

Protocol No.: MDCO-PCS-17-03 (ORION-9)

A Placebo-Controlled, Double-Blind, Randomized Trial to Evaluate the Effect Of 300 mg of Inclisiran Sodium Given as Subcutaneous Injections in Subjects with Heterozygous Familial Hypercholesterolemia (HeFH) and Elevated Low-Density Lipoprotein Cholesterol (LDL-C)

CLINICAL STUDY PROTOCOL

31 January 2019

NCT03397121

Investigational New Drug

INCLISIRAN

**A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED
TRIAL TO EVALUATE THE EFFECT OF 300 MG OF
INCLISIRAN SODIUM GIVEN AS SUBCUTANEOUS
INJECTIONS IN SUBJECTS WITH HETEROZYGOUS
FAMILIAL HYPERCHOLESTEROLEMIA (HeFH) AND
ELEVATED LOW-DENSITY LIPOPROTEIN CHOLESTEROL
(LDL-C)**

ORION-9

Protocol No.: MDCO-PCS-17-03

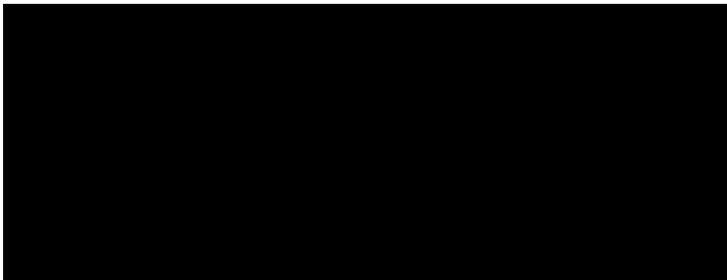
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Development Phase: III

Sponsor: The Medicines Company
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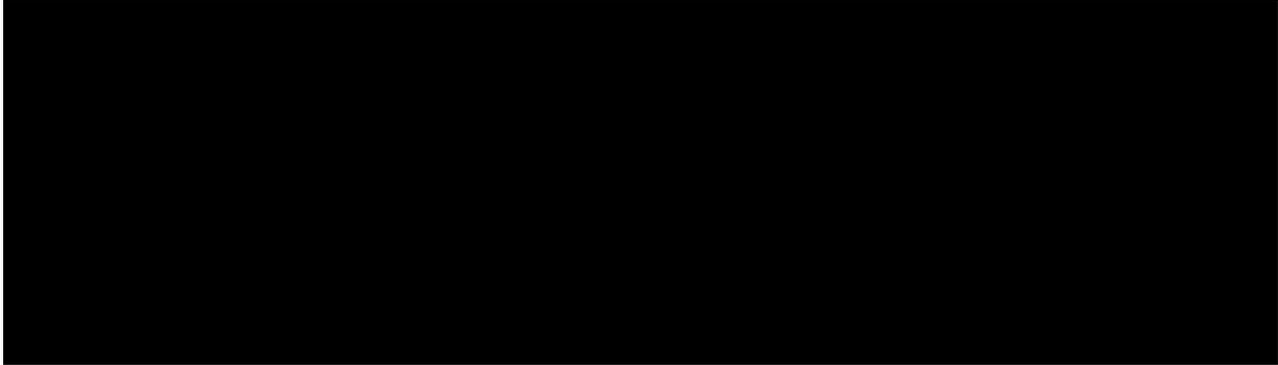
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**This study will be conducted in compliance with Good Clinical Practice (GCP) and protection of the subject
as required by the regulations and directives in operation at this time.**

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Telephone Number
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PROTOCOL SYNOPSIS

Name of Sponsor/Company: The Medicines Company
Name of Finished Product: Inclisiran for Injection
Name of Active Ingredient: inclisiran sodium
Title of Study: A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C)
Phase of Development: III
Study Centers: Multicenter, international study (approximately 100 sites); specific list is maintained by the Sponsor.
Central Facilities: This list is maintained by the Sponsor
Number of Subjects: Approximately 400 eligible subjects will be randomized (200 subjects randomized to inclisiran and 200 subjects randomized to placebo). Assuming about a 5% drop out rate, the sample size will be approximately 380 subjects that are evaluable for efficacy across the placebo and inclisiran dose groups. Due to faster than expected enrollment, actual enrollment was 482 subjects.
Principal Investigator: [REDACTED]
Study Period: The estimated study period for the study will be 24 months from when the first subject is enrolled to when the last subject completes the study.
Objectives: <u>Primary:</u> The primary objective is to evaluate the effect of inclisiran treatment on: <ul style="list-style-type: none">• LDL-C levels at Day 510• Time adjusted percent change in LDL-C levels from baseline after Day 90 and up to Day 540 levels <u>Secondary:</u> The secondary objectives are to evaluate the effect of inclisiran on: <ul style="list-style-type: none">• Proprotein convertase subtilisin/kexin type 9 (PCSK9), total cholesterol, ApoB, and non-high-density lipoprotein cholesterol (HDL-C) at Day 510• LDL-C and PCSK9 levels over time to Day 540• Mean maximum reduction in LDL-C levels• LDL-C and PCSK9 levels over time in individual subjects• Other lipids, lipoproteins, apolipoproteins• Proportion of subjects achieving prespecified LDL-C targets• Safety and tolerability profile of inclisiran <u>Exploratory:</u> The exploratory objectives are to collect/evaluate the effect of inclisiran on the following: <ul style="list-style-type: none">• Cardiovascular (CV) events such as CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI), and non-fatal stroke (ischemic and hemorrhagic)• Response of LDL-C reduction by underlying causal mutations of HeFH

Methodology: This study is a Phase III, placebo-controlled, double-blind, randomized study in 400 subjects with HeFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of subcutaneous inclisiran injection(s).

Subjects will be screened and approximately 400 eligible subjects will be randomized: 200 subjects will be randomized to inclisiran sodium 300 mg and 200 subjects randomized to placebo. Due to faster than expected enrollment, actual enrollment was 482 subjects. Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will receive four subcutaneous injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450.

On Day 1, all eligible subjects will be randomized and will receive the first subcutaneous (SC) injection of investigational product (inclisiran or placebo). After the first SC injection, the subject will be observed in the clinic for at least 4 hours post injection in order to have additional laboratory assessments and vital signs completed before being discharged. Subjects will return on Day 90, Day 270, and Day 450 to receive additional investigational product. During these subsequent dosing visits, subjects will be observed in the clinic for at least 30 minutes after administration of each injection and have additional laboratory assessments completed if needed. Subjects will also have in-clinic visits on Day 30, Day 150, Day 330, and Day 510 for follow-up and limited laboratory assessments. The end of study (EOS) visit will be conducted on Day 540.

Pharmacodynamic assessments will be collected at various visits and include LDL-C levels as well as other lipids and lipoproteins (eg, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein cholesterol [VLDL-C], apolipoprotein A1 [Apo-A1], apolipoprotein B [ApoB], lipoprotein(a) [Lp(a)], high sensitivity C-reactive protein [hsCRP], and PCSK9).

All subjects will be invited to consent to pharmacogenetic analyses, unless underlying causal mutations of HeFH are well documented by a validated specialized laboratory. A blood sample will be collected, preferably during screening, only from subjects who sign a separate consent for pharmacogenetics.

Safety assessments including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and safety laboratory parameters will also be collected during the study. In addition, formation of anti-drug antibodies (ADA) and further characterization of ADA will be evaluated.

End of study evaluations will be conducted at the Day 540 visit.

Subjects who have completed the study to Day 540 will be given the opportunity to enroll in a separate open-label long-term extension study to collect long-term safety and efficacy data for inclisiran.

The independent Data Monitoring Committee (IDMC) will review safety data after the first 40 subjects receive the first SC injection of inclisiran or placebo and have completed 1 month follow-up. Thereafter the IDMC will review safety data every 3 months until the end of study (EOS) unless requested otherwise by the IDMC. A recommendation may be taken to stop or amend the study at any of these reviews.

