

Investigational New Drug

**ALN-PCSSC**

**A PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED TRIAL TO COMPARE THE EFFECT OF DIFFERENT DOSES OF ALN-PCSSC GIVEN AS SINGLE OR MULTIPLE SUBCUTANEOUS INJECTIONS IN SUBJECTS WITH HIGH CARDIOVASCULAR RISK AND ELEVATED LDL-C**

**Protocol No.: MDCO-PCS-15-01**

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PROTOCOL VERSION: Amendment 03: 12 Apr 2016

Amendment to Protocol Amendment 02: 22 Mar 2016

Drug Development Phase:	II
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Issue Date:	<b>12 April 2016</b>

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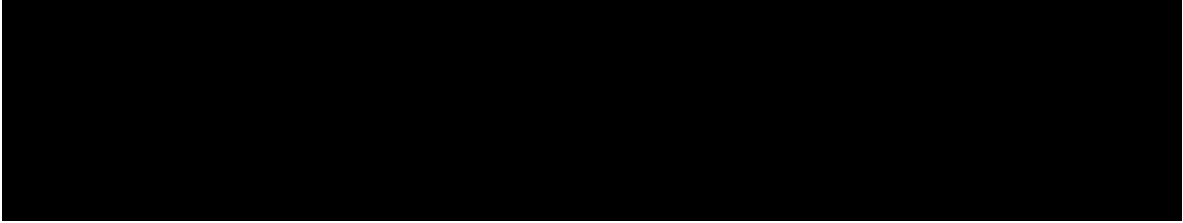
**This study will be conducted in compliance with Good Clinical Practice (GCP) and protection of the subject as required by the regulations and directives in operation at this time.**

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## PROCEDURES IN CASE OF EMERGENCY

### Emergency Contact Information

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## PROTOCOL SYNOPSIS

<b>Name of Sponsor/Company:</b> The Medicines Company
<b>Name of Finished Product:</b> ALN-PCSSC
<b>Name of Active Ingredient:</b> ALN-PCSSC is a synthetic, chemically modified small interfering ribonucleic acid (siRNA) targeting proprotein convertase subtilisin kexin type 9 (PCSK9) messenger ribonucleic acid (mRNA [ALN-60212]) with a covalently attached triantennary N-acetylgalactosamine (GalNAc) ligand. The investigational product (ALN-PCSSC) will be administered by subcutaneous (SC) injection as a formulation of ALN-60212. It will be supplied as a sterile 100 mg vial (200 mg/mL solution) for SC injection.
<b>Title of Study:</b> A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of ALN-PCSSC given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated low-density lipoprotein cholesterol (LDL-C).
<b>Phase of Development:</b> II
<b>Study Centers:</b> Multi-center study in North America and Europe [REDACTED]
<b>Principal Investigator:</b> [REDACTED]
<b>Study Period:</b> The estimated study period for the study will be 17 to 18 months from first subject enrolled in the study to last subject completed.
<b>Objectives:</b> <u>Primary:</u> <ul style="list-style-type: none"><li>To evaluate the effect of ALN-PCSSC treatment on LDL-C levels at Day 180.</li></ul> <u>Secondary:</u> <ul style="list-style-type: none"><li>To evaluate the effect of ALN-PCSSC on the following:<ul style="list-style-type: none"><li>LDL-C levels at Day 90</li><li>LDL-C levels at other time points</li><li>PCSK9 levels over time</li><li>Other lipids, lipoproteins, apolipoproteins</li><li>Proportion of subjects achieving prespecified global lipid guidelines</li><li>Individual responsiveness to different doses</li><li>Duration of lipid-lowering effect of different doses</li><li>Safety and tolerability profile of ALN-PCSSC</li></ul></li></ul> <u>Exploratory:</u> <ul style="list-style-type: none"><li>To collect/evaluate the effect of ALN-PCSSC on the following:<ul style="list-style-type: none"><li>Cardiovascular (CV) events such as CV death, non-fatal myocardial infarction (MI), resuscitated cardiac arrest, and non-fatal stroke (ischemic and hemorrhagic)</li><li>Evaluation of anti-drug antibodies (ADA) for the investigational product</li></ul></li></ul>
<b>Methodology:</b> This study will be a Phase II, placebo-controlled, double-blind, randomized trial in 480 subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of ALN-PCSSC injection(s). Subjects will be screened and 480 eligible subjects will be randomized: 60 subjects per each of six ALN-PCSSC dose groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six drug dose groups). Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will either receive either one or two injections on Day 1 only or a single injection on Day 1 and a second injection on Day 90 of blinded ALN-PCSSC or placebo.

Formation of ADA will be assessed on Day 1 (prior to and 4 hours after the injection) and on Days 30, 60, 90, 120, 150, 180 (Days 150 and 180 only in subjects who receive a second dose of study drug), and 210 or until any ADA response becomes negative within the study duration. For subjects in whom LDL-C levels have not returned to >80% of baseline values, formation of ADA will also be assessed either when LDL-C has returned to normal limits or at the 1-year follow-up visit.

The independent Data Monitoring Committee (DMC) will review safety data beginning after the first 40 subjects receive the first injection of ALN-PCSSC or placebo and complete the Day 14 follow-up visit. Thereafter the DMC will review safety data every 2 months until the end of the trial. A recommendation may be taken to stop or amend the study at any of these reviews.

On Day 1, all eligible subjects will be randomized and receive the first SC administration of ALN-PCSSC or placebo. After first study drug administration, the subject will be observed in the clinic for at least 4 hours post injection before being discharged. Subjects will return at Day 14 and Day 30 and then at monthly intervals for 6 months. Subjects randomized to receive a second dose of study drug will receive the second injection of ALN-PCSSC or placebo at the Day 90 visit and will have an extra visit on Day 104 (14 days after the second dose on Day 90).

Efficacy assessments will include the measure the effects of ALN-PCSSC on levels of LDL-C lipids and lipoproteins including total cholesterol, triglycerides, high-density lipoprotein cholesterol (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.

End of study (EOS) evaluations will be conducted at the EOS visit (Day 210).

