ● Percentage change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG ● Absolute change from baseline at Day 150 in TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG

Objective(s)	Endpoint(s)
● To evaluate the effect of inclisiran as monotherapy on percentage and absolute change in LDL-C from baseline at Day 330.	● Percentage change in LDL-C from baseline at Day 330 for inclisiran group ● Absolute change in LDL-C from baseline at Day 330 for inclisiran group
● To evaluate the safety and tolerability of inclisiran as monotherapy compared to placebo during core part.	● Adverse Events (AEs), vital signs and safety laboratory values
● To evaluate the safety and tolerability of inclisiran as monotherapy during extension part.	● Adverse Events (AEs), vital signs and safety laboratory values

[redacted]

3.1 Primary estimands

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

The clinical question of primary interest is: what is the reduction in LDL-C, quantified by difference of mean percentage change from baseline at Day 150, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy, who receive inclisiran as monotherapy, compared to placebo, regardless of discontinuation from study treatment, if other lipid-lowering therapy were not taken, and where death due to CV or non-CV causes is considered an unfavorable outcome.

The primary estimand is described by the following attributes:

Population: Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy.

Endpoint: Percentage change from baseline at Day 150 in LDL-C.

Treatments of interest: Inclisiran as monotherapy compared to the use of placebo, regardless of study treatment discontinuation.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be handled with a treatment policy strategy, keeping treatment labels as assigned at randomization.
- Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 150 visit assessment or other LLT taken within 30 days before Day 150 visit assessment) will be treated with a hypothetical strategy of what would happen had those LLT not been taken and those participants behaved like other participants in the same treatment group.
- Participants who died will be handled with a composite strategy, death is considered an unfavorable outcome.

Summary measure: the summary measure to be used is the difference of mean percentage changes.

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 9.3.

3.2 Secondary estimands

3.2.1 Secondary estimands for core part

The secondary estimands for core part address the same clinical question as the primary estimand, albeit for different endpoints. They share the same population, intercurrent events, summary measure, as well as the same treatments as the primary estimand. They differ by the definition of the endpoints, these being:

- Absolute change in LDL-C from baseline at Day 150
- Percentage and absolute change in PCSK9, TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG from baseline at Day 150

The statistical methods and inference approaches are described in Section 9.4.

3.2.2 Secondary estimands for extension part

The clinical question of interest in extension part is: what is the reduction in LDL-C, quantified by mean percentage or absolute change from baseline at Day 330, in Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy, who receive inclisiran as monotherapy, regardless of discontinuation from study treatment, if other lipid-lowering therapy were not taken, and where death due to CV or non-CV causes is considered an unfavorable outcome.

The secondary estimand for extension part is described by the following attributes:

Population: Chinese adults with low or moderate ASCVD risk and elevated LDL-C who are not on any lipid-lowering therapy.

Endpoint: Percentage or absolute change from baseline at Day 330 in LDL-C for inclisiran group.

Treatments of interest: Inclisiran as monotherapy, regardless of study treatment discontinuation.

Handling of intercurrent events:

- Permanent discontinuation of study treatment will be handled with a treatment policy strategy, keeping treatment labels as assigned at randomization.
- Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 330 visit assessment or other LLT taken within 30 days before Day 330 visit assessment) will be treated with a hypothetical strategy of what would happen had those LLT not been taken and those participants behaved like other participants in the same treatment group.
- Participants who died will be handled with a composite strategy, death is considered an unfavorable outcome.

Summary measure: the summary measure to be used is the mean percentage or absolute change.

Complete details on the statistical methods and inference, including missing data handling and sensitivity analyses are provided in Section 9.4.

4 Study design

4.1 Overall design

This study is designed as a randomized, double-blind, multi-center phase 3 trial, with a placebo-controlled period and an open label treatment period, to evaluate the efficacy and safety of inclisiran sodium 300mg s.c. in participants aged 18~75 years with low or moderate ASCVD risk and fasting LDL-C value of ≥ 130 mg/dL but < 190 mg/dL who are not on any lipid lowering therapy.

The study design is depicted in Figure 1-1. The study consists of 3 parts:

- **Screening**: a screening period of up to 14 days for all participants
- **Core Part:** a double-blind, placebo-controlled treatment period of 180 days in which eligible participants will be randomized 1:1 to receive either inclisiran sodium 300mg s.c. (Inclisiran Group) or matching placebo s.c. (Control Group) on Day 1 and Day 90. The end of core part (EOC) visit will be conducted on Day 180. The database lock for the core part is planned to occur after all randomized participants have completed the EOC visit (or have discontinued from the study before EOC). The primary endpoint analysis will be conducted after the database lock for the core part.
- **Extension Part:** an extended treatment period of 180 days. After all "Core part" study assessments are completed on Day 180, the extension part starts. In the extension, all patients randomized to inclisiran in the core part will continue on inclisiran while patients initially randomized to placebo will transit to inclisiran therapy. The extension part starts from a dose of study treatment on Day 180 (placebo in the inclisiran group and inclisiran for patients originally randomized to the control group) . Thereafter, all participants will

receive inclisiran sodium 300mg s.c. on Day 270. Treatment on Day 270 will be open-label. Participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (inclisiran vs placebo) until final database lock. The EOS visit (Day 360) will be the last visit of the study.

The overall study duration is approximately 374 days but can vary depending on individual screening and the visit window.

At screening, participants will sign the Informed Consent Form (ICF) and their eligibility will be assessed through the review of study inclusion/exclusion criteria. The ICF must be signed before initiation of any study-specific procedures and assessments. If at the time of ICF signature the participant is not fasting, he/she has to return for the blood test in a fasting state. During the screening visit, the participant's ASCVD risk will be assessed under guidance of 2016 China lipid guideline(Zhao et al 2016). The investigator must ensure each participant has not been treated with any lipid lowering therapy for at least 90 days prior to the screening visit, nor exposure to inclisiran or any other non-mAb PCKS9-targeted therapy 2 years prior to the screening visit. The screening period can be up to 14 days to allow adequate time for the eligibility evaluations. A participant who enters screening and is determined not eligible during the screening period or at the time of randomization will be considered a screen failure.

On Day 1 (Baseline), eligible participants who meet all inclusion and not meet any exclusion criteria will be randomized 1:1 to Inclisiran Group and Control Group. Study visits of core part will occur on Day 1 (baseline visit), Day 30, Day 90, Day 150 and Day 180. On Day 1 and Day 90 visits, inclisiran s.c. or placebo s.c. will be administered at the site by a healthcare professional. The primary endpoint will be assessed at Day 150. The EOC visit will be conducted on Day 180.

The extension part starts with a dose on Day 180 after all core part assessment are completed. In order to maintain the blind for the treatment group assignment, participants randomized to Control Group will receive inclisiran, while participants randomized to Inclisiran Group will receive placebo on Day 180. All participants will then receive inclisiran sodium 300 mg on Day 270, which will be the third dose of inclisiran for Inclisiran Group, and the second dose of inclisiran for Control Group. All injections will be administered at the site by a healthcare professional. The EOS visit (Day 360) will be the last visit of the study.