Diagnosis and Main Criteria for Selection:

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

1. Male or female subjects ≥ 18 years of age.
2. History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease that may indicate FH ([APPENDIX A](#))
3. Stable on a low-fat diet (eg, NCEP)

4. Serum LDL-C ≥ 2.6 mmol/L (≥ 100 mg/dL) at screening
5. Fasting triglyceride < 4.52 mmol/L (< 400 mg/dL) at screening.
6. Calculated glomerular filtration rate > 30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology.
7. Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF) (APPENDIX B).
8. Subjects not receiving statins must have documented evidence of intolerance to all doses of at least two different statins (APPENDIX B).
9. Subjects on lipid-lower therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥ 30 days before screening with no planned medication or dose change during study participation.
10. Subjects must be willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

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

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction $< 25\%$.
4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
5. Major adverse cardiovascular event within 3 months prior to randomization.
6. Uncontrolled severe hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg prior to randomization despite antihypertensive therapy.
7. 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 confirmed by a repeat abnormal measurement at least 1 week apart.
8. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 2 years.
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
10. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of highly effective contraception (failure rate less than 1% per year) (eg combined oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion:
 - a. Women > 2 years postmenopausal (defined as 1 year or longer since last menstrual period) AND more than 55 years of age.

- b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomization.
- c. Women who are surgically sterilized at least 3 months prior to enrollment.
11. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
12. Known history of alcohol and/or drug abuse within the last 5 years.
13. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
14. Planned use of other investigational products or devices during the course of the study.
15. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
 - a. Subjects who are unable to communicate or to cooperate with the investigator.
 - b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
 - c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
 - d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.
 - e. Persons directly involved in the conduct of the study.
16. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

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

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

Duration of Treatment: The expected duration of the subjects' involvement in the study will be approximately 554 days which includes screening, investigational product administration, and the EOS period to Day 540.

- Screening: Day -14 to -1
- Randomization, initiation of investigational product: Day 1
- Treatment Phase:
 - Dosing: Day 1, Day 90, Day 270 and Day 450 (final dose)
 - Additional clinic visits: Day 30, Day 150, Day 330 and Day 510
- EOS visit: Day 540 (90 days after final dose)

Reference Therapy, Dose, and Mode of Administration: Placebo will be administered as SC injections of saline solution. Placebo volume will be matched to test product volume within each dose and injection ie, the 300 mg dose will be administered as 1.5 mL of placebo.

Criteria for Evaluation:

Efficacy:

Primary Endpoints:

- Percentage change in LDL-C from baseline to Day 510
- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

Key Secondary Endpoints:

- Absolute change in LDL-C from baseline to Day 510
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK 9, total cholesterol, ApoB, and non-HDL-C

Other Secondary Endpoints:

- Mean maximum percentage change in LDL-C
- Absolute change from baseline to Day 510 in PCSK9, total cholesterol, ApoB and non-HDL-C
- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540
- Proportion of subjects in each group who attain global lipid targets for their level of atherosclerotic cardiovascular disease (ASCVD) risk

Exploratory Endpoints:

- Incidence of CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic)
- Response of LDL-C reduction by underlying causal mutations of HeFH

Safety: Adverse event, SAEs, vital signs, clinical laboratory values (hematology, coagulation testing, chemistry, and urinalysis), and electrocardiograms (ECGs) will be collected at specified visits through the EOS visit (Day 540). Cardiovascular events will be reported as AEs for the compilation of information on CV events such as CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic). In addition, formation of ADA and subsequent characterization of ADA will be evaluated for the investigational product.

Statistical Methods:

Sample Size and Power

The sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL. Assuming about a 5% drop out rate, the sample size will be approximately 380 subjects that are evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 380 evaluable subjects, will provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025. Due to faster than expected enrollment, actual enrollment was 482 subjects. This increased sample size will contribute additional safety data and not appreciably affect power calculations.

Primary Endpoint Analysis:

The family-wise type I error rate is controlled at one-sided significance level of $\alpha=0.025$ by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 will be tested first. If the null hypothesis is rejected at one-sided significance level of $\alpha=0.025$ and superiority of inclisiran over placebo is claimed, then the time adjusted percentage change in LDL-C from baseline after-Day 90 and up to Day 540 will be tested, also at one-sided significance level of $\alpha=0.025$. Mixed-effect models for repeated measures (MMRM) will be performed on the percent change in

LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo. Missing data will be imputed using a multiple imputation washout model. Results will be combined using Rubin's method. Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 will be calculated from the MMRM with imputed data discussed above. Linear combinations of the estimated means after Day 90 and up to Day 540 will be used to compare treatments. Results will be combined using Rubin's method.

Key Secondary Endpoint Analysis:

The secondary efficacy endpoints will not be tested if either one of the co-primary efficacy endpoints' null hypothesis failed to be rejected.

The Hochberg procedure will be applied to control the family-wise type I error rate at one-sided significance level of $\alpha=0.025$ for the key secondary endpoints. The key secondary endpoints will be analyzed using the same methods as in the primary efficacy analysis.

Other Secondary and Exploratory Endpoint Analysis:

The analysis of the secondary and exploratory endpoints will include descriptive and graphical summaries by treatment group. Least squares means (95% Confidence Intervals) will be provided for continuous variables. Nominal p-values will be provided when applicable.

Interim Analysis:

No interim analysis will be performed in this study.

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LIST OF ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo-A1	apolipoprotein A1
ApoB	apolipoprotein B
aPTT	activated partial thromboplastin
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the curve
BUN	total protein urea
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CHD	coronary heart disease
CK	creatine kinase
C _{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRF	case report form
CT	computed tomography
CTA	Computed tomographic angiography
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVD	cerebrovascular disease
dL	deciliter(s)
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GPV	Global Pharmacovigilance
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol

HeFH	Heterozygous Familial Hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
IDMC	Independent Data Monitoring Committee
IFN- γ	interferon-gamma
IL6	interleukin 6
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	injection site reaction
ITT	intent-to-treat
IV	intravenous
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LNP	lipid nanoparticles
Lp(a)	lipoprotein(a)
Lp-PLA2	lipoprotein-associated phospholipase A2
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDCO	The Medicines Company
MDCT	multidetector computed tomography
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mITT	Modified intent-to-treat
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	millimole
MMRM	mixed-effect models for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PCS	potentially clinical significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PEF	peak expiratory flow
PT	prothrombin time
REML	Restricted Maximum Likelihood
RISC	RNA-induced silencing complex

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

1. INTRODUCTION

The Medicines Company is developing a novel synthetic ribonucleic acid (RNA) interference (RNAi) therapeutic, Inclisiran for Injection (subcutaneous [SC] use) for the treatment of hypercholesterolemia. This protocol describes a study to evaluate the effect of inclisiran treatment on low density lipoprotein cholesterol (LDL-C) levels at Day 510. This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. Background

1.1.1. Disease Overview

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

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

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

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

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a key role in controlling the levels of low-density lipoprotein receptors (LDLR) on the surface of hepatocytes [Khorova, 2017]. PCSK9 is expressed and secreted into the bloodstream predominantly by the liver, binds LDLR both intracellularly and extracellularly and promotes the lysosomal degradation of these receptors in hepatocytes, [Lakoski et al, 2009; Mousavi et al, 2009] thereby increasing the circulating LDL-C levels. Loss of function

mutations in PCSK9 have been found to lead to increased LDLR in liver, reduced serum LDL-C, and a lower risk for CHD [Berge et al, 2006; Cohen et al, 2006; Kotowski et al, 2006; Zhao et al, 2006] with no apparent negative health consequences. [Zhao et al, 2006; Hooper et al, 2007; Horton et al, 2009].

Recently developed and approved PCSK9-blocking monoclonal antibodies reduce circulating PCSK9 levels and lower LDL-C levels. Preliminary reports indicate that treatment with such antibodies can lead to reduction of cardiovascular events compared with placebo [Hooper et al, 2005; Navarese et al, 2015; Zhang et al, 2015; Robinson et al, 2015; Sabatine et al, 2015]. Results from the first completed large CV outcomes trial (FOURIER) were reported in March 2017. Repatha® (evolocumab) significantly reduced the risk of cardiovascular events. The study in approximately 27,000 patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) met its primary composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or coronary revascularization) and the key secondary composite endpoint (cardiovascular death, nonfatal MI or nonfatal stroke) [Sabatine et al, 2015].