Subjects whose LDL-C levels have returned to baseline levels and who have completed the study to Day 210 will be given the opportunity to enroll in a separate long-term extension study to collect long-term efficacy and safety data.

Any subjects in whom LDL-C levels have not returned to >80% of baseline values will continue to be followed as part of this study until either this level has been reached or until a maximum of Day 360 at which point they will be given the opportunity to enroll in the long-term extension study. At each visit, LDL-C levels, adverse events (AEs), serious adverse events (SAEs), concomitant medications, and safety laboratory assessments will be collected.

**Number of Subjects:** 480 planned; at least 400 evaluable

**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  $\geq 18$  years of age.
2. History of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia, including subjects whose 10-year risk of a cardiovascular [CV] event assessed by Framingham Risk Score\* or equivalent has a target LDL-C of < 100 mg/dL).
3. Serum LDL-C  $\geq 1.8$  mmol/L ( $\geq 70$  mg/dL) for ASCVD subjects or  $\geq 2.6$  mmol/L ( $\geq 100$  mg/dL) for ASCVD-risk equivalent subjects at screening.
4. Fasting triglyceride < 4.52 mmol/L (< 400 mg/dL) at screening.
5. Calculated glomerular filtration rate > 30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology.
6. Subjects on statins should be receiving a maximally tolerated dose (investigator's discretion).
7. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for  $\geq 30$  days before screening with no planned medication or dose change during study participation.
8. Willing and able to give informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

\*By Framingham Risk Score > 20%

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 II, III or IV heart failure or last known left ventricular ejection fraction <30%.
4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
5. Any history of hemorrhagic stroke.
6. Major adverse cardiac event within 6 months prior to randomization.
7. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
8. Poorly controlled Type 2 diabetes, ie, glycated hemoglobin A1c (HbA1c) >10.0% prior to randomization.
9. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained alanine aminotransferase (ALT), aspartate aminotransferase (AST), elevation >2x the upper limit of normal (ULN), or total bilirubin elevation >1.5x ULN at screening confirmed by a repeat measurement at least 1 week apart.
10. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses). This includes all cancers with the exception of treated basal-cell carcinoma occurring >5 years before screening.
11. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation)\*\*. Women who are >2 years postmenopausal defined as  $\geq 1$  year since last menstrual period AND if <55 years old with a negative pregnancy test within 24 hours of randomization or surgically sterile are exempt from this exclusion.
12. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
13. Known history of alcohol and/or drug abuse with the last 5 years.
14. Treatment with other investigational medicinal products or devices within 30 days or five half-lives, whichever is longer.
15. Use of other investigational medicinal products or devices during the course of the study.
16. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
  - a. Inappropriate for this study, including 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. Involved with, or a relative of, someone directly involved in the conduct of the study.
  - f. Any known cognitive impairment (eg, Alzheimer's disease).
17. Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

\*\*For the entire duration of the study

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

**Test Product, Dose and Mode of Administration:** ALN-PCSSC will be administered as either a single SC injection (doses: 200 mg, 300 mg), or two injections (dose: 500 mg) on Day 1 or two SC injections (doses: 100 mg, 200 mg, or 300 mg) on Day 1 and Day 90.

**Duration of Treatment:** The expected duration of the subjects' involvement in the study will be approximately 224 days which includes screening, study drug administration, the course of single or multiple injections, and the follow-up period to Day 210; if additional follow-up is necessary, the expected maximum duration of involvement in the study will be 374 days.

Single Dose (one or two injections on Day 1):

- Screening: Day -14 to -1
- Randomization, initiation of study drug: Day 1
- Treatment Phase: Day 1
- Follow-up:
  - Follow-up: Days 2 to 210; EOS on Day 210
  - Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values; subjects will return each month for follow-up until this level has been reached or until Day 360): Days 240, 270, 300, 330, and 360

Two Doses (one injection each on Day 1 and Day 90):

- Screening: Day -14 to -1
- Randomization, initiation of study drug: Day 1
- Treatment Phase: Day 1 to Day 90
- Follow-up:
  - Follow-up: Days 91 to 210; EOS on Day 210
  - Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values; subjects will return each month for follow-up until this level has been reached or until Day 360): Days 240, 270, 300, 330, and 360

**Reference Therapy, Dose, and Mode of Administration:** Placebo will be administered as either one or two SC injections of saline solution. Placebo volume will be matched to test product volume within each dose and injection regimen but not between injection regimens. For example, the placebo group for the 200 mg dose will receive 1.0 mL of placebo whereas the placebo group for the 300 mg dose will receive 1.5 mL of placebo.

**Criteria for Evaluation:**

**Efficacy:**

Primary Endpoint:

- Percentage change in LDL-C from baseline to Day 180

Secondary Endpoints:

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 104, 120, 150, and 210
- Proportion of subjects in each group with LDL-C greater than 80% of the baseline value at Day 180 and Day 210
- Duration of time on treatment for subjects to return to 80% of baseline or greater LDL-C or PCSK9 protein
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of

<25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 90, 120, and 180

- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at Days 90, 120, and 180
- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, 180, and 210
- Percentage change in other lipids, lipoproteins, apolipoproteins, from baseline at each subsequent visit to Day 210
- Proportion of subjects in each group who attain global lipid modification targets for their level of ASCVD risk

**Safety:** AEs, 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 210). AEs, SAEs, and clinical laboratory values will continue to be assessed during the additional monthly follow-up visits (for subjects in whom LDL-C levels have not returned to >80% of baseline values). Cardiovascular events will be reported as AEs for the compilation of information on CV events such as CV death, non-fatal MI, resuscitated cardiac arrest, and non-fatal stroke (ischemic and hemorrhagic). In addition, 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 I trial) that the difference in change from baseline between the active dose groups and the placebo group for LDL-C will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL, using a Dunnett multiple t-test procedure for six comparisons.

Assuming about a 15% drop out rate, the sample size will be approximately 100 evaluable subjects total across the placebo groups and approximately 50 subjects in each of six ALN-PCSSC dose groups. This sample size of at least 400 evaluable subjects will provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one ALN-PCSSC dose group.