At Day 1 (Baseline), all participants will be instructed to comply with lifestyle adjustment according to clinical guidelines, including but not limited to diet and regular exercise. These instructions will be reinforced at every visit throughout the study.

Participants who discontinue from study treatment should continue to attend the rest of the scheduled visits as indicated in Section 1.3.

Participants who discontinue from study should be scheduled for an Early Exit visit if they agree. This Early Exit visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable. The Early Exit visit contains the same assessments of the EOS visit. No data beyond Early Exit visit will be collected in the electronic Case Report Form (eCRF).

Investigators, site staff, participants, and the study team should be blinded to on-treatment lipid measurement results throughout the core part after randomization. Investigators, site staff and

participants should continue to remain blinded to the on-treatment lipid measurement results and original randomized treatment group assignment (inclisiran vs placebo) throughout the study until final database lock.

4.2 Scientific rationale for study design

Though the efficacy and safety of inclisiran in reducing LDL-C has been demonstrated in multiple previous studies, most of them were conducted in high or very high ASCVD risk patients and on top of maximally tolerated statin treatment. It is well recognized that use of statin may up-regulate PCSK9 levels. Thus, therapies that target PCSK9 may perform differently as monotherapy than when added to statin treatment. This study is aimed to evaluate the efficacy and safety of inclisiran sodium 300mg, administrated as monotherapy to participants without background lipid lowering therapies.

As described in Section 2.2, the needs of LDL-C lowering for low or moderate ASCVD risk patients are far from being satisfied with many patients not reaching LDL-C targets. Considering the baseline LDL-C of low to moderate ASCVD risk patients is below 190 mg/dL, while the recommended LDL-C target is 130 mg/dL, an LDL-C reduction of 30~40% may fulfill most patients' needs. Therefore, inclisiran may have the ability to provide sufficient LDL-C reduction when used alone in these patients. To evaluate the efficacy and safety of inclisiran as monotherapy in this population, this study will include low or moderate risk patients with baseline LDL-C over recommended lipid target (130 mg/dL). Current Chinese guideline suggests these patients to start from lifestyle adjustment first, and consider lipid lowering therapy only if patients can not reach lipid targets with 3~6 months of lifestyle adjustment. In this study, all participants will be instructed to comply with lifestyle adjustment according to clinical guidelines throughout study participation. Participants randomized to Control Group will receive placebo treatment only during core part, which will be no longer than 6 months. In the extension part, all participants will be treated with inclisiran, which is proved to be effective and safe in lowering LDL-C in previous studies.

The extension part of this study is to provide additional efficacy and safety information of inclisiran monotherapy. The extended treatment period design for the study is appropriate to obtain additional long-term data, while allowing all patients to obtain the investigational, active drug at least at the second part of the study (i.e., 6 months after randomization).

4.2.1 Rationale for choice of background therapy

The participants must fulfill the requirement of not being on any lipid-lowering background therapy within 90 days prior to the screening, nor exposure to inclisiran or any other non-mAb PCKS9-targeted therapy 2 years prior to the screening visit. Furthermore, there must be no plan to start any other LLT in the foreseeable future (during the study period). The purpose is to remove any potential confounding effect caused by statin intolerance or concomitant LLT such as statins or ezetimibe in the monotherapy setting.

4.3 Justification for dose

The same dose regimen of the first two or three doses in previous Phase 3 studies (300 mg s.c. at Day1, Day 90 and Day 270 for Inclisiran Group, and at Day 180 and Day 270 for Control

Group) will be used in this study. This is also the approved dose by the United States Food and Drug Administration (FDA) and in the European Union (EU).

Based on the results from Phase I (ALN-PCSSC-001) and Phase II (ORION-1) clinical studies, at all doses tested, inclisiran inhibited PCSK9 synthesis and reduced LDL-C after single or multiple injections. The maximum reduction of PCSK9 and LDL-C was observed at a dose of 300 mg with no incremental reductions of clinical importance at higher doses tested. In ORION-1, a similar reduction was observed in LDL-C at Day 270 compared to Day 90 along with the time-adjusted mean LDL-C change of -50.5% over this time interval, further supporting the dose regimen of dosing every 6 months after a second loading dose at Day 90. In ORION-9, -10, and -11, the dose regimen used in the present study resulted in placebo-adjusted percentage reductions in LDL-C from baseline at Day 510 of 50% to 58%. In addition, in ORION-18, two initial injections (Day 1 and Day 90) following by a third injection at Day 270 also led to a similar percentage reduction in LDL-C at Day 330. Based on above and nonclinical data as well as pharmacodynamic (PD) modeling in adult participants, the proposed dose regimen is expected to provide robust, persistent, and durable reductions in PCSK9 and LDL-C. In those studies, this dose regimen also showed good tolerability of inclisiran, with a safety profile similar to placebo, except for a higher incidence of AEs at the injection site.

In three Phase I studies (ALN-PCSSC-001, ORION-6, ORION-7), inclisiran was administered to participants (healthy participants or participants with increased LDL-C level) with or without other lipid lowering therapy (e.g. statin). At Day 180 after 300 mg single dose administration, for those non-ASCVD participants who used inclisiran without other lipid lowering therapy, the percentage change of LDL-C level from baseline was generally similar to the ASCVD (or ASCVD-risk equivalents) patients in ORION-1 who used inclisiran on top of statin, and both of which had no significant safety issues. In addition, it has been demonstrated that concomitant use of statin has no clinically significant impact on the LDL-C lowering efficacy.

Therefore, under the proposed dose regimen, the efficacy of inclisiran in the population of the current study and without statin use is expected to be similar to that in previous phase III studies, and with no safety concerns.

4.3.1 Rationale for study duration

The study primary endpoint will be assessed at Day 150, after 2 injections of inclisiran/placebo on Day 1 and Day 90. It is supported with:

- ORION-1 demonstrated that 2 injections on Day 1 and on Day 90 produced a significant percentage LDL-C reduction of 52.6% at Day 180
- In ORION-9, -10 and -11, 2 initial injections (Day 1 and Day 90) led to a similar percentage reduction in LDL-C at Day 150. The magnitude of this reduction was then maintained with subsequent injections every 6 months
- No difference was observed in PK/PD between Chinese and non-Chinese population in ORION-14
- ORION-18 showed the consistency of efficacy with ORION-9, -10 and -11 in Chinese population with a significant percentage LDL-C reduction at Day 150. The magnitude of this reduction was also maintained in the following visit after the third injection at Day 330.

Based on the above data, a 180-day duration of the core part with 2 injections is deemed as sufficient for evaluating the effect of inclisiran as monotherapy, compared with placebo. The primary endpoint will be assessed on Day 150, which is expected to be the nadir of LDL-C lowering effect. In addition, this duration will leave placebo-treated participants with the shortest unprotected period of no LLT covered.