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

1.1.2. PCSK9 Biology and Target Rationale

PCSK9 is a member of the subtilisin serine protease family. Proprotein convertase subtilisin kexin type 9 is predominantly expressed by the liver and is critical for the down regulation of hepatocyte low-density lipoprotein receptor (LDLR) expression [Mousavi et al, 2009]. LDL-C levels in plasma are markedly elevated in humans with gain of function mutations in PCSK9, classifying them as having severe familial hypercholesterolemia [Abifadel et al, 2003]. Data from genetic association studies have identified loss of function alleles in human PCSK9 that result in lower PCSK9 protein levels and lower LDL-C levels [Zhao et al, 2006; Hooper et al, 2007; Horton et al, 2009]. In one published study, heterozygous individuals (carrying a single copy of a loss of function PCSK9 mutation) had significantly lower LDL-C with median levels of approximately 70 mg/dL (1.81 mmol/L) [Cohen et al, 2006]. Over a 15-year period of retrospective data analysis, this sustained lowering in LDL-C levels translated to an 88% lower risk of risk for CHD. Follow-up publications describe two adult individuals that are compound heterozygous for loss of function alleles of PCSK9. These individuals lack detectable plasma PCSK9 protein, have LDL-C levels ≤ 20 mg/dL, and yet are otherwise healthy [Zhao et al, 2006; Hooper et al, 2007]. Additionally, recent human clinical trials with PCSK9 blocking antibodies have shown significant lowering of LDL-C in healthy volunteers and across a range of high cardiovascular (CV)-risk populations and with elevated LDL-C both with and without statins [Banerjee et al, 2012; Dias et al, 2012; Milazzo et al, 2012; Raal et al, 2012; Roth et al, 2012; Stein et al, 2012; Sullivan et al, 2012; Hooper et al, 2013]. Two monoclonal agents to inhibit PCSK9 are currently approved in Europe and North America. Recent cardiovascular outcomes trials have further confirmed that PCSK9 is a validated drug target whose inhibition results in LDL-C lowering and

significant outcomes benefit without otherwise negatively impacting overall health [Ridker et al, 2017; Sabatine et al, 2017].

1.1.3. Mechanism of RNA Interference

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

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

1.2. Inclisiran, an siRNA Therapeutic for Hypercholesterolemia

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

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

When introduced into the hepatocyte, inclisiran engages the natural pathway of RNAi by binding intracellularly to the RNA-induced silencing complex (RISC), enabling it to cleave

messenger RNA (mRNA) molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein. A single siRNA-bound RISC is catalytic and cleaves many transcripts and the duration of action is anticipated to be longer than other mechanisms.

1.2.1. Nonclinical Studies

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

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

Additional non-clinical studies are ongoing or planned.

1.2.2. Clinical Studies

1.2.2.1. Clinical pharmacology

Inclisiran is inactive in plasma and acts directly in the hepatocytes leading to inhibition of PCSK9 protein synthesis. After SC administration of inclisiran, peak plasma concentrations were observed by 4 hours and became undetectable in plasma in 24 to 48 hours with a fast elimination half-life ($t_{1/2}$) of 7.3 hours and dose-proportional increase in exposure parameters of maximum plasma concentration (C_{max}) and area under the curve (AUC). There was no accumulation of inclisiran plasma concentrations following multiple weekly, biweekly or monthly dosing. Mean fraction excreted unchanged in the urine was around 25%. In vitro

studies using hepatic P450 metabolic enzymes showed that inclisiran neither inhibited nor induced common hepatic metabolic pathways.

Additional clinical pharmacology studies are ongoing or planned.

1.2.2.2. Clinical

Inclisiran has been studied in one completed Phase I (ALN-PCSSC-001) study (N=69) and one Phase II (ORION-1) study (N=501); dosing has completed in ORION-1 and the extended follow-up is ongoing.

ALN-PCSSC-001: Doses up to 800 mg as a single dose and two doses or more doses up to 500 mg were administered.

ORION-1: Up to 500 mg as a single dose on Day 1 or two doses on Day 1 and Day 90 (100 mg, 200 mg or 300 mg) were administered.

The efficacy data generated in these two studies show robust and prolonged reductions in PCSK9 and LDL-C levels in plasma. PCSK9 was reduced from baseline by around 75%. Mean LDL-C was reduced by around 50% with one dose of 300 mg and 55% with two doses of 300 mg given 30 or 90 days apart in both the Phase I and the ORION-1 study, respectively. This effect is still significant 210 days after a single dose and remains at around a mean of 50% when measured 120 days after the second dose given at Day 90 in the ORION-1 study. Other lipids and lipoproteins are also modified as would be expected from a drug acting on PCSK9 with a potentially beneficial modification of the overall atherogenic lipid profile [Ray et al, 2017].

To date, no clinically relevant safety concerns have arisen in these studies of inclisiran; collection and analysis of data up to Day 360 is ongoing in the ORION-1 (Phase II) study.

Based on these efficacy and safety data, 300 mg has been selected as the dose for subsequent clinical studies with a dosing at Day 1, Day 90, and every 6 months subsequently.

Safety:

In the ongoing Phase II (ORION-1) study with a follow up of more than 210 days, single doses of up to 500 mg on Day 1 or two doses (100 mg, 200 mg or 300 mg) (given 90 days apart) were also generally well tolerated and the majority of adverse events (AEs) in inclisiran-treated subjects with ASCVD and ASCVD risk equivalents were mild or moderate in intensity. Injection site reactions have been reported in around 5% of subjects receiving either one or two doses of inclisiran [Ray et al, 2017]. The emerging safety profile will be further evaluated in the ongoing Phase II (ORION 1) study and the subsequent planned studies.

Efficacy:

In the ongoing Phase II (ORION-1) study, in all single dose groups, maximal LDL-C reduction was observed between Day 30 and Day 60. At Day 30 the mean LDL-C reduction from baseline was approximately 45% to 55% and at Day 60 was 44% to 51% in a dose dependent fashion with doses of 200 mg, 300 mg and 500 mg. Mean LDL-C remained significantly reduced from baseline over the course of the study in all inclisiran groups to Day 210.

In all groups, maximal reduction in PCSK9 levels was observed at Day 30 and the mean reduction from baseline was 66%, 71% and 74% in the 200 mg, 300 mg and 500 mg groups respectively.

In all double dose groups, maximal LDL-C reduction was observed after the second dose given at Day 90. At Day 120 the mean LDL-C reduction from baseline was 41% to 55% in a dose dependent fashion with doses of 100 mg, 200 mg and 300 mg.

At Day 180, the mean LDL-C reduction was between 35% and 53% in a dose dependent fashion across the dose range.

For subjects treated on Day 1 and Day 90, maximal reduction in PCSK9 levels was observed at Day 120 and the mean reduction from baseline was 60%, 73% and 75% with the 100 mg, 200 mg and 300 mg dose groups respectively. PCSK9 levels remained significantly reduced compared to baseline over the course of the study to Day 210 in all groups.

1.3. Known and Potential Risks and Benefits

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

An expanded risk-benefit summary is provided in the IB [[Investigator's Brochure](#)].

1.4. Study Rationale

1.4.1. Study Rationale

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

1.4.2. Dose Rationale

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

1.5. Study Population

This study will include male or female subjects ≥ 18 years of age with a history of Heterozygous Familial Hypercholesterolemia (HeFH) and elevated LDL-C.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

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

- LDL-C levels at Day 510
- Time adjusted percent change in LDL-C levels from baseline after Day 90 and up to Day 540 levels

2.2. Secondary Objectives

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

- PCSK9, total cholesterol, ApoB and non-HDL-C at Day 510
- LDL-C and PCSK9 levels over time to Day 540
- Mean maximum reduction in LDL-C levels
- LDL-C and PCSK9 levels over time in individual subjects
- Other lipids, lipoproteins, apolipoproteins
- Proportion of subjects achieving prespecified LDL-C targets
- Safety and tolerability profile of inclisiran

2.3. Exploratory Objectives

The exploratory objectives of this study are to collect/evaluate the effect of inclisiran on the following:

- CV events such as CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic)
- Response of LDL-C reduction by underlying causal mutations of HeFH

3. STUDY DESIGN

3.1. Type/Design of Study

This study will be a Phase III, placebo-controlled, double-blind, randomized study in 400 subjects with HeFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of subcutaneous inclisiran injection(s). The study will be a multicenter, international study. Informed consent will be obtained from subjects before the initiation of any study-specific procedures.