Primary Endpoint Analysis:

Two sample t-tests will be performed to test the superiority of any dosing group over placebo. A Dunnett multiple t-test procedure will be applied to adjust for multiple comparisons with six different dosing regimens.

Secondary and Exploratory Endpoint Analysis:

The analysis of the secondary and exploratory endpoints will be descriptive.

Interim Analysis:

An interim analysis of lipids and PCSK9, unblinded by dose cohort only, will be prepared upon completion of Day 90 by the Statistical Reporting Organization. The interim analysis will be performed for all subjects completing Day 90 and these data will be used to help select the ALN-PCSSC dose for subsequent clinical trials.

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## LIST OF ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
AESIs	Adverse Events of Special Interest
ALT	alanine aminotransferase
Apo-A1	apolipoprotein A1
Apo-B	apolipoprotein B
aPTT	activated partial thromboplastin
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BUN	total protein urea
CHD	coronary heart disease
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
dL	Deciliter(s)
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPV	Global Pharmacovigilance Department
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN- $\gamma$	interferon-gamma
IL6	interleukin 6
INR	International normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat

IWRS	Interactive web response system
Kg	kilogram(s)
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LNP	lipid nanoparticles
Lp(a)	lipoprotein a
MD	multiple dose
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	myocardial infarction
mITT	Modified intent-to-treat
mL	milliliter(s)
mm	millimeter(s)
mmHg	millimeters of mercury
mmol	Millimole
mRNA	messenger ribonucleic acid
NA	not applicable
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
PCSK9	proprotein convertase subtilisin/kexin type 9
PEF	peak expiratory flow
pH	$-\log[H^+]$
pM	picomolar
PP	per protocol
PT	protrombin time
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAD	single ascending dose
SAE	serious adverse event
SC	Subcutaneous
siRNA	small interfering ribonucleic acid
TEAE	treatment emergent adverse event
TNF- $\alpha$	tumor necrosis factor-alpha
TTR	Target transthyretin
ULN	upper limit of normal
US	United States
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood count
WHO	World Health Organization

## 1. INTRODUCTION

This protocol describes a study to evaluate the effect of ALN-PCSSC treatment on low-density lipoprotein cholesterol (LDL-C) levels at Day 180. 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

According to the World Health Organization (WHO), atherosclerotic cardiovascular disease (ASCVD), comprised mainly of coronary heart disease (CHD) and stroke, is the leading cause of death worldwide, resulting in 17 million deaths annually [WHO Cardiovascular Statistics, 2011]. Data from the INTERHEART case-control study estimates that 45% of myocardial infarctions (MI) in Western Europe and 35% of myocardial infarctions in Central and Eastern Europe are due to abnormalities in blood lipids [Yusef et al, 2004]. In particular, elevated LDL-C, has been shown in multiple studies to be one of the major risk factors for CHD with a continuous and graded relationship between plasma LDL-C concentration and CHD risk. For every 30 mg/dL (0.78 mmol/L) change in LDL-C, the relative risk for CHD changes by approximately 30% [Grundy et al, 2004]. In addition a large meta-analysis of 21 statin studies concluded that for every 1 mmol/L (39 mg/dL) reduction in LDL-C (with statin therapy) there is an approximate 22% reduction in cardiovascular events [CTT et al, 2010]. While statins are the treatment of choice for hyperlipidemia and the primary and secondary prevention of ASCVD there is still a need for additional lipid-lowering therapies for patients who do not reach target LDL-C levels or sufficient percent reductions in LDL-C to attenuate their ASCVD risk. Furthermore, in many patients, statin therapy cannot be optimized as patients are either intolerant of statins due to side effects (most commonly muscle pain, myopathy myositis) or because of other adverse effects such as elevations in liver enzymes. These limitations of contemporary therapy are particularly relevant among patients with pre-existing ASCVD such as diabetes, or patients with familial hypercholesterolemia who are at the highest risk of future cardiovascular (CV) events, and hence require the most intensive and aggressive management of hypercholesterolemia [Davidson et al, 2005; Nag et al, 2007; Reiner et al, 2011; Stone et al, 2014]. Among these high-risk subjects, less than 50% achieved the target LDL-C goal of <100 mg/dL at 6 months post-statin treatment despite close monitoring and drug regimen optimization [Foley et al, 2003; Kearney et al, 2008; CTT et al, 2010; Foody et al, 2010]. Thus, there remains a clear unmet medical need for lowering LDL-C, especially in certain patient populations.

#### 1.1.2. PCSK9 Biology and Target Rationale

Proprotein convertase subtilisin kexin type 9 (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  $\leq 20$  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 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]. Thus, the overall scientific and clinical data suggests that PCSK9 is a well-validated drug target whose inhibition results in significant LDL-C lowering without otherwise negatively impacting overall health most recently culminating in the approval (in Europe and North America) of two monoclonal agents to inhibit PCSK9.

### 1.1.3. Mechanism of RNA Interference

Ribonucleic acid (RNA) 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. ALN-PCSSC, an RNAi Therapeutic for Hypercholesterolemia**

ALN-PCSSC Solution for Injection (subcutaneous [SC] use) is comprised of the PCSK9 siRNA, ALN-60212, formulated in phosphate buffer. The PCSK9 siRNA is a chemically synthesized double stranded oligonucleotide covalently linked to a ligand containing GalNAc residues. This synthetic investigational RNAi therapeutic has been designed to suppress the liver production of PCSK9 when administered via SC injection. Inhibition of PCSK9 synthesis through an RNAi mechanism has the potential to lower tissue and circulating plasma PCSK9 protein levels, resulting in higher expression of LDLR in the liver, and consequently lower LDL-C levels in the blood stream. The initial proposed indication for ALN-PCSSC is the treatment of subjects with hypercholesterolemia who are not achieving therapeutic LDL-C goals despite maximally tolerated lipid-lowering therapy, or for subjects who are intolerant of statins.

### **1.2.1. Preclinical Studies**

The safety pharmacology and toxicology of ALN-PCSSC was evaluated in a series of in vitro and in vivo nonclinical studies.