The duration with both core part and extension part is also suitable to assess the longer-term efficacy as well as safety and tolerability. The additional treatment administered in an extension part of the study is suitable to collect meaningful additional long-term data on inclisiran, which will be assessed as secondary [redacted].

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

A placebo-controlled arm will be used in the core part of the study. It is a standard design in drug development to assess efficacy and safety and ensures that differences in outcome will be a reliable and realistic measure of the treatment effect of inclisiran. The use of placebo as a comparator is justified in the trial population that consists of patients with low and moderate ASCVD risk who are not suggested to consider lipid lowering treatment（unless LDL-C targets are not met over a period of time despite lifestyle adjustment), according to current Chinese guideline. Moreover, the risk of having a placebo arm in a short duration (6 months) is generally acceptable in this population given their relatively low risk. And all participants will be treated with investigational medication in the extension part. Therefore, it is reasonable to use a placebo arm in the core part of this study.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.7 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure or follow-up shown in Section 1.3 Schedule of Activities for the last participant in the study.

Study completion is defined as when the last participant finishes his/her last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator (e.g. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available in the scope of the trial).

5 Study population

The study population consists of approximately 200 randomized Chinese adult participants (≥18 to ≤75 years of age) with low or moderate ASCVD risk and elevated LDL-C (fasting LDL-C ≥130mg/dL but ＜190 mg/dL) who are not on any lipid-lowering therapy.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Adults ≥ 18 to ≤ 75 years of age
3. Fasting LDL-C value of ≥ 130 mg/dL (equivalent to 3.4 mmol/L) but < 190 mg/dL (equivalent to 4.9 mmol/L) at screening
4. Triglycerides ≤ 400 mg/dL (equivalent to 4.5 mmol/L) at screening
5. Categorized as low or moderate ASCVD risk by the 2016 Chinese Guideline for the Management of Dyslipidemia in Adults at screening(See Section 10.7)
6. No plan of introducing any lipid lowering therapy other than study treatment during the study participation

5.2 Exclusion criteria

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

1. Use of any lipid-lowering therapy including statins (including Xuezhikang), ezetimibe, bempedoic acid, fibrates, bile-acid sequestrants, PCSK9 monoclonal antibodies, niacin and omega-3 fatty acids (Docosahexaenoic acid (DHA) and/or Eicosapentaenoic acid (EPA)) within 90 days prior to screening visit
2. Previous exposure to inclisiran or any non-mAb PCSK9-targeted therapy, either as an investigational or marketed drug within 2 years prior to screening visit
3. History of ASCVD (including acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, and peripheral artery disease including aortic aneurysm)
4. Diabetes mellitus or fasting plasma glucose at screening ≥ 7.0 mmol/L (equivalent to 126 mg/dL) or HbA1c ≥ 6.5% (equivalent to 7.8 mmol/L or 140 mg/dL)
5. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN), or total bilirubin (TBL) > 2 x ULN at screening
6. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening
7. Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome at screening.
8. Pregnant or nursing (lactating) women at screening
9. Women who are of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. The effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Barrier method of contraception: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps).
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

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

10. Severe concomitant disease that carries the risk of reducing life expectancy to less than 2 years
11. Participation in another investigational device or drug study currently, or within 5 half-lives (if drug) or 30 days whichever is longer, prior to screening
12. Any condition that according to the investigator could interfere with the conduct of the study at screening, such as but not limited to
    - Unlikely to understand or comply with the protocol requirements, instructions, and study-related restrictions
    - Have any medical or surgical condition, which in the opinion of the investigator would put the participant at increased risk from participating in the study
    - Persons directly involved in the conduct of the study

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen

failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants,who randomized in error, are randomized and fail to start treatment, will be considered an early terminator. The reason should be recorded on the appropriate Case Report Form.

Individuals who do not meet the criteria for participation in this study (screen failure) may be only rescreened once. Each case must be discussed and agreed with Novartis on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified range, the participant must be excluded from the study.

5.3.1 Replacement policy

Not Applicable.

5.3.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the Investigator chooses to rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

The sponsor will provide the following investigational and control drugs as single-use pre-filled syringes for s.c. injection.

All participants will be randomized 1:1 to inclisiran sodium 300mg s.c. or matching placebo s.c. without other lipid lowering therapies on Day 1. Inclisiran Group will receive inclisiran treatment on Day 1 and Day 90, and receive placebo treatment on Day 180. While Control Group will receive the placebo on Day 1 and Day 90 and inclisiran on Day 180. On Day 270, participants from both groups will be treated with inclisiran sodium 300mg s.c. without other lipid lowering therapies. Inclisiran and placebo will be administered via pre-filled syringe by qualified study site personnel.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*) in 1.5 mL	Solution for injection	Subcutaneous Use	Double Blind supply; prefilled syringe**	Sponsor (global)
Matching s.c. placebo in 1.5 mL	Solution for injection	Subcutaneous Use	Double Blind supply; prefilled syringe**	Sponsor (global)

* Inclisiran is also referred to as KJX839

** The prefilled syringe (PFS) is a device component of the combination product, and it is regulated as part of the combination product in the context of this clinical trial. The PFS is not investigational and no separate approval is required.

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Treatment arms/group

At baseline, all participants will be randomized 1:1 to one of the two treatment groups:

- **Inclisiran Group:** 100 participants. Treated with inclisiran sodium 300mg s.c. on Day 1, Day 90 and Day 270, and with matching placebo s.c. on Day 180.
- **Control Group:** 100 participants. Treated with matching placebo s.c. on Day 1 and Day 90, and with inclisiran sodium 300mg on Day 180 and Day 270.

Subcutaneous injections of the Inclisiran/placebo will not be dispensed to the participants but rather administered by qualified personnel at the study site on Day 1, Day 90, Day 180 and Day 270.

6.1.3 Treatment duration

The expected duration of the participant's involvement in the study will be approximately 374 days, which includes a screening period (14 days), a subsequent 180-day double-blind, placebo-controlled treatment period (core part), and a 180-day open label treatment period (extension part).

Participants may be discontinued from the study treatment earlier due to any reasons, at the discretion of the investigator or the participant. They will continue to be followed up in the study until EOS as per Assessment Schedule (Table 1-2).

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section. A unique medication number is printed on the study medication label.

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

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

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

6.2.2 Handling of other treatment

Not applicable

6.2.3 Instruction for prescribing and taking study treatment

Blinded s.c. injections of inclisiran/placebo, will not be dispensed to the participants, but will be administered by qualified personnel at the study site.

The preferred site of injection is the abdomen. Alternative injection sites include the upper arm or thigh. Injections should not be made into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos, or skin infections.