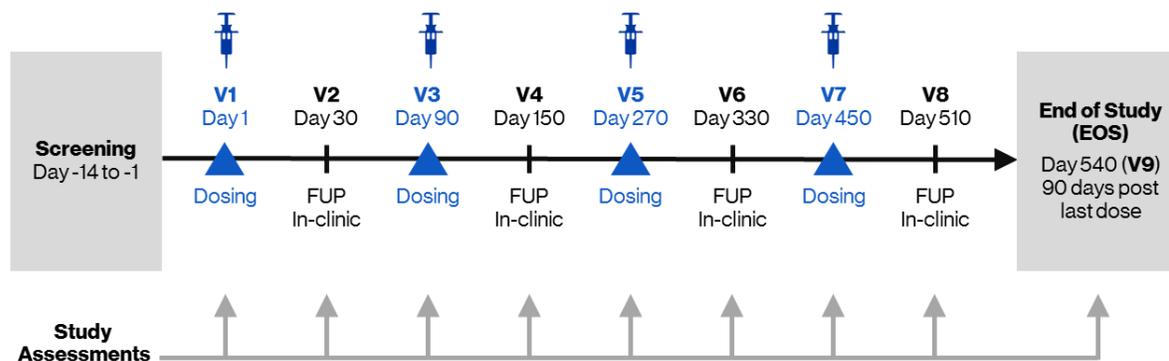
Subjects will be screened and approximately 400 eligible subjects will be randomized: 200 subjects will be randomized to inclisiran sodium 300 mg and 200 subjects randomized to placebo. Due to faster than expected enrollment, actual enrollment was 482 subjects.

Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Enrollment of statin intolerant subjects will be capped at 15% of total study enrollment. Each subject will receive an injection on Day 1 of blinded inclisiran or placebo, a second injection on Day 90 and subsequent injections on Day 270 and Day 450.

Subjects who have completed the study to Day 540 will be given the opportunity to enroll in a separate long-term extension study to collect long-term efficacy and safety data.

3.2. Schematic Diagram of Study Design

Figure 1: Schematic Diagram of Study Design



FUP=follow-up; V=visit

3.3. Primary Endpoints

The primary endpoints of this study are:

- Percentage change in LDL-C from baseline to Day 510
- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

3.4. Secondary Endpoints

The key secondary endpoints of this study are:

- Absolute change in LDL-C from baseline to Day 510
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C

The other secondary endpoints of this study are:

- Mean maximum percentage change in LDL-C
- Absolute change from baseline to Day 510 in PCSK9, total cholesterol, ApoB and non-HDL-C
- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540
- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk
- Safety and tolerability profile of inclisiran as measured by AEs, SAEs, vital signs, clinical laboratory values, ECG measurements and formation of ADA and subsequent characterization of ADA

3.5. Exploratory Endpoints

The exploratory endpoints of this study are:

- Incidence of CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic)
- Response of LDL-C reduction by underlying causal mutations of HeFH

3.6. Measures to Minimize/Avoid Bias

3.6.1. Blinded Study

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

4. SUBJECT POPULATION

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

4.1. Number of Subjects

Approximately 400 subjects (at least 380 evaluable) will be randomized. Due to faster than expected enrollment, actual enrollment was 482 subjects.

4.2. Inclusion Criteria

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

1. Male or female subjects ≥ 18 years of age.
2. History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease may indicate FH ([APPENDIX A](#))
3. Stable on a low-fat diet (eg, NCEP)
4. Serum LDL-C ≥ 2.6 mmol/L (≥ 100 mg/dL) at screening
5. Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening.
6. Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized clinical methodology.
7. Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF) (see [APPENDIX B](#)).
8. Subjects not receiving statin must have documented evidence of intolerance to all doses of at least two different statins (see [APPENDIX B](#)).
9. Subjects on lipid-lower therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥ 30 days before screening with no planned medication or dose change during study participation.
10. Subjects must be willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

4.3. Exclusion Criteria

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

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk (according to investigator's [or delegate] judgment) if he/she participates in the clinical study.
2. An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) might interfere with interpretation of the clinical study results.
3. New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%.
4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
5. Major adverse cardiovascular event within 3 months prior to randomization.
6. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
7. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.
8. Severe concomitant noncardiovascular disease that carries the risk of reducing life expectancy to less than 2 years.
9. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
10. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of highly effective contraception (failure rate less than 1% per year) (eg, combined oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, or intrauterine device) for the entire duration of the study. Exemptions from this criterion:
 - a. Women >2 years postmenopausal (defined as 1 year or longer since last menstrual period) AND more than 55 years of age.
 - b. Postmenopausal women (as defined above) and less than 55 years of age with a negative pregnancy test within 24 hours of randomization.
 - c. Women who are surgically sterilized at least 3 months prior to enrollment.

11. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
12. Known history of alcohol and/or drug abuse within the last 5 years.
13. Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
14. Planned use of other investigational products or devices during the course of the study.
15. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
 - a. Subjects who are unable to communicate or to cooperate with the investigator.
 - b. Unable to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study (including subjects whose cooperation is doubtful due to drug abuse or alcohol dependency).
 - c. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study).
 - d. Have any medical or surgical condition, which in the opinion of the investigator would put the subject at increased risk from participating in the study.
 - e. Persons directly involved in the conduct of the study.
16. Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

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

4.4. Withdrawal Criteria

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

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

The applicable reason above will be recorded in the eCRF. It is imperative to obtain complete follow-up data for all subjects whether or not they receive their assigned treatment or have discontinued investigational product. All data collected up until the time of subject withdrawal is to be entered into the eCRF. In addition, every attempt should be made to collect follow-up information except for those subjects who specifically withdraw consent release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the investigational product should be carried out when possible whether or not a subject continues to receive treatment according the protocol. The attempts and any reason(s) for missing data as a result of the withdrawal will be captured in the source.

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

4.4.1. Withdrawal from Study Medication

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

It is imperative to obtain complete follow-up data (through Day 540 procedures) for all randomized subjects whether or not they receive their assigned treatment or have discontinued investigational product.

4.5. Stopping Criteria

4.5.1. Individual Subject Dosing Stopping Criteria

During the double-blind, active treatment phase subjects will have clinic visits at regular intervals. Dosing with blinded study medication (inclisiran and/or matching placebo) should be temporarily discontinued or stopped in subjects with:

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

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

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

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

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

5. TREATMENT OF SUBJECTS

5.1. Study Medications

5.1.1. Inclisiran

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

Table 1: Investigational Product

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

Investigational product preparation: The pharmacist or qualified designee will prepare the investigational product under aseptic conditions to be administered to the subject on that day.

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

Investigational product administration: Subjects will be administered a single SC injection of 300 mg Inclisiran for Injection at predefined time points as described in the Schedule of Assessments (Table 2). Investigational product injection will be administered by qualified clinical study site staff under the supervision of the investigator or designee. The site of injection is the abdomen, alternating sides for each injection. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

5.1.2. Placebo

Placebo will be supplied by The Medicines Company to clinical study site as sterile normal saline (0.9% sodium chloride in water for injection) for SC injection. The placebo vials will be blinded and look identical to the inclisiran vials. Placebo will be administered as an SC injection in an amount matched to the doses within the active inclisiran arm (Table 1).

5.1.3. Packaging and Labeling

Investigational product (inclisiran for Injection and matching placebo) will be provided by the sponsor in a blinded fashion. All vials, inclisiran or placebo, will look identical. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

The Inclisiran for Injection (SC use) is packaged in a glass vial (vials contain 300 mg of inclisiran sodium [equivalent to 284 mg of inclisiran per 1.5 mL]). The container closure system consists of a Type I glass vial, a Teflon-faced bromobutyl 13 millimeter stopper, and a flip off Truedge aluminum seal. Each vial will have a yellow shroud over the vial to maintain the blind.

5.1.4. Storage

Investigational product will be stored at room temperature (up to 25°C [77°F]) as specified in the Pharmacy Manual. Access should be strictly limited to the investigator, pharmacists, and their designees. No special procedures are required for the safe handling of Inclisiran for Injection.