The drug substance in ALN-PCSSC (ALN-60212) is designed to match the human and cynomolgous monkey mRNA transcripts for PCSK9, sharing a substantial partial match to the rat PCSK9 mRNA. ALN-60212 was informatically identified from a large collection of possible siRNAs targeting PCSK9 based on its predicted potency and selectivity. ALN-PCSSC reduced the expression of PCSK9 in Hep3B liver cells with a median inhibitory concentration of 20 pM and inhibited hPCSK9 serum protein levels in a transgenic mouse model with a single dose effective dose causing 50% inhibition of approximately 2 mg/kg and an effective dose causing 80% inhibition of approximately 6 mg/kg. In single- and multi-dose regimen studies in cynomolgus monkeys, ALN-PCSSC exhibited dose-dependent sustainable suppression of PCSK9 protein that was paralleled by lowering of serum LDL-C with the same kinetics. The time to reach PCSK9 and LDL-C nadir was approximately 20 days and there was no difference in time to nadir between different dose levels. In single-dose studies, the maximal mean PCSK9 and LDL-C inhibition was 85% and 68%, respectively, which was observed at the two highest doses of ALN-PCSSC administered (6 and 10 mg/kg); however, the duration of PCSK9 silencing and LDL-C lowering was markedly extended at the higher 10 mg/kg dose. In multi-dose studies, the maximal mean PCSK9 and LDL-C inhibition was 93% and 74%, respectively, which was similar to that observed in the single-dose study. Following discontinuation of ALN-PCSSC administration, recovery of PCSK9 levels was slow, returning to baseline after 100 days in the single-dose study and only showing partial recovery between doses in the multi-dose regimen. There were no ALN-PCSSC-related changes to the levels of high-density lipoprotein cholesterol (HDL-C) or triglycerides in any of the groups. As expected, total cholesterol levels were reduced by up to 30% reflecting the decrease in LDL-C.

Good Laboratory Practices (GLP) compliant repeat-dose studies of 4 and 15 weeks duration have been conducted in rats and monkeys. These studies included toxicokinetic analysis of ALN-PCSSC in plasma and in tissues, including the liver which is the target organ and the kidney which is the main organ of elimination. The GLP 4-week toxicology studies in rats and

monkeys involved every other week administration of ALN-PCSSC at dose levels of 10, 50, and 250 mg/kg and once a week administration of 10 mg/kg for rats and 30 mg/kg for monkeys. The GLP 15-week toxicology studies in rats and monkeys involved once monthly administration of ALN-PCSSC at dose levels of 10, 50, and 250 mg/kg and once every other week administration of 125 mg/kg for rats and 25 mg/kg for monkeys. Each toxicology study also included an 8-week treatment-free recovery period for all dose groups. ALN-PCSSC was well tolerated in all studies and there were no dose-limiting toxicities. The most common findings were related to the pharmacological effects of ALN-PCSSC on lipid profiles. There were consistent decreases in LDL-C and total cholesterol which were expected. Histopathological findings included 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 were not associated with changes in clinical pathology parameters and are consistent with class effects of oligonucleotides and were not considered adverse. In a non-GLP dose-range-finding study conducted in monkeys, ALN-PCSSC did not stimulate pro-inflammatory cytokines, activate complement, or impact coagulation. ALN-PCSSC also did not stimulate pro-inflammatory cytokines following single dose administration to mice. In a cardiovascular and respiratory study in telemetered conscious cynomolgus monkeys, ALN-PCSSC had no immediate or delayed effects on clinical observations, qualitative or quantitative electrocardiogram (ECG) parameters, hemodynamic parameters, respiration rate, or body temperature at any dose level. In addition, ALN-PCSSC did not induce gene mutations or chromosomal damage in a battery of in vitro and in vivo genotoxicity studies.

Further information is in the Investigator's Brochure (IB).

### **1.2.2. Clinical Studies**

One ongoing Phase I study has been conducted to date (Study ALN-PCSSC-001). This was a randomized, single-blind, placebo-controlled, single-dose escalation and multiple-dose study of ALN-PCSSC administered SC to subjects with elevated LDL-C. The study was conducted in two phases: a single ascending dose (SAD) phase and a multiple dose (MD) phase. During the SAD phase, 24 subjects were assigned to either receive placebo or one of five doses of ALN-PCS ranging from 25 mg to 800 mg. Those who received doses of at least 100 mg saw their LDL-C drop at least 40%; at the 500 mg dose, LDL-C levels dropped as much as 78%. At 140 days after the treatment was given, subjects still had an average LDL-C reduction of about 40%.

In the MD phase, 45 subjects received multiple doses of either ALN-PCS (125mg weekly x4, 250 mg bi-weekly x2, 300 mg and 500 mg twice given 1 month apart) or placebo. These subjects had maximal LDL-C reductions of 80% and average LDL-C reductions of 50% to 60%. To date, the drug appears to be generally safe and well tolerated. One subject on statin comedication had elevated liver enzymes with alanine aminotransferase (ALT) >4x the upper limit of normal (ULN), which resolved on stopping the statin.

### **1.2.3. 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 ALN-PCSSC or placebo. Reduction of LDL-C has been

associated with reduced CV risk both by epidemiology and in controlled clinical trials. The safety profile observed to date is considered acceptable for this clinical trial.

An expanded risk-benefit summary is provided in the IB.

### **1.3. Study Rationale**

#### **1.3.1. Study Rationale**

The overall safety data from ALN-PCSSC in nonclinical studies and clinical data from the Phase I ALN-PCSSC-001 study, the ALN-PCS02-001 study, 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 II study.

Results of this study will be used to select a dose(s) for future studies.

#### **1.3.2. Dose Rationale**

Previous studies using PCSK9-targeting siRNAs formulated in LNPs (ALN-PCS02) or using PCSK9 antibodies, and one Phase I study with ALN-PCSSC in which subjects received single-doses ascending from 25 mg to 800 mg, have demonstrated that substantial lowering of PCSK9 is safe and well-tolerated in humans. Doses for the Phase I study were calculated using the rat and monkey no observed adverse effect levels (NOAELs) based on body weight and body surface area (mg/m<sup>2</sup>). Collectively, the results of nonclinical studies with ALN-PCSSC supported a starting dose of 25 mg for subjects participating in the SAD phase of the previous Phase I study.