Participants will be administered an injection of blinded s.c. inclisiran/placebo on Day 1,Day 90, Day 180 and Day 270 as specified in the Assessment Schedule (Table 1-2) after all other study assessments have been completed for the visit.

Table 6-2 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran*)	300 mg	Day 1, Day 90, Day 180 and Day 270
matching s.c. placebo	0 mg	Day 1, Day 90 and Day 180

* also known as KJX839

All kits of study treatment assigned by the IRT will be recorded in the IRT system. All injections of inclisiran/placebo given to the participant as well as study drug interruptions/discontinuations (i.e., no injection at a designated dosing visit) during the study must be recorded on an appropriate eCRF and within IRT.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At baseline visit (Day 1) , all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

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

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

6.3.2 Treatment blinding

Participants, Investigator, site staff, persons performing the assessments, monitors and the Novartis CTT will remain blinded to the identity of the treatment throughout the core part after randomization. Participants, investigators and site staff should continue to remain blinded throughout the study until final database lock.

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

The following methods will be used to maintain the blind:

(1) Randomization data will be kept strictly confidential until the time of final database lock.

(2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

(3) data with unblinding potential, such as lipid results and PCSK9 results collected after the screening visit, will be kept blind until the time of final database lock.

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

After an emergency unblinding, study treatment should be permanently discontinued. The participant will continue to be followed up in the study unless informed consent is withdrawn (Section 7.3)or until participant have completed the EOS visit as per Assessment Schedule (Table 1-2)

6.4 Study treatment compliance

The treatment information must be captured in the source documents, the appropriate Case Report/Record Form (CRF) and in the Drug Accountability Log.

6.4.1 Recommended treatment of adverse events

AEs should be treated according to local practice and guidelines, and is at the discretion of the investigator and treating physician.

For participants with injection site reaction, antihistamines, local or systemic steroids can be used at the investigator's discretion depending on the severity of the reaction.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.5 Dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Follow-up for toxicities

All participants must be followed up for adverse events and serious adverse events for 30 days following the last dose of inclisiran/placebo.

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

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant’s baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT >300 U/L], whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Perform relevant examinations (Ultrasound or Magnetic resonance imaging (MRI), Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule-out an extrahepatic cause of cholestasis. Cholestasis (is defined as an Alkaline Phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-3provides guidance on specific clinical and diagnostic assessments which can be performed to rule-out possible alternative causes of observed Liver function test (LFT) abnormalities.

Table 6-3 Guidance on clinical and diagnostic assessments to rule out alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-Hepatitis A Virus (HAV); Hepatitis B virus surface antigen (HBsAg), IgM & IgG anti-HBc, Hepatitis B Virus (HBV) Deoxyribonucleic acid (DNA); anti-Hepatitis C Virus (HCV), HCV RNA, IgM & IgG anti-Hepatitis E Virus (HEV), HEV RNA
Cytomegalovirus (CMV), Herpes simplex virus (HSV), Epstein-Barr virus (EBV) infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, Mean Corpuscular Volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e. >50% likely), if it appears greater than all other possible causes

of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant" and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Continued access to study treatment after the end of the study

6.6.1 Post trial access

There is no plan for post trial access to study treatment after the end of the study.

6.7 Treatment of overdose

In the event of an overdose, the investigator/ site staff should:

- Contact the monitor immediately.
- Evaluate the participant to determine, in consultation with the monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

All other medications, procedures and significant non-drug therapies used by the participant within 30 days prior to the screening visit must be recorded on the appropriate eCRFs independent if these will be continued during the study or not. Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medication identified as "prohibited" as listed in Table 6-4. Specifically, participants should receive full supportive care and guidance on lifestyle management during the study. It is preferred to keep the dose of all concomitant therapy stable during study participation.

SARS-CoV-2 (also referred to as COVID-19) vaccines are permitted among participants in this trial. There is no evidence to suggest that participants receiving inclisiran are at increased risk for AEs following a COVID-19 vaccination. However, since both inclisiran/placebo and COVID-19 vaccines are administrated s.c., it is recommended that the COVID-19 vaccine is administered +/- 7 days from s.c. inclisiran/placebo administration. Further, it is recommended that a different anatomical location is used for COVID-19 vaccine and s.c. inclisiran/placebo to help differentiate potential local adverse reactions. COVID-19 vaccination administration that occur either within 30 days prior to the Screening Visit and during the course of this study should be documented on the appropriate eCRF.

Other vaccines are also permitted among participants in this trial. Similar to the recommendations on COVID-19 vaccines, a 7-day window between these vaccines and s.c. inclisiran/placebo administration and a different anatomical location are suggested.

6.8.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed. This table is not considered all-inclusive. If in doubt, the investigator should contact Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue his/her participation in the study.

Table 6-4 Prohibited medication

Medication	Prohibition period	Action taken
Any lipid-lowering therapy other than PCSK9 targeted therapies including statins (including Xuezhikang), ezetimibe, bempedoic acid, fibrates, bile-acid sequestrants, niacin and omega-3 fatty acids (DHA and/or EPA with a total dose $>$ 1000mg), or any drug with unknown ingredients taken for the purpose of lipid-lowering, including over-the-counter or herbal therapies.	At least 90 days prior to screening and throughout the study.	Investigators should request participants to stop taking these medications. If participants decide to continue taking them, or need to take them in the judgment of the investigators, it must be recorded in the source documentation and on an appropriated eCRF page.
PCSK9 monoclonal antibodies	At least 90 days prior to screening and throughout the study.	Discontinue study treatment
Any other non-mAb PCSK9-targeted therapy other than study drug (also including commercially available inclisiran).	At least 2 years prior to screening and throughout the study	Discontinue study treatment
Any RNAi-based therapeutics, including but not limited siRNA or Antisense Oligonucleotide (ASO) therapeutics.	At least 2 years prior to screening and throughout the study	Discontinue study treatment
Any other investigational treatment	At least 30 days or 5 half-lives, whichever is longer, prior to screening and throughout the study	Discontinue study treatment

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding

- Any laboratory abnormalities that in the judgement of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study.

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

Participants who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent **Where possible, they should continue attending site visits for the assessments** indicated in Section 1.3 Schedule of Activities.

If the Participant does not wish to attend any further visits, the participants would return to site for early exit visit.This visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an EOS visit as soon as possible is also acceptable.

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

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

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

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

7.2 Participant discontinuation from the study

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

If the participant agrees, he/ she should then return to the study site to complete Early Exit visit as detailed in Section 1.3 Schedule of Activities. This Early Exit visit is suggested to be scheduled at least 30 days after last injection. If not possible, to set an Early Exit visit as soon as possible is also acceptable.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

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

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to)

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come in

for a final visit(s) that the safety follow up period must be completed if applicable and which visits to be performed. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the early termination of the trial.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.