5.1.5. Accountability

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

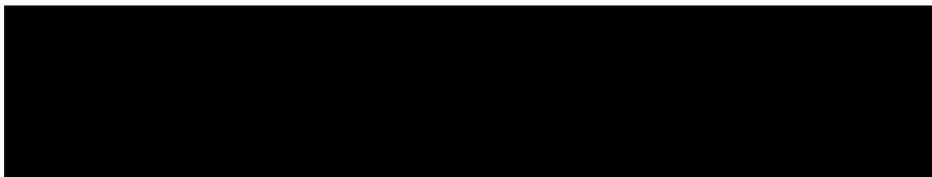
The investigational product supplied for use in this study is to be prescribed only by the Principal Investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

During the study, all used investigational product containers (eg, empty vials) will be kept until the monitor has reviewed the accountability records.

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

5.1.6. Product Complaints

Sites are required to report any product complaints to The Medicines Company (MDCO) immediately but no later than 24 hours from the time of awareness, by phone or e-mail as follows:



Product Complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, durability, reliability, quality, safety, effectiveness or performance of a product, after it is released for distribution (European Union [EU] DIR 2001/83/EC). (Derived from Ref United States [US] 21 CFR 211.198).

Technical Quality Complaint: A report of dissatisfaction with the product with regard to its efficacy, strength, integrity, purity, or quality; thus a potential failure to meet product specifications. Examples include:

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

5.2. Concomitant Medications

5.2.1. Prohibited Concomitant Medications

The following medications/treatments are not permitted to be added during the study:

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

5.2.2. Permitted Concomitant Medications

The following medications/treatments are permitted during the study:

- Hormone replacement therapy
- Lipid-lower medications; subjects already on a stable (≥ 30 days before screening) lipid-lower medications (such as statins and/or ezetimibe) should remain on the dose that they have received during participation in the original protocol unless clinically indicated

- Prescription medications prescribed to treat preexisting medical conditions such as diabetes and hypertension
- Prescription or nonprescription medications, when necessary to treat an AE, and at the discretion of the investigator

5.3. Medical Management Guidelines

5.3.1. Adverse events

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

5.3.2. Pregnancy

Pregnant women are excluded from the study. If a subject (or a study subject's partner) becomes pregnant during the course of the study, the investigational product administration must be discontinued and the pregnancy should be followed through to outcome. Follow-up evaluation of fetus and newborn should also be performed. Reporting of pregnancy and any associated AEs are specified in [Section 8.4.3.2](#).

5.4. Restrictions

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

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

5.5. Blinding

5.5.1. Blinding of study medications

This is a double-blind placebo-controlled study. Study medication will be blinded prior to distribution to the site. Each investigational product vial, inclisiran or placebo, will contain a yellow shroud to blind the vial.

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

5.5.2. Method and Maintenance of Blinding

Investigational product will be blinded prior to distribution to sites. All vials of investigational product (inclisiran/placebo) will contain a yellow shroud over the glass vial. In addition, all study sites will be provided a bulk supply of single use syringes that will be used to withdraw investigational product from the vial and to administer investigational product to randomized study subjects.

5.6. UNBLINDING

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

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

5.6.1. In the Event of an Emergency: Unblinding a Code

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

6. SCHEDULE AND SEQUENCE OF PROCEDURES

The Schedule of Assessments ([Table 2](#)) summarizes the study assessments by time point. This study consists of four periods: Screening, Randomization, Treatment, and End of Study.

- **Screening period (Days -14 to -1):** occurs prior to randomization and consists of confirming eligibility and collecting baseline assessments.
- **Randomization (Day 1):** occurs on the day of initial administration of investigational product.
- **Treatment period (Day 1 through Day 510):** occurs from the start of investigational product administration through the final clinic visit.
 - Dosing: Day 1, Day 90, Day 270, and Day 450 (final dose)
 - Additional clinic visits: Day 30, Day 150, Day 330, and Day 510
- **End of study (EOS) visit:** Day 540 (90 days after final dose)

The expected duration of a subject's participation in this study is approximately 554 days from screening/informed consent to the EOS, which occurs 90 days after the final dose of investigational product.

6.1. Schedule of Assessments

The schedule of assessments is provided in [Table 2](#).

Table 2: Schedule of Assessments

Visits	Screening	Randomization	Treatment							EOS ¹
		V1 (baseline)	V2	V3	V4	V5	V6	V7	V8	V9 (90 days post last dose)
Timelines	Day -14 to -1	Day 1	Day 30	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540
Visit windows (± days)			±2	±30	±30	±30	±30	±30	±14	±14
Informed consent	X									
Assessment of eligibility	X	X ²								
Demographics and medical history	X									
Pregnancy test	X ³	X ³		X ³		X ³		X ³	X ³	X ³
Randomization		X								
Investigational product administration		X ^{4,5}		X ^{4,5}		X ^{4,5}		X ^{4,5}		
Physical examination	X									X
Neurological examination		X								X
Weight/height/waist circumference	X ⁶									X
Vital signs ⁷	X	X		X		X		X		X
12-lead ECG	X	X								X
Fasted lipid profile/biomarkers ⁸	X	X		X	X	X	X	X	X	X
ADA		X ⁹	X ⁹	X ⁹						
Full Serum chemistry ¹⁰		X								X
Limited serum chemistry ¹⁰	X			X	X	X	X	X	X	
Urinalysis (local) ¹¹	X	X								X
Hematology and coagulation ¹²	X	X			X					X
Pharmacogenetic sample ¹³	X									
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X
AEs/SAE reporting	X	X	X	X	X	X	X	X	X	X

ADA=anti-drug antibodies; AE=adverse event; ECG=electrocardiogram; EOS=end of study; V=visit; SAE=serious adverse event

1. For subjects who decide to prematurely and permanently discontinue from study treatment and who decline further follow-up visits, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.
2. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
3. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test)

4. Subjects will be observed in the clinic for at least 4 hours following the first injection only (Randomization visit) and 30 minutes for each subsequent visit in order to have additional vital and/or laboratory assessments completed if needed.
5. For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as logically possible).
6. Height will be measured at baseline only and used to calculate body mass index.
7. On Day 1 vital signs will be measured prior to injection and 4 hours post injection; all other visits, vital signs will be measured only prior to injection. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit.
8. See [Section 7.2](#) for details of specific tests to be analyzed.
9. ADA serum samples will be collected on Day 1 prior to injection and 4 hours after injection. At all other visits, ADA serum samples will be collected prior to injection only, if an injection is scheduled for that visit. As presented in [Section 6](#), serum samples for analysis are collected at every visit but assessment of ADA will only occur for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. Samples will be stored for assessment (if needed) for samples collected at the following visits: Randomization (after injection), Day 90, Day 270, Day 450, End of Study Visit.
10. See [Section 7.1.8.3](#) for details of specific tests to be analyzed.
11. See [Section 7.1.8.5](#) for details of specific tests to be analyzed.
12. See [Section 7.1.8.1](#) and [Section 7.1.8.2](#) for details of specific tests to be analyzed.
13. Sample may be taken during screening or anytime during study to be processed and stored, but only after separate consent has been signed.

6.2. General Conduct of the Study

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

Please see the Schedule of Assessments ([Table 2](#)) for a detailed schedule and [Section 7](#) for details of all tests required in each panel.

6.3. Screening Period (Days –14 to –1)

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

The following procedures will be performed within 14 days prior to randomization:

- Informed consent
- Assessment of inclusion and exclusion criteria
- Demographics and medical history
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only)
- Physical examination (including height, weight, and waist circumference)
- Vital signs (blood pressure and heart rate) ([Section 7.1.3](#))
- 12-lead ECG
- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Central clinical laboratory (limited serum chemistry, hematology and coagulation) ([Section 7.1.8](#))
- Urinalysis (performed locally, using central laboratory supplies)
- Previous and concomitant medications
- AE/SAE reporting (beginning from time of consent)
- Pharmacogenetics (stored samples, only if separate consent has been signed) ([APPENDIX C](#))

Central laboratory blood draws should be performed after all other screening tests have been confirmed. Results must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria ([Section 4.2](#) and [Section 4.3](#)). Please refer to [Section 7.1.8](#) and [Section 7.2](#) for details of laboratory tests performed during the screening period.