In Phase I Study ALN-PCSSC-001, clinically significant reductions in LDL-C levels were seen with single ALN-PCSSC doses as low as 25 mg with larger decreases seen with higher doses and a plateau at 300 mg. Subjects at ALN-PCSSC doses of 300 mg or higher had maximal LDL-C reductions of up to 78.1% and average least squares mean group nadir reductions of 50 to 59%. In the MD phase, 45 subjects received multiple doses of either ALN-PCS (125 mg weekly x4, 250 mg biweekly, 300 mg and 500 mg twice given 1 month apart) or placebo. Subjects at ALN-PCSSC doses of 300 mg or higher had maximal LDL-C reductions of 83% and average least squares mean group nadir LDL-C reductions of 53.4% to 59.9% at all dose levels tested.

Based on the interim results of the Phase I Study ALN-PCSSC-001, where maximum effect on LDL-C was seen by 84 days and a significant effect was still observed at 180 days, the Phase II study has been designed to test the efficacy of a single dose (200 mg, 300 mg, or 500 mg) or two doses 90 days apart (100 mg, 200 mg, or 300 mg). This will allow dose selection for Phase III. The dosing regimens used in Phase II are therefore fully supported by the findings of the Phase I study.

### **1.4. Study Population**

This study will include male or female subjects  $\geq 18$  years of age with a history of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia), or a  $>20\%$  ten-year risk of a CV event assessed by Framingham Risk Score or equivalent and receiving maximum-tolerated lipid-lowering therapy.

## **2. TRIAL OBJECTIVES AND PURPOSE**

This trial is designed to evaluate the efficacy, safety, and tolerability of ALN-PCSSC injection(s).

### **2.1. Primary Objective**

The primary objective of this study is to evaluate the effect of ALN-PCSSC treatment on LDL-C levels at Day 180.

### **2.2. Secondary Objectives**

The secondary objectives of this study are to evaluate the effect of ALN-PCSSC on the following:

- LDL-C levels at Day 90
- LDL-C levels at other time points
- PCSK9 levels over time
- Other lipids, lipoproteins, apolipoproteins
- Proportion of subjects achieving pre-specified global lipid guidelines
- Individual responsiveness to different doses
- Duration of lipid-lowering effect of different doses
- Safety and tolerability profile of ALN-PCSSC

### **2.3. Exploratory Objectives**

The exploratory objectives of this study are to collect and evaluate the effect of ALN-PCSSC on the following:

- CV events such as CV death, non-fatal MI, resuscitated cardiac arrest, and non-fatal stroke (ischemic and hemorrhagic)
- Evaluation of anti-drug antibodies (ADA) for the investigational product

### 3. TRIAL DESIGN

#### 3.1. Type/Design of Trial

This study will be a Phase II, placebo-controlled, double-blind, randomized trial in subjects with ASCVD or ASCVD-risk equivalents (eg, diabetes and familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies to evaluate the efficacy, safety, and tolerability of ALN-PCSSC injection(s). The study will be a multi-national, multi-center study (approximately 60 centers). Informed consent will be obtained from subjects before the initiation of any study-specific procedures.

Subjects will be screened and 480 eligible subjects will be randomized: 60 subjects per each of six ALN-PCSSC dose groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six dose groups) as outlined in Table 1. Treatment allocation will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will receive either one or two injections of ALN-PCSSC or placebo at the doses specified in Table 1.

**TABLE 1: DOSING REGIMENS**

Drug and dose	No. Subjects Randomized	Volume (mL)
<b>Single Dose: One or Two injections on Day 1</b>		
Placebo for 200 mg	20	1.0
200 mg ALN-PCSSC	60	1.0
Placebo for 300 mg	20	1.5
300 mg ALN-PCSSC	60	1.5
Placebo for 500 mg	20	2.5 <sup>a</sup>
500 mg ALN-PCSSC	60	2.5 <sup>a</sup>
<b>Two Doses: One Injection on Day 1 and Day 90</b>		
Placebo for 100 mg	20	0.5
100 mg ALN-PCSSC	60	0.5
Placebo for 200 mg	20	1.0
200 mg ALN-PCSSC	60	1.0
Placebo for 300 mg	20	1.5
300 mg ALN-PCSSC	60	1.5

<sup>a</sup> 500 mg will be administered as two injections, one of 300 mg (1.5 mL), and one of 200 mg (1.0 mL) in two different injection sites. 1.5 mL is the maximum injection volume for a single injection site.

An independent Data Monitoring Committee (DMC) will review safety data beginning after the first 40 subjects have received the first dose of ALN-PCSSC or placebo and complete the Day 14 follow-up visit. Thereafter the DMC will review safety data every 2 months until the end of the trial. A recommendation may be taken to stop the study at any of these reviews.

All eligible subjects will be randomized and receive the first SC administration of ALN-PCSSC or placebo on Day 1. Subjects randomized to receive a second dose of study drug will receive the

second injection of ALN-PCSSC or placebo at the Day 90 visit and will have an extra visit on Day 104 (14 days after the second dose on Day 90).

After first study drug administration, the subject will be observed in the clinic for at least 4 hours post injection and will then be discharged. Subjects will return on Day 14 and Day 30 and then at monthly intervals for 6 months. Subjects whose LDL-C levels have returned to baseline levels and who have completed the study to Day 210 will be given the opportunity to enroll in a separate long-term extension study in order to collect long-term efficacy and safety data.

Any subjects in whom LDL-C levels have not returned to >80% of baseline values by Day 210 will continue to be followed on a monthly visit schedule in this study until either this level has been reached or until a maximum of Day 360 at which point they will be given the opportunity to enroll in the long-term extension study. At each visit, LDL-C levels, adverse events (AEs), serious adverse events (SAEs), concomitant medications, and safety laboratory assessments will be collected.