Except the screening visit, all lipid parameter measurements results and PCSK9 results that could unblind the study will not be reported to investigative sites or other blinded personnel until core part database lock. After core part database has been locked, all lipid parameter measurements results and PCSK9 results should still remain blind to the participants and investigators/site staff until final database lock.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

Screening activities must be initiated only after the ICF has been signed.

If a safety laboratory assessment during the screening period is outside of the range specified in the exclusion criteria, the assessment may be repeated one time prior to randomization. If the repeat value remains outside of the specified ranges, the participant will be considered as screen failure.

The investigator may consider re-screening the participant at a later time if he/she believes that the participant's condition has changed and they may potentially be eligible. A participant may be re-screened up to 1 time. A minimum of 4 weeks from the Screening visit must elapse before re-screening.

Re-screened participants must provide new written informed consent. A new participant number will be assigned to the re-screened participants and the site must record the re-screening information in the corresponding eCRF and in IRT. All screening procedures will need to be re-performed.

8.2 Participant demographics/other baseline characteristics

China specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies within 30 days prior to the screening visit must be documented. See the protocol Section 6.8.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever, in their judgement, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy assessments

Planned time points and requirements for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

All efficacy assessments [redacted] will be analyzed at a central lab. Participants must be in a fasted state for all of these laboratory assessments.

The results from all lipid parameter measurements and PCSK9 results will not be reported to the site except the screening visit and will be blinded to the participants, investigator, site staff, persons performing the assessment, monitors and the Novartis Clinical Trial Team (CTT) until the core part database lock. After core part database has been locked, all lipid parameter measurements results and PCSK9 results should still remain blind to the participants and investigators/site staff until after final database lock.

8.3.1 LDL-C

The primary efficacy assessment will be LDL-C, which will be collected at the frequency shown in Table 1-2.

LDL-C value assessed during Screening visit will be reported to the site for the eligibility decision. The following visits' results of the assessments after randomization must be blinded to participants, investigators, site staff, persons performing the assessment, monitors and the CTT until the core part database lock. After core part database lock, LDL-C value should remain blind to the participants and investigators/site staff until after final database lock.

Investigators and site staff involved in the conduct of this trial and all medical personnel involved in the participant's care and management should refrain from obtaining LDL-C value locally between the time from randomization to final database lock. If an LDL-C value is inadvertently obtained, all reasonable actions must be taken to ensure the study participant and/or study personnel are not informed of the results.

8.3.2 Additional efficacy assessments

Additional efficacy assessments will include Total cholesterol, triglycerides, HDL-C, non-HDL-C, ApoA-1, Apo B, Lp(a) and PCSK9, which will be collected at the time points in Table 1-2.

Similar to LDL-C values, the results of the total cholesterol, triglycerides, HDL-C, non-HDL-C, ApoA-1, Apo B, Lp(a) and PCSK9 will not be reported to the site except the screening visit, and will be blinded for the participants, investigator, site staff, persons performing the assessment, monitors and the CTT until the core part database lock. After core part database has been locked, all above lipid parameter measurements results and PCSK9 results should still remain blind to the participants and investigators/site staff until final database lock.

Investigators and site staff involved in the conduct of this trial and all medical personnel involved in the participant's care and management should refrain from obtaining lipid panels locally between the time from randomization to final database lock. If a lipid panel is inadvertently obtained, all reasonable actions must be taken to ensure the study participant and/or study personnel are not informed of the results.

8.3.3 Appropriateness of efficacy assessments

Inclisiran is a siRNA which acts to inhibit the synthesis of PCSK9 protein, which consequently reduces LDL-C in circulation. LDL-C is a well-defined and validated laboratory parameter and is routinely assessed in clinical trials. LDL-C reduction is an accepted surrogate for CV risk reduction, e.g., for statins and PCSK9- blocking monoclonal antibodies. While multiple factors contributing to the development of ASCVD have been described, strong and consistent evidence from genetics, epidemiology, Mendelian randomization studies, and randomized trials have established that LDL-C is not only a laboratory parameter of increased risk, but also a causal and modifiable factor in ASCVD (Mach et al 2020). Laboratory tests related to the primary and secondary endpoints are in line with the expected efficacy of inclisiran.

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (blood pressure (BP) [Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)] and pulse). A short physical exam will be conducted at all visits starting from visit 1 except where a complete physical examination is required (see above).

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 1-2.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with the back supported and both feet placed on the floor, pulse and systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Clinically notable vital signs are defined in Section 10.3.

8.4.3 Electrocardiograms

Not applicable.

8.4.4 Clinical safety laboratory tests

Clinically notable laboratory findings are defined in Section 10.3.1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-1 Safety Laboratory Assessments

Test Category	Test Name
Hematology	Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular HGB Concentration (MCHC), MCV, Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Platelets, Differential (% of Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), HbA1c
Chemistry (full panel)	Albumin, ALP, ALT, Amylase, AST, Blood Urea Nitrogen (BUN) Calcium, Chloride, Creatine kinase (CK), Creatinine, Direct Bilirubin, eGFR, Fasting Plasma Glucose (FPG), GGT, Indirect Bilirubin, Lipase, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Uric Acid
Chemistry (limited panel)	AST, ALT, ALP, GGT, TBL, Creatinine, eGFR, FPG, CK

Test Category	Test Name
Urinalysis[a]	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	PT, INR, Activated partial thromboplastin time (APTT)
Liver Event Testing and Liver Follow-Up Testing	Albumin, ALP, ALT, AST, CK, GGT, GLDH, INR, PT, and Total Bilirubin (TBL). Test for hemolysis (haptoglobin, reticulocytes, unconjugated [indirect] bilirubin. These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring
Renal follow-up	Urine Albumin and Albumin (for Albumin:creatinine ratio (ACR)), Serum Creatinine. Repeat standard chemistry testing and standard urinalysis (Microscopic Panel (Casts, Crystals, Bacteria, Epithelial cells, Erythrocytes, Leukocytes.) and Macroscopic panel (Dipstick) (Color, Bilirubin, Glucose, Ketones, Leukocytes esterase, Macroscopic Blood, Nitrite Occult Blood, pH, Protein, Specific Gravity, Urobilinogen)) These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.6, Renal safety monitoring
Pregnancy Test and Assessments of Fertility	Serum pregnancy test Urine pregnancy test Follicle Stimulating Hormone (refer to Section 8.4.5)

a. In case of abnormal results, microscopic urinalysis will be performed at the central lab. Microscopic Panel: Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelia cells.

8.4.5 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have a serum pregnancy testing at the screening visit and urine pregnancy testing at other study visits, the time points refer to Table 1-2.

Additional pregnancy testing might be performed if requested by local requirements.

As per Section 4.5, during a public health emergency as declared by local authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document. In such cases,

FSH testing is required of any female participant regardless of reported reproductive/ menopausal status at screening visit.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.1and Section 8.6.2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

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

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The severity grade:
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome (i.e. recovery status or whether it was fatal)

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

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

Adverse event monitoring should be continued for at least 30 days following the last study treatment visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.