6.4. Randomization

Randomization should only occur once subject eligibility is confirmed and will be conducted via an automated IRT to assign subjects to investigational product. All treatment groups will be studied concurrently. A total of 400 randomized subjects are planned for inclusion in the study: 200 subjects per group. Due to faster than expected enrollment, actual enrollment was 482 subjects.

The following procedures will be performed prior to the injection:

- Assessment of inclusion and exclusion criteria
- Pregnancy test (performed locally, using central laboratory supplies) (women of childbearing potential only)
- Randomization
- Neurological examination ([APPENDIX D](#))
- Vital signs: blood pressure and heart rate ([Section 7.1.3](#))
- 12-lead ECG
- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Central clinical laboratory (full serum chemistry, hematology and coagulation) ([Section 7.1.8](#))
- Urinalysis (performed locally, using central laboratory supplies)
- Assessment of ADA ([Section 7.1.8.8](#))

The following procedures will be performed after the injection:

- Vital signs: blood pressure and heart rate (4 hours after injection) ([Section 7.1.3](#))
- Collection and storage of serum samples for possible future use to detect the formation of ADA (4 hours after injection)
- Concomitant medications
- AE/SAE reporting

Investigational product administration will occur at this visit for all subjects as per [Section 5.1.1](#) and the Pharmacy Manual.

Subjects must be observed in the clinic for at least 4 hours after injection.

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

If a local reaction around the injection site occurs that requires the patient be seen between visits or if a reaction is noticeable on a subsequent visit, photographs of the injection site should be obtained at first presentation and at each of the follow-up visits until the injection site reaction resolves, if possible. Photographs should be submitted to the study inbox.

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

6.5. Day 30 Visit

Subjects will return to the clinic for a follow-up visit 30 days following the first dose of investigational product. The following assessment will be completed during this visit:

- Assessment of ADA ([Section 7.1.8.8](#))
- Concomitant medications
- AE/SAE reporting

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

Subjects will return on Day 90 for a second investigational product injection. Subsequent investigational product injections will be administered on Day 270 and Day 450.

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

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Vital signs: blood pressure and heart rate ([Section 7.1.3](#))
- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Collection and storage of serum samples for possible future use to detect the formation of ADA ([Section 7.1.8.8](#))
- Central clinical laboratory (limited serum chemistry) ([Section 7.1.8](#))
- Concomitant medication
- AE/SAE reporting

Administration of the investigational product is identical to Day 1 and is per [Section 5.1.1](#) and the Pharmacy Manual.

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

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

6.7. Additional NON DOSING Clinic Visits (Days 150, 330, and 510)

Subjects will return to the clinic for dosing follow-up visits 60 days following each dose of investigational product. The following assessments will be completed during these visits:

6.7.1. Day 150

- Fasting lipid profile/biomarkers ([Section 7.2](#))

- Assessment of ADA ([Section 7.1.8.8](#))
- Central clinical laboratory (limited serum chemistry and hematology and coagulation) ([Section 7.1.8](#))
- Concomitant medications
- AE/SAE reporting

6.7.2. Day 330

- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Assessment of ADA ([Section 7.1.8.8](#))
- Central clinical laboratory (limited serum chemistry) ([Section 7.1.8](#))
- Concomitant medications
- AE/SAE reporting

6.7.3. Day 510

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Assessment of ADA ([Section 7.1.8.8](#))
- Central clinical laboratory (limited serum chemistry) ([Section 7.1.8](#))
- Concomitant medications
- AE/SAE reporting

6.8. End of Study (EOS) Visit (Day 540 – 90 days post last dose)

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

- Pregnancy test (performed locally, using central laboratory supplies, if applicable) (women of childbearing potential only)
- Physical examination (including weight and waist circumference)
- Neurological examination ([APPENDIX D](#))
- Vital signs: blood pressure and heart rate ([Section 7.1.3](#))
- 12-lead ECG
- Fasting lipid profile/biomarkers ([Section 7.2](#))
- Collection and storage of serum samples for possible future use to detect the formation of ADA ([Section 7.1.8.8](#))

- Central clinical laboratory (full serum chemistry, hematology and coagulation) ([Section 7.1.8](#))
- Urinalysis (performed locally, using central laboratory supplies)
- Concomitant medication
- AE/SAE reporting
- All ongoing SAEs have been followed to resolution ([Section 8.4.1](#))

7. PROTOCOL ASSESSMENTS

7.1. Assessment of Safety

7.1.1. Adverse Events

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

7.1.2. Demographics and Medical History

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

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

7.1.3. Vital Signs

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

7.1.4. Physical Examination

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

7.1.5. Neurological Evaluation

A full neurological examination ([APPENDIX D](#)) will be performed as per the Schedule of Assessment ([Table 2](#)).

7.1.6. Electrocardiograms

Twelve lead ECGs will be collected at the time points in the Schedule of Assessments ([Table 2](#)) only, unless clinically indicated.

7.1.7. Cardiovascular Events

Information on CV events such as CV death, resuscitated cardiac arrest, non-fatal MI, and non-fatal stroke (ischemic and hemorrhagic) will be collected as AE data.

7.1.8. Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments ([Table 2](#)).

Subjects will be in a fasted state for all clinical laboratory assessments. Screening laboratory tests will be performed by the Central Laboratory, with the exception of urinalysis and pregnancy test, which will be done in-house at the participating institution's laboratory using

testing materials supplied by the Central Laboratory. Results from these screening tests related to eligibility must be available before the start of investigational product injection on Day 1 to confirm subjects meet eligibility criteria. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual. Note: Efficacy laboratory assessments (eg, LDL-C and PCSK9) are described in [Section 7.2](#).

7.1.8.1. Hematology

Blood draws for hematology will include:

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

7.1.8.2. Coagulation

Blood draws for coagulation will include:

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

7.1.8.3. Chemistry

Blood draws for chemistry will be performed per the Schedule of Assessments ([Table 2](#)). Analysis will vary based on visit day as follows:

- **Full serum chemistry - Baseline (Day 1) and EOS (Day 540)**
AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, urea (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), glycated hemoglobin A1C (HbA1C), and tryptase (as required).
- **Limited serum chemistry - Screening, Days 90, 150, 270, 330, 450 and 510**
ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, fasting glucose, HbA1C (not at Day 150, 330 and 510) and tryptase (as required).

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

The hsCRP is performed routinely for safety throughout the study and is part of the central laboratory draws.

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

7.1.8.5. Urinalysis

Urinalysis will be performed at the time points defined in the Schedule of Assessments (Table 2) and evaluated by dipstick analyses at the investigational site (a standardized dipstick test will be supplied by the Central Laboratory). Urinalysis will be performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

The following parameters will be assessed:

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

7.1.8.6. Urine Pregnancy

Urine pregnancy testing will be performed locally at the visits specified in the Schedule of Assessments (Table 2), using the supplies provided by the Central Laboratory.

7.1.8.7. Lipids / Lipoproteins

Lipids and lipoproteins assessments are described in Section 7.2.

7.1.8.8. Anti-drug Antibodies

A serum sample for analysis of the induction of antibodies will be collected at the time points in the Schedule of Assessments (Table 2). Collection will be prior to and 4 hours after first investigational product administration (injection) and then as per the Schedule of Assessments. As presented in Section 6, serum samples for analysis are collected at every visit but assessment of ADA will only occur for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. Samples will be stored for assessment (if needed) for samples collected at the following visits: Randomization (after injection), Day 90, Day 270, Day 450, End of Study Visit.

7.1.9. Stored samples

The central laboratory will take aliquots of serum and plasma samples from the received routine blood sampling noted above and will store these as frozen samples to permit future analysis of the effect of inclisiran on the expression of these exploratory biomarkers. Analyses may include markers of CV risk (eg, hsCRP, IL6, P-selectin, Lp-PLA2, adiponectin). Biological samples for biomarker research will be retained on behalf of the Sponsor for a maximum of 1 year following the last subject's last visit in the study. Details regarding the collection, processing, storage, and shipping will be in the Study Laboratory Manual.