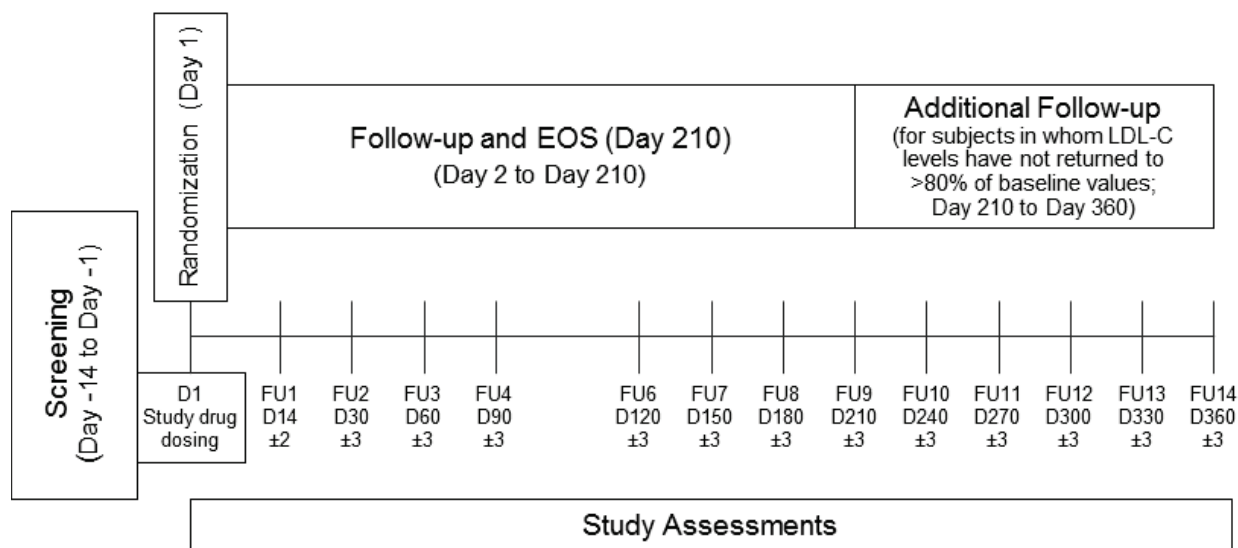
An interim analysis of lipids and PCSK9, unblinded by dose cohort only, will be prepared upon completion of Day 90 by the Statistical Reporting Organization. The interim analysis will be performed for all subjects completing Day 90 and these data will be used to help select the ALN-PCSSC dose for subsequent clinical trials.

### 3.2. Schematic Diagram of Trial Design

#### 3.2.1. One Dose (one or two injections on Day 1)

The study design for one dose is presented in Figure 1.

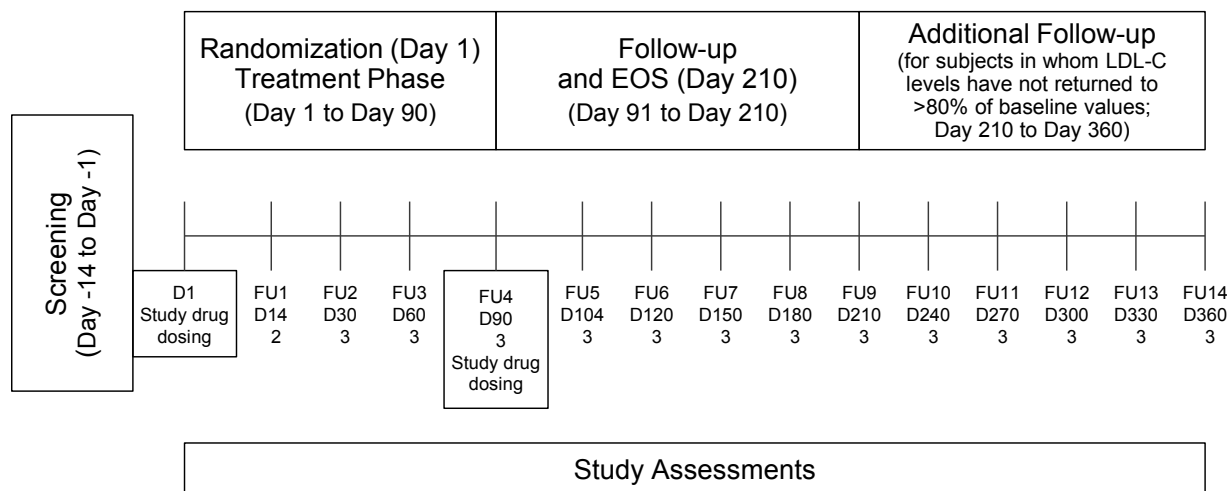
**Figure 1: Study Design for One Dose**



### 3.2.2. Two Doses (one injection each on Day 1 and Day 90)

The study design for two doses is presented in Figure 2.

**Figure 2: Study Design for Two Doses**



### 3.3. Primary Endpoint(s)

The primary endpoint of this trial is percentage change in LDL-C from baseline to Day 180.

### 3.4. Secondary Endpoints

The secondary endpoints of this trial are:

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 104, 120, 150, and 210
- Proportion of subjects in each group with LDL-C greater than 80% of the baseline value at Day 180 and Day 210
- Duration of time on treatment for subjects to return to 80% of baseline or greater LDL-C or PCSK9 protein
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Days 90, 120, and 180
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at Days 90, 120, and 180
- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, 180, and 210
- Percentage change in other lipids, lipoproteins, apolipoproteins from baseline at each subsequent visit to Day 210

- Proportion of subjects in each group who attain global lipid modification targets for their level of ASCVD risk

### **3.5. Exploratory Endpoint(s)**

The exploratory endpoints of this trial are:

- CV events such as CV death, non-fatal MI, resuscitated cardiac arrest, and non-fatal stroke (ischemic and hemorrhagic)
- Evaluation of ADA for the investigational product

### **3.6. Measures to Minimize/Avoid Bias**

#### **3.6.1. Blinded Study Where Pharmacist is Unblinded**

The study will be conducted using a double-blind design, with placebo matched by volume within each dose and regimen but not between regimens. Specifics on how the blind for the study drug is maintained are provided in [Section 5.4.1](#). Allocation of treatment is not disclosed to the study team. Study medication will be prepared by the unblinded hospital pharmacist and will be dispensed in a blinded syringe as randomized by the interactive web response system (IWRS). Pharmacists will be required by signature to keep the study personnel blinded. Blinding is achieved by placing an over label on each unique syringe dispensed by the pharmacist. The over label will cover the outside of the syringe masking the color of the solution within.