8.6.2 Serious adverse events

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

- fatal
- life-threatening

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

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

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

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

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

If an SAE occurs, investigators is encouraged to take any appropriate actions immediately based on their judgments and relevant clinical guidance.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit (or 90 days after the last administration of study drug, whichever is longer) must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Consider the following 2 categories to determine SAE reporting timeframes:

1. Screen Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated Participants: SAEs collected between time participant signs ICF until 30 days after the last study visit (or 90 days after the last administration of study drug, whichever is longer)

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Novartis procedures and applicable global regulations or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last study visit (or 90 days after the last administration of study drug, whichever is longer) should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not Applicable.

8.6.6 Adverse events of special interest

Not Applicable.

8.7 Pharmacokinetics

PK parameters are not evaluated in this study.

[redacted]

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics OR Medical resource utilization and health economics

Not Applicable.

9 Statistical considerations

The primary analyses will be conducted after the database lock for the core part, when all randomized participants have completed the visit at Day 180 (or have discontinued from the study before EOC). The final analyses will be conducted when the trial ended.

Details of the statistical analysis and data reporting will be summarized in the statistical analysis (SAP) document finalized before database lock.

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

9.1 Analysis sets

The following analysis sets will be used for statistical analyses:

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

The Randomized Analysis Set (RAS) consists of all participants who received a randomization number, regardless of receiving trial medication.

The Full Analysis Set (FAS) consists of all randomized participants with the exception of those participants who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat (ITT) principle, participants will be analyzed according to the treatment they have been assigned to at randomization.

The Safety Analysis Set (SAF) includes all participants who received at least one dose of study drug. Participants will be analyzed according to the study treatment actually received.

Note: The last part of the definition of the FAS is what is often referred to as mis-randomized participants i.e. participants for whom IRT calls were made by the site either prematurely or inappropriately prior to confirmation of the participant's final randomization eligibility and double-blind medication was not administered to the participant. These participants would subsequently not continue to take part in the study or be followed-up. Mis-randomized participants will not be included in the FAS, but they will be included in the RAS. Further

exclusions from the FAS may only be justified in exceptional circumstances (e.g., serious Good Clinical Practice (GCP) violations).

9.2 Statistical analyses

Details of the statistical analysis and data reporting will be summarized in the Statistical Analysis Plan (SAP) document finalized before the database lock.

9.2.1 General considerations

Efficacy variables will be analyzed based on the FAS. The SAF will be used for the analyses of safety variables.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be summarized descriptively by treatment group for the FAS. Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented by treatment group. For selected parameters, 25th and 75th percentiles will also be presented by treatment group.

Relevant medical histories will be summarized by system organ class and preferred term, separately by treatment group.

9.2.3 Treatments

The SAF will be used for the analyses in this section.

Study treatment

The number and percentage of participants receiving study dose at each dosing visit will be summarized by treatment group. The number of doses received during the core part (excluding Day 180 dose) and during the extension part (including Day 180 dose) will also be summarized by treatment group.

Prior and concomitant therapies

Prior or concomitant medications will be summarized for the SAF in separate tabulations based on the coding dictionary used. Medications will be presented in alphabetical order, by Anatomical Therapeutic Chemical (ATC) class and preferred terms. Tables will show the overall number and percent of participants receiving at least one drug of a particular ATC class and at least one drug in a particular preferred term.

Prior medications and significant non-drug therapies will be summarized by treatment group. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by treatment group and by part.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary aim of the study is to demonstrate the superiority of inclisiran as monotherapy, compared to placebo, in reducing LDL-C.

The FAS will be used for the primary efficacy analysis.

9.3.1 Definition of primary endpoint(s)

The primary endpoint of the study is the percentage change from baseline at Day 150 in LDL-C.

9.3.2 Statistical model, hypothesis, and method of analysis

The primary objective is to demonstrate the superiority of inclisiran as monotherapy, compared to placebo, in reducing LDL-C as measured by percentage change from baseline at Day 150. The justification of the corresponding primary estimand is detailed in Section 3.1.

The primary statistical hypothesis is stated as below.

- H_0: the mean difference (inclisiran minus placebo) in percentage change from baseline at Day 150 in LDL-C is no less than zero.
- H_1: the mean difference (inclisiran minus placebo) in percentage change from baseline at Day 150 in LDL-C is less than zero.

The study can be claimed a success if the null hypothesis (H_0) is rejected at the one-sided significance level of 0.025.

The primary efficacy endpoint will be analyzed using an Analysis of Covariance (ANCOVA) model, in which the response variable will be the percentage change from baseline at Day 150 in LDL-C, treatment will be included as fixed-effect factor and baseline LDL-C will be included as a covariate.

Based on the ANCOVA model, the estimate and the 95% confidence interval will be provided for the adjusted mean difference between inclisiran and placebo, and for the adjusted mean for both inclisiran and placebo groups. The one-sided p-value will be provided for the primary null hypothesis.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

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

- **Discontinuation of study treatment:** Retrieved drop out (RDO) data collected after discontinuation from study treatment will be used for the analysis (treatment policy). Missing data after discontinuation from study treatment will be multiply imputed based on RDO data, and when there are no sufficient RDO data, a control-based Pattern-Mixture Model (PMM) will be used for multiple imputation.
- **Use of prohibited LLT:** Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 150 visit assessment or other LLT taken within 30 days before Day 150 visit assessment) will be treated in a hypothetical scenario of what would happen had those LLT not been taken and those participants behaved like other participants in the same treatment group (hypothetical strategy). Data after those intercurrent events will be excluded for the analysis and will be multiply imputed under missing at random assumption.
- **Death:** Death due to CV or non-CV causes is considered as an unfavorable outcome (composite strategy). Data after death will be set using the subject's baseline values.

The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's rule. The details will be described in the SAP.

9.3.4 Handling of missing values not related to intercurrent event

Missing values not related to intercurrent event will be multiply imputed under missing at random assumption. The primary analysis will be conducted on each multiply imputed dataset, and the treatment effects estimated from each of those imputed datasets will be combined using Rubin's rule. Details will be given in the SAP.

9.3.5 Multiplicity adjustment (if applicable)

Not applicable.

9.3.6 Sensitivity analyses

Sensitivity analyses will be planned and described in the SAP.

9.3.7 Supplementary analysis

Two sets of supplementary analyses will be conducted.

For the first one, all three intercurrent events, including discontinuation of study treatment, use of prohibited LLT under certain conditions and death due to CV or non-CV causes, will be handled with a hypothetical strategy. Data after all these intercurrent events will be multiply imputed under missing at random assumption. Missing values not related to intercurrent events will also be multiply imputed under missing at random assumption.