7.2. Assessment of Efficacy

Subjects will be in a fasted state for all efficacy laboratory assessments of lipids/lipoproteins/biomarkers. Specimens will be obtained at the time points in the Schedule of Assessments (Table 2). Parameters to be assessed will include:

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

7.2.1. Change from Day 1 in LDL-C

The primary efficacy endpoints are the percentage change in LDL-C from baseline to Day 510, and the time adjusted percent change in LDL-C from baseline after Day 90 and up to Day 540.

In addition, this study will assess:

- Absolute change in LDL-C from baseline to Day 510
- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, 70 mg/dL, and <100 mg/dL at Day 510
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline

Blood samples for determination of LDL-C concentrations will be collected at the time points in the Schedule of Assessments (Table 2). Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

7.2.2. Change from Day 1 in Lipids/Lipoproteins

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

Additional aliquots of plasma and serum will be collected at each time point and stored for additional analyses, including future analysis of biomarkers of CV risk.

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

7.3. Assessment of Pharmacodynamics

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

7.4. Assessment of Pharmacogenetics

All subjects will be invited to consent to pharmacogenetic analyses, unless underlying causal mutations of HeFH are well documented by a validated specialized laboratory.

A blood sample will be collected, preferably during screening, only from subjects who sign a separate consent for pharmacogenetics. Samples will be processed as described in the Laboratory Manual and stored. Genetic assessment will be performed by an accredited laboratory. This assessment will determine if there is a different response for LDL-C lowering based on the type of mutation(s).

8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Event

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

8.1.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

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

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

8.1.3. Special Situations

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

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

8.2. Collection and Assessment of Adverse Events

8.2.1. Pre-existing Conditions

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

8.2.2. Adverse Event Severity

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

- 1 = Mild: Discomfort noticed, but no disruption to daily activity.
- 2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- 3 = Severe: Inability to work or perform normal daily activity.

8.2.3. Relationship to Investigational Product

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

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

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

8.3. Requirements For Additional Safety Data Collection

8.3.1. Special Situations

Special Situations designated for this study include:

- Medication errors that fall into the following categories
 - wrong investigational product
 - wrong dose (including overdose, underdose, change in dosing regimen, strength, form concentration, amount)

- wrong route of administration
- wrong subject (ie, not administered to the intended subject)
- accidental exposure
- Pregnancy/lactation exposures with or without any AEs related to the parent or child
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions

8.3.2. Other safety related information

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

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

- Abnormal neurological examination, eg, peripheral sensory and motor evaluation, an assessment of gait, pain, position, strength and reflexes ([APPENDIX D](#)).
- Potential anaphylactic reactions assessed by Sampson criteria ([APPENDIX E](#)). If Sampson criteria are positive, confirm by elevation of tryptase in blood plasma measured within 30 minutes of symptoms.
- Hyperglycemia-related AEs:
 - Report ‘New onset of diabetes’ in subjects with no medical history of diabetes when:
 - HbA1C becomes $\geq 6.5\%$ and/or
 - Two consecutive values of fasting plasma glucose that are ≥ 126 mg/dL
 - If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected.

Report ‘Worsening of the glycemic control’ or ‘diabetic complications’ in subjects with a medical history of disease (HbA1C $\geq 6.5\%$ at baseline) when:

- HbA1C increases from baseline $> 0.5\%$ and/or
- New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

8.4. Procedure for Adverse Event Reporting

8.4.1. Serious Adverse Events (SAEs)

All SAEs that occur during the designated study period from consent through EOS must be reported to MDCO GPV Department within 24 hours of awareness of the event using the

provided study specific SAE Report Form. Each SAE must also be recorded on the source documents and on the appropriate page of the eCRF.

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

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

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

8.4.2. Non-Serious AEs

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

8.4.3. Special situations

8.4.3.1. Medication Errors

Medication errors with or without an associated AE should be recorded as medication errors in the eCRF.

Medication errors and an associated SAE should be recorded in the eCRF and also reported to MDCO GPV Department as described in [Section 8.4.1](#).

Medication errors and an associated non-serious AE should be recorded in the eCRF as described in [Section 8.4.2](#).

A mis-dosing protocol deviation ([Section 12.3](#)) should be reported as a medication error if it was an “unintended error”.

8.4.3.2. Pregnancy/Lactation Exposure

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

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

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

8.5. Expectedness

8.5.1. Expectedness Determination

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

8.6. Study Stopping Criteria

8.6.1. Independent Data Monitoring Committee (IDMC) Stopping Rules

The IDMC will use all available evidence and its collective judgment in making a recommendation to stop or modify the ORION-9 study for safety. Any statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise. Details will be provided in the IDMC charter.

8.6.2. Sponsor Discontinuation Stopping Criteria

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

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

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

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

9. DATA COLLECTION

An electronic data capture (EDC) system which is 21 CFR Part 11 compliant will be used for this study. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A UserID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site 3 days after each visit. It is not expected that the eCRF will serve as source for any data collected in this study. If there is a reason for a site to do so, it must be approved by Sponsor and documented in the site files.

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

10. STATISTICAL PLAN

This study will be a Phase III, placebo-controlled, double-blind, randomized study in 400 subjects with HeFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of inclisiran injection(s). The study will be a multicenter, international study. A separate Statistical Analysis Plan (SAP) document will provide more detailed specifications in data analysis and presentation.

10.1. Sample Size

The sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL.

Assuming about a 5% drop out rate, the sample size will be approximately 380 subjects that are evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 380 evaluable subjects, will provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025. Due to faster than expected enrollment, actual enrollment was 482 subjects. This increased sample size will contribute additional safety data and not appreciably affect power calculations.

10.2. RANDOMIZATION

Subjects will be screened and approximately 400 eligible subjects will be randomized by the IRT system: 200 subjects will be randomized to inclisiran sodium 300 mg and 200 subjects randomized to placebo. Due to faster than expected enrollment, actual enrollment was 482 subjects. Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will receive four subcutaneous (SC) injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450.

10.3. General Statistical Considerations and Definitions

10.3.1. General Statistical Methods

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

10.3.2. Analysis Population

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

10.3.2.1. Intent-to-Treat (ITT) Population

All subjects randomized into the study will comprise the intent-to-treat (ITT) population. Treatment classification will be based on the randomized treatment. The ITT population will be used for analysis of the primary and secondary endpoints.

10.3.2.2. Full Analysis Set (FAS)

All subjects who are randomized into the study, take any study medication and have at least one post treatment lipid data measured. Treatment classification will be based on the randomized treatment.

10.3.2.3. Modified Intent-to-Treat (mITT) Population

All randomized subjects who receive at least one dose of investigational product and have both the baseline and the 510 day follow-up LDL-C assessment will comprise the modified intent-to-treat (mITT) population. Treatment classification will be based on the randomized treatment.

10.3.2.4. Safety Population

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

10.3.3. Analysis Windows and Baseline

The observational period for the study includes the screening period (Day -14 to Day -1), the treatment period (Day 1 to Day 510), and the EOS visit (Day 540). Any event occurring beyond the defined observational period, even if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

Analysis windows will be defined to maximize the amount of data that are included in the analysis models. Full details will be provided in the SAP.

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

10.3.4. Missing Data Handling

Primary and key secondary efficacy endpoints will have missing data imputed using multiple imputation techniques (a primary method and sensitivity/exploratory methods). The primary imputation method will utilize a washout model for subjects in the inclisiran arm where it will be assumed that early terminating inclisiran sodium 300 mg subjects have missing data after their last observed assessment (monotone missing data) return to baseline values. The baseline values will be randomly sampled from a population estimated using baseline data from all subjects. One sensitivity technique includes control-based pattern mixture models which utilize placebo data for monotone missing inclisiran sodium 300 mg treatment data. Additional sensitivity data imputation techniques will be utilized. Retrieved data will be

utilized in all analyses where possible. Full details, including how intermittent missing data and missing placebo data will be handled, will be provided in the SAP.

Unless otherwise specified, other missing data will not be imputed.

10.4. Statistical Analyses

10.4.1. Demographic and Background Characteristics

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

10.4.2. Investigational Product and Concomitant Medications

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

10.4.3. Efficacy Analysis

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

10.4.3.1. Primary Efficacy Endpoints

The primary efficacy endpoints are described in [Section 3.3](#).