## 4. SUBJECT POPULATION

### 4.1. Number of Subjects

This will be a multi-center study conducted in North America and Europe. A total of 480 randomized subjects are planned for inclusion in the study: 60 subjects per each of six ALN-PCSSC treatment groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six drug groups). Assuming about a 15% drop out rate, the sample size will be approximately 100 evaluable subjects total across the placebo groups and approximately 50 subjects in each of six ALN-PCSSC treatment groups. This sample size of at least 400 evaluable subjects will provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one ALN-PCSSC dose group.

### 4.2. Inclusion Criteria

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

1. Male or female subjects  $\geq 18$  years of age.
2. History of ASCVD or ASCVD-risk equivalents (symptomatic atherosclerosis, Type 2 diabetes, familial hypercholesterolemia, including subjects whose 10-year risk of a cardiovascular [CV] event assessed by Framingham Risk Score\* or equivalent has a target LDL-C of  $< 100$ mg/dL).
3. Serum LDL-C  $\geq 1.8$  mmol/L ( $\geq 70$  mg/dL) for ASCVD subjects or  $\geq 2.6$  mmol/L ( $\geq 100$  mg/dL) for ASCVD-risk equivalent subjects at screening.
4. Fasting triglyceride  $< 4.52$  mmol/L ( $< 400$  mg/dL) at screening.
5. Calculated glomerular filtration rate  $> 30$  mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology.
6. Subjects on statins should be receiving a maximally tolerated dose (investigator's discretion).
7. Subjects on lipid-lower therapies (such as statin and/or ezetimibe) should be on a stable dose for  $\geq 30$  days before screening with no planned medication or dose change during study participation.
8. Willing and able to give written and informed consent before initiation of any study-related procedures and willing to comply with all required study procedures.

\*By Framingham Risk Score  $> 20\%$

### 4.3. Exclusion Criteria

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 II, III or IV heart failure or last known left ventricular ejection fraction <30%.
  4. Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
  5. Any history of hemorrhagic stroke.
  6. Major adverse cardiac event within 6 months prior to randomization.
  7. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite anti-hypertensive therapy.
  8. Poorly controlled Type 2 diabetes, ie, glycated hemoglobin A1c (HbA1c) >10.0% prior to randomization.
  9. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained ALT, aspartate aminotransferase (AST), elevation >2x ULN or total bilirubin elevation >1.5x ULN at screening confirmed by a repeat measurement at least 1 week apart.
  10. Serious comorbid disease in which the life expectancy of the subject is shorter than the duration of the trial (eg, acute systemic infection, cancer, or other serious illnesses). This includes all cancers with the exception of treated basal-cell carcinoma occurring >5 years before screening.
  11. Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long- term injectable contraception, intrauterine device or tubal ligation)\*\*. Women who are >2 years postmenopausal defined as  $\geq 1$  year since last menstrual period AND if <55 years old with a negative pregnancy test within 24 hours of randomization or surgically sterile are exempt from this exclusion.
  12. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
  13. Known history of alcohol and/or drug abuse within the last 5 years.
  14. Treatment with other investigational medicinal products or devices within 30 days or five half-lives, whichever is longer.
  15. Use of other investigational medicinal products or devices during the course of the study.
  16. Any condition that according to the investigator could interfere with the conduct of the study, such as but not limited to:
    - a. Inappropriate for this study, including 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. Involved with, or a relative of, someone directly involved in the conduct of the study
  - f. Any known cognitive impairment (eg, Alzheimer's disease)
17. Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

\*\*For the entire duration of the study

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

#### **4.4. Withdrawal Criteria**

All subjects have the right to withdraw 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 for any subject study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

- AE
- Death
- Subject withdrew consent
- Physician decision
- Lost to follow-up

Upon occurrence of a serious or intolerable AE, the investigator or designee will make every possible attempt to confer with the Sponsor before discontinuing the subject, and the DMC will be notified.

It is imperative to obtain complete follow-up data for all randomized subjects whether or not they receive their assigned treatment or have discontinued study drug. 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 Study Drug should be carried out when possible

whether or not a subject continues to receive treatment according the protocol. Subjects will not be replaced in this trial.

#### **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 DMC may be notified.

As noted in [Section 4.4](#), it is imperative to obtain complete follow-up data for all randomized subjects whether or not they receive their assigned treatment or have discontinued study drug.

## 5. TREATMENT OF SUBJECTS

### 5.1. Study Medications

#### 5.1.1. ALN-PCSSC

Treatments will be assigned as outlined in [Table 1](#). Study drug (ALN-PCSSC) information is described in [Table 2](#).

**TABLE 2: INVESTIGATIONAL PRODUCT**

	Investigational Product
<b>Product Name:</b>	ALN-PCSSC
<b>Dosage Form:</b>	Solution for Injection
<b>Unit Dose</b>	100 mg vial (200 mg/mL)
<b>Route of Administration</b>	SC use
<b>Physical Description</b>	Clear, colorless to pale yellow solution essentially free of particulates
<b>Manufacturer</b>	AAI Pharma Inc., Charleston, SC, United States (US).

#### 5.1.2. Placebo

Placebo will be supplied by the clinical study site as sterile normal saline 0.9% for SC injection. Placebo will be administered as an SC injection in an amount matched to the doses within each injection regimen (see [Table 1](#)).

#### 5.1.3. Packaging and Labeling

Study drug will be provided by Catalent Pharma Solutions, Philadelphia, Pennsylvania, US. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

The ALN-PCSSC Solution for Injection (subcutaneous use) is packaged in 2 mL glass vials with a fill volume of no less than 0.55 mL. The container closure system consists of a Type I glass vial, a Teflon-faced 13 mm stopper, and a flip-off aluminum seal.