For the second one, the intercurrent events of discontinuation of study treatment and death due to CV or non-CV causes will be handled in the same way as in the primary analysis. Use of prohibited LLT under certain conditions will be treated with a treatment policy strategy, keeping treatment labels as assigned at randomization. Retrieved drop out (RDO) data collected after use of prohibited LLT under certain conditions will be used for the analysis. If no RDO data was collected, missing data will be multiply imputed using a control-based PMM. Missing values not related to intercurrent events will also be multiply imputed using a control-based PMM.

Details of supplementary analyses will be described in the SAP.

Subgroup analyses

Subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline characteristics may be performed. All subgroup analyses will be defined in the SAP prior to database lock.

9.4 Secondary endpoint(s)/estimand(s) analysis

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

The FAS will be used for all below efficacy analyses.

9.4.1.1 Efficacy and/or pharmacodynamic endpoints for core part

The secondary efficacy endpoints for core part are listed as follows:

- Absolute change in LDL-C from baseline at Day 150
- Percentage and absolute change in PCSK9, TC, HDL-C, non-HDL-C, ApoB, ApoA-1, Lp(a) and TG from baseline at Day 150

All secondary efficacy endpoints for core part will be analyzed using the same ANCOVA model as for the primary efficacy endpoint. Lipoprotein (a) will be log-transformed before modeling. The model will include treatment as fixed effect, and baseline value as a covariate. The adjusted mean difference between inclisiran and placebo and corresponding two-sided 95% CIs will be provided separately.

Details of the analyses for secondary efficacy endpoints for core part and sensitivity analyses if necessary will be specified in the SAP.

9.4.1.2 Efficacy and/or pharmacodynamic endpoints for extension part

The secondary efficacy endpoints for extension part are listed as follows:

- Percentage change in LDL-C from baseline at Day 330 for inclisiran group
- Absolute change in LDL-C from baseline at Day 330 for inclisiran group

The secondary efficacy endpoints for extension part will be analyzed descriptively. Mean percentage and absolute change from baseline at Day 330 in inclisiran group will be provided, respectively, as well as the 95% confidence intervals.

The secondary analysis for extension part will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment:** Retrieved drop out (RDO) data collected after discontinuation from study treatment will be used for the analysis (treatment policy). Missing data after discontinuation from study treatment will be multiply imputed based on RDO data, and when there are no sufficient RDO data, a control-based PMM (using the core part data) will be used for multiple imputation.
- **Use of prohibited LLT:** Use of prohibited LLT (PCSK9 monoclonal antibodies taken before Day 330 visit assessment or other LLT taken within 30 days before Day 330 visit assessment) will be treated in a hypothetical scenario of what would happen had those LLT not been taken and those participants behaved like other participants in the same treatment group (hypothetical strategy). Data after those intercurrent events will be excluded for the analysis and will be multiply imputed under missing at random assumption.
- **Death:** Death due to CV or non-CV causes is considered as an unfavorable outcome (composite strategy). Data after death will be set using the subject's baseline value.

Missing values not related to intercurrent events will also be multiply imputed under missing at random assumption. The details will be described in SAP.

9.4.2 Safety endpoints

For safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Baseline data will be summarized where appropriate (for change from baseline summaries).

Adverse events

The adverse events will be coded using the MedDRA dictionary and will be allocated into each study part according to the event start date. All information obtained on adverse event CRFs will be summarized by treatment group and by part as described below.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, study part, primary system organ class and preferred term;
- by treatment, study part, primary system organ class, preferred term and maximum severity;
- by treatment, study part, and preferred term.

Separate summaries by treatment, study part, primary system organ class and preferred term will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A participant with multiple adverse events within a primary system organ class will be only counted once towards the total of the primary system organ class.

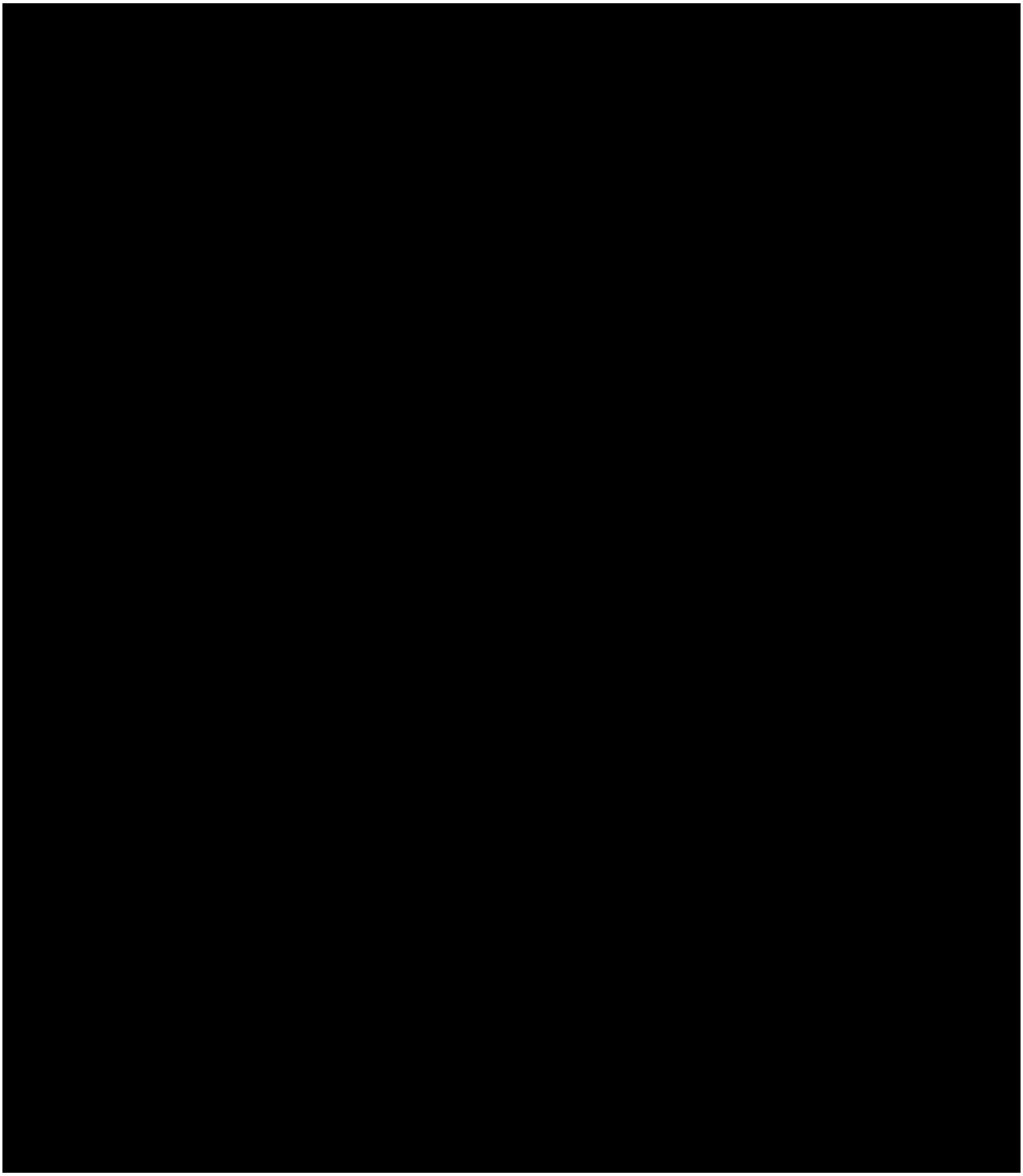
Vital signs

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

Clinical laboratory evaluations

Summary statistics will be provided by treatment group and visit. Shift tables using the low, normal, or high classification will be used to compare baseline to the worst on-treatment value by treatment group and by part. The number (and percentage) of participants meeting clinically significant criteria will be provided by treatment group and by part.