The family-wise type I error rate is controlled at one-sided significance level of $\alpha=0.025$ by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 will be tested first. If the null hypothesis is rejected at one-sided significance level of $\alpha=0.025$ and superiority of inclisiran over placebo is claimed, then the time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 will be tested, also at one-sided significance level of $\alpha=0.025$.

Mixed-effect models for repeated measures (MMRM) will be performed on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo. The model will include fixed effect for treatment, visits, baseline value, interaction between treatment and visits, and current use of statins or other lipid-modifying therapies. The Restricted Maximum Likelihood (REML) estimation approach will be used with covariance structure set as “Unstructured”. Missing data will be imputed using a multiple imputation washout model as noted in [Section 10.3.4](#). A total of 100 imputed datasets will be created and results will be combined using Rubin’s method. Full details on the model and imputation will be provided in the SAP.

The time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 will be calculated from the MMRM with imputed data discussed above. Linear combinations of the estimated means after Day 90 and up to Day 540 will be used to

compare treatments. Results will be combined using Rubin's method. Full details will be provided in the SAP.

10.4.3.1.1. Sensitivity Analysis for Primary Efficacy Endpoints

As noted in [Section 10.3.4](#), additional methods to impute and analyze data will be utilized as sensitivity/exploratory analyses for the co-primary endpoints. A MMRM without any imputation (assuming data are missing at random) will also be performed.

10.4.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will not be tested if either one of the co-primary efficacy endpoints' null hypothesis failed to be rejected.

Key secondary and other efficacy endpoints are described in [Section 3.4](#).

Key Secondary Endpoint Analysis: The Hochberg procedure will be applied to control the family-wise type I error rate at one-sided significance level of $\alpha=0.025$ for the key secondary endpoints. The key secondary endpoints will be analyzed using the same methods as in the primary efficacy analysis.

The two-sided 95% confidence interval for least squares means will be provided for continuous variables. Odds ratio and 95% confidence interval for the odds ratio will be provided for binary variables. Nominal p-values will be provided when applicable.

Descriptive and graphical summaries by treatment group will also be presented.

10.4.3.3. Exploratory Endpoints

The exploratory objectives are described in [Section 3.5](#).

The analysis of the exploratory endpoints will be similar to that of the secondary endpoints.

10.4.4. Safety Analysis

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

10.4.4.1. Adverse Events

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

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

10.4.4.2. Laboratory Tests

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

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

10.4.4.3. Vital Signs

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

10.4.4.4. Neurological Examinations

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

10.4.4.5. Pharmacodynamic Parameters

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

10.5. Interim Analysis

No interim analysis will be performed in this study.

10.5.1. Interim Safety Reviews

The independent Data Monitoring Committee (IDMC) will review safety data 90 days after the first 40 subjects receive the first injection of inclisiran or placebo. Thereafter the IDMC will review safety data every 3 months until the EOS unless requested otherwise by the IDMC. A recommendation may be taken to stop or amend the study at any of these reviews.

11. RECORDS RETENTION

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

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

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

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

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

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

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

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

12.2. Auditing

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

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

12.3. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. The investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures.

In an effort to minimize deviations and missing data, the investigator and pertinent study staff will be trained on the operational aspects of implementing the study protocol and all required procedure by the sponsor/sponsor representatives. These trainings occur either as part of an Investigator Meeting or Site Initiation Visit. Retraining will occur at subsequent interim site monitoring visits as needed.

The following Protocol Deviations will require additional information in the eCRF explaining why the deviation occurred and what will be done to prevent it from re-occurring:

- Inclusion criteria violation
- Exclusion criteria violation
- Laboratory assessments not drawn at Day 1, Day 510 or Day 540 (EOS) visits
- Mis-Dosing for any reason other than subject safety or withdrawal (defined as missing dose or a dose delayed by more than 30 days)*
- Subject taking any prohibited concomitant medication
- Change in baseline statin or other lipid-lowering therapy dose
- SAEs not reported to MDCO within 24 hours
- Informed Consent not signed prior to study entry

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

13. ETHICS AND RESPONSIBILITY

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

13.1. Informed Consent

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

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

13.2. Institutional Review Board/Ethics Committee

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

14. CONFIDENTIALITY

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

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

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

15. INVESTIGATOR AGREEMENT

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

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

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

Principal Investigator (Signature)

Date

Principal Investigator (Printed Name)

Protocol Version: Global
Amendment 4

Institution Name

16. REFERENCES

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APPENDIX A: SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

Definite Familial Hypercholesterolemia:

Required laboratory = high cholesterol levels:

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

Plus at least one of the two:

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

OR

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

Possible Familial Hypercholesterolemia:

Laboratory – high cholesterol levels:

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

Plus at least one of the two:

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

OR

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

Source: Austin, et al, 2004.

APPENDIX B: REQUIREMENTS FOR BACKGROUND LIPID LOWERING TREATMENT

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

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

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

Background lipid lowering treatment exceptions

The following background lipid lowering treatment exceptions are permitted:

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

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

2. Regulatory limitations:

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

3. Alternative statins:

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

4. No background statin therapy:

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

APPENDIX C: GENETIC INFORMED CONSENT

Purpose and Selection of subjects:

The purpose of the genetic test is to confirm the subject's diagnosis of HeFH and to assess the response of inclisiran on LDL-C reduction by underlying causal mutations of HeFH. The genetic research analysis is an optional test that will be offered to all patients.

Specimen collection:

For subjects that agree to participate, a blood sample will be taken at any visit throughout the study and the Central lab will utilize a validated, next generation sequencing pipeline to analyze DNA for variants in four genes (LDLR, APOB, PCSK9, and LDLRAP1) that are associated with familial hypercholesterolemia to confirm the subject has HeFH.

Blood samples taken for this optional research will not be used for any additional study or purpose and be destroyed one year after the main study is complete. A single-coded system will be used for all blood samples during the study and will be taken without using names of the subjects, medical record numbers, or other common identifiers that would allow for the linking of the code to the subject's identity. The blood sample for the genetic research analysis will be labeled with the same code number.

Results:

Currently, the information obtained from the genetic testing does not contain clinical or therapeutic implications for the individual subject. Results will only be reported to the attending physician, Sponsor, and patient (if requested). No additional follow up beyond what is required in the main study is required.

Withdraw of consent:

A subject can withdraw their consent for participation in this optional portion of the study at any time. If consent is withdrawn when the blood sample has been taken but before it is sent for genetic research analysis, the study doctor will arrange to have it destroyed. If consent is withdrawn after the blood sample has been sent for genetic research analysis, The Medicines Company and the study doctor will ensure that the blood sample and any DNA that has been extracted from it are destroyed. If consent is withdrawn after the genetic research analysis has already been performed, The Medicines Company is not obliged to destroy the results of this research. In this case only the blood sample and any DNA extracted will be destroyed.

APPENDIX D: RECOMMENDED NEUROLOGICAL EXAMINATION

MOTOR FUNCTION

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

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

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

Assessment of a Conscious Patient

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

Grade Strength

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

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

Lower Extremities

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

Upper Extremities

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

Assessment of an Unconscious Patient

Upper Extremities

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

Lower Extremities

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

SENSORY FUNCTION

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

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

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

Sensory Tests:

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

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

TONE and REFLEXES

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

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

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

Reflex responses:

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

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

Biceps Reflex (C5 – C6):

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

Triceps Reflex (C7-C8):

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

Brachioradialis Reflex (C5-C6):

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

Quadriceps Reflex (Knee jerk) L2 – L4:

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

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

Achilles Reflex (ankle jerks) L5 – S2:

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

Heel Lift:

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

Babinski Response:

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

CEREBELLAR FUNCTION

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

1. Finger to finger test: have the patient touch their index finger to your index finger (repeat several times).
2. Finger to nose test: perform with eyes open and then eyes closed.
3. Tandem walking: heel to toe on a straight line.

4. Romberg test: stand with feet together and arms at their sides. Have patient close his/her eyes and maintain this position for 10 seconds. If the patient begins to sway, have them open their eyes. If swaying continues, the test is “positive” or suggestive of cerebellum problems.

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

APPENDIX E: SAMPSON CRITERIA FOR DIAGNOSING ANAPHYLAXIS

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

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

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

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