[redacted]



9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

Not applicable.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

This study is designed to randomize approximately 200 Participants (with randomization ratio of 1:1 to inclisiran and placebo arms) in order to provide adequate information to characterize the safety profile of inclisiran as well as to have sufficient power for the primary efficacy endpoint.

[redacted]

9.9.2 Secondary endpoint(s)

Statistical power will not be assessed for secondary endpoints.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochureand other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

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

The Investigator will be responsible for the following:

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

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

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

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable)and all other applicable local regulations

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

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

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

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

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

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

The following informed consents are included in this study:

- Main study consent, which also included:

  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

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

As per Section 4.5, during a public health emergency as declared by local authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

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

10.1.3 Data protection

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

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

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

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Steering Committee

The Steering Committee (SC) will be established comprising Investigators participating in the study, i.e. not being Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the steering committee charter.

10.1.5 Data quality assurance

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

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

10.1.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

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

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

10.1.5.2 Database management and quality control

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

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

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system

will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated Contract Research Organization (CRO)) at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

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

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

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

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

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

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT or CTIS public website etc.).

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

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

10.1.8 Protocol adherence and protocol amendments

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

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

10.1.8.1 Protocol amendments

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

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

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

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANCOVA	Analysis of covariance
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
APTT	Activated Partial Thromboplastin time
ASCVD	Atherosclerotic Cardiovascular Disease
ASGPR	Asialoglyco Protein Receptors
ASMA	Anti-smooth muscle antibody
ASO	Antisense Oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
cm	centimeter(s)
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
COA	Clinical Outcome Assessment
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTIS	Clinical Trials Information System
CTT	Clinical Trial Team
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DHA	Docosahexaenoic acid
DILI	Drug-Induced Liver Injury
dL	deciliter(s)
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic Case Report Forms
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate

EMA	European Medicines Agency
EOC	End of core part
EOS	End of Study
EPA	Eicosapentaenoic acid
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GalNAc	N-Acetylgalactosamine
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
HAV	Hepatitis A Virus
HbA1c	Glycated hemoglobin (hemoglobin A1c)
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
HTN	Hypertension
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	Low Density Lipoprotein Receptor
LFT	Liver function test
LLT	Lipid-Lowering Therapy
Lp(a)	Lipoprotein (a)
LPLV	Last participant last visit

MACE	Major adverse cardiovascular event
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
non-HDL-C	non-High-Density Lipoprotein Cholesterol
PCR	Protein-creatinine ratio
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PD	Pharmacodynamic(s)
PDC	Proportion of days covered
PFS	Prefilled syringe
PMM	Pattern-Mixture Model
PT	prothrombin time
R Value	ALT/ALP x ULN
RAS	Randomized Set
RDO	Retrieved Drop Out
RISC	Ribonucleic acid-Induced Silencing Complex
RNA	Ribonucleic acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV- 2	Severe acute respiratory syndrome coronavirus 2 also referred to as COVID-19
SBP	Systolic Blood Pressure
SCR	Screened Set
siRNA	small interfering RNA
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides
ULN	upper limit of normal
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.

Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.

Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

10.4 Appendix 4: Participant Engagement

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

- Thank You letter
- Plain language trial summary - after Clinical study report (CSR) publication
- Individual study results - after CSR publication

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-1 in Section 10.5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-2 Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) ● ALT or AST > 3 × ULN and INR > 1.5 ● Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) ● Any clinical event of jaundice (or equivalent term) ● ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ● Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	● ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 10-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline AND >5x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. Follow-up for symptoms. Initiate close monitoring and workup for competing etiologies. Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline AND >3x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline AND >3x ULN, OR ALT > 300 U/L	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Discontinue the study treatment immediately ● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g.	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)

Criteria	Actions required	Follow-up monitoring
	conmeds, med hx, lab)in the appropriate CRF	
Any AE potentially indicative of a liver toxicity	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

10.6 Appendix 6: Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the Investigator or designated trial staff.

10.7 Appendix 7: Diagnostic Criteria for Low or Moderated ASCVD risk

Diagnosis of low or moderate ASCVD risk in this study follows the ASCVD Risk Assessment Flowchart recommended by 2016 Chinese Guideline for the Management of Dyslipidemia in Adults （Zhao et al 2016）.

Table 10-4 ASCVD Risk Assessment Flowchart

Those who meet any of the following conditions can be directly classified as Very High Risk or High Risk: **Very High Risk:** Established ASCVD **High Risk:** 1) LDL-C≥ 4.9 mmol/L or TC≥ 7.2 mmol/L 2) Diabetes patients over 40 years old with 1.8 mmol/L≤LDL-C<4.9 mmol/L (or) 3.1 mmol/L≤TC<7.2 mmol/L			
If not meet above condition, need to further assess 10-year ASCVD risk as follows.			
No. of Risk Factors*	Serum Cholesterol Level Classification (mmol/L)		
	3.1 ≤ TC <4.1 (or) 1.8 ≤ LDL<-C <2.6	4.1 ≤ TC <5.2 (or) 2.6 ≤ LDL-C <3.4	5.2 ≤ TC <7.2 (or) 3.4 ≤ LDL-C <4.9
Without hypertension 0~1	Low Risk	Low Risk	Low Risk
2	Low Risk	Low Risk	Moderate Risk
3	Low Risk	Moderate Risk	Moderate Risk
With hypertension 0	Low Risk	Low Risk	Low Risk
1	Low Risk	Moderate Risk	Moderate Risk
2	Moderate Risk	High Risk	High Risk
3	High Risk	High Risk	High Risk
For Moderate Risk patients under 55 years old, assess lifetime residual risk			
• Those who meet any 2 of the following risk factors can be classified as High Risk: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg Non-HDL-C ≥ 5.2 mmol/L (200 mg/dL) HDL-C < 1.0 mmol/L (40 mg/dL)			

BMI ≥ 28 kg/m3 Smoking

*Risk Factors: Smoking, low HDL-C, Male≥45 years old or Female≥55 years old

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