#### 5.1.4. Storage

ALN-PCSSC will be stored in a secure refrigerator or at the appropriate conditions as specified in the Pharmacy Manual. Access should be strictly limited to the investigator, pharmacists, and their designees. No special procedures for the safe handling of ALN-PCSSC are required.

#### 5.1.5. Accountability

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

The study drug 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 study drug containers (eg, empty vials/bottles) will be kept until the monitor has reviewed the accountability records.

All unused study drug will be destroyed on site (or returned to the packaging and labeling facility for destruction if destruction on site is not possible) once the study drug has been inventoried and the monitor has reviewed the accountability records. In the event that study drug(s) needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.

## **5.2. Concomitant Medications**

### **5.2.1. Prohibited Concomitant Medications**

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

- Medications used to lower LDL-C (eg, statins, ezetimibe, lomitapide, mipomersen, niacin, colesvelam, bile acid absorption inhibitors, monoclonal antibodies for PCSK9).

### **5.2.2. Permitted Concomitant Medication(s)**

The following medications/treatments are permitted during the study:

- Hormone replacement therapy
- Lipid-lower medications; subjects on lipid-lower medications (such as statins and/or ezetimibe) should be on a stable dose for  $\geq 30$  days before screening with no planned medication or dose change during study participation
- Prescription medications prescribed to treat pre-existing 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. 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

## **5.4. Blinding**

### **5.4.1. Blinding of Study Medication**

This is a double-blind placebo-controlled study. Study medication will be blinded within each injection regimen: either one or two injections on Day 1 or a single injection on Day 1 and on Day 90. Only the pharmacist will have knowledge of the treatment assignment.

Randomization via an automated IWRS will be used to assign subjects to blinded study drug. The clinical study site pharmacist will maintain the double blind according to site-specific procedures and the Pharmacy Manual. It should be noted that ALN-PCSSC may be visually distinguishable from placebo; therefore, syringes containing dispensed study drug will be masked in the pharmacy prior to transfer to the clinic.

## 6. SCHEDULE AND SEQUENCE OF PROCEDURES

The Schedule of Events/Assessments (Table 3) summarizes the study assessments by time point.

This study consists of 10 (one dose) or 11 (two doses) visits and four phases:

Single Dose (one or two injections on Day 1):

- Screening: Day -14 to -1
- Randomization, initiation of study drug: Day 1
- Treatment Phase: Day 1
- Follow-up:
  - Follow-up: Days 2 to 210; end of study (EOS) on Day 210
  - Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values; subjects will return each month for follow-up until this level has been reached or until Day 360): Days 240, 270, 300, 330, and 360

Two Doses (one injection each on Day 1 and Day 90):

- Screening: Day -14 to -1
- Randomization, initiation of study drug: Day 1
- Treatment Phase: Day 1 to Day 90
- Follow-up
  - Follow-up: Days 91 to 210; EOS on Day 210
  - Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values; subjects will return each month for follow-up until this level has been reached or until Day 360): Days 240, 270, 300, 330, and 360

The expected duration of the subjects' involvement in the study will be approximately 224 days, which includes screening, study drug administration, the course of one or two injections, and the follow-up period to Day 210.

Subjects whose LDL-C levels have returned to baseline levels and who have completed the study to Day 210 will be given the opportunity to enroll in a separate long-term extension study in order to collect long-term efficacy and safety data.

Any subjects in whom LDL-C levels have not returned to >80% of baseline values by Day 210 will continue to be followed on a monthly visit schedule as part of this study until either this level has been reached or a maximum of Day 360 at which point they will be given the opportunity to enroll in the long-term extension study. At each visit, LDL-C levels, AEs, SAEs, concomitant medications, and safety laboratory assessments will be collected. For these subjects, the expected maximum duration of involvement in the study will be 374 days.



**6.1. Schedule of Events/Assessments**

**TABLE 3: STUDY DESIGN AND SCHEDULE OF ASSESSMENTS**

	Screening	Randomization and Treatment	Follow-Up								End of Study (EOS)	Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values)
			Treatment Phase				Follow-Up					
<b>Study Day: One Dose</b>	<b>-14 to -1</b>	<b>1</b>	FU1 14 (± 2)	FU2 30 (± 3)	FU3 60 (± 3)	FU4 90 (± 3)	NA	FU6 120 (± 3)	FU7 150 (± 3)	FU8 180 (± 3)	FU9 210 (± 3)	FU10 (Day 240) (± 3) FU11 (Day 270) (± 3) FU12 (Day 300) (± 3) FU13 (Day 330) (± 3) FU14 (Day 360) (± 3)
<b>Study Day: Two Doses</b>	<b>-14 to -1</b>	<b>1</b>	FU1 14 (± 2)	FU2 30 (± 3)	FU3 60 (± 3)	FU4 90 (± 3)	FU5 104 (± 3) <sup>a</sup>	FU6 120 (± 3)	FU7 150 (± 3)	FU8 180 (± 3)	FU9 210 (± 3)	FU10 (Day 240) (± 3) FU11 (Day 270) (± 3) FU12 (Day 300) (± 3) FU13 (Day 330) (± 3) FU14 (Day 360) (± 3)
Informed consent	X											
Medical History (including prior meds)	X											
Physical Examination <sup>b</sup> (including full neurological examination)	X										X	
Inclusion/Exclusion Criteria	X	X										
Randomization		X										
Vital Signs	X	X <sup>c</sup>	X	X	X	X <sup>c</sup>	X	X	X	X	X	
12 Lead ECG <sup>d</sup>	X	X									X	
HbA1c <sup>g</sup>	X <sup>f</sup>	X				X				X		X (Day 270 and 360)
Clinical labs (local) <sup>e,k</sup>	X <sup>f</sup>											
Clinical labs (central) <sup>e,g,k</sup>		X	X	X	X	X	X	X	X	X	X	X

	Screening	Randomization and Treatment	Follow-Up								End of Study (EOS)	Additional Follow-Up (for subjects in whom LDL-C levels have not returned to >80% of baseline values)
			Treatment Phase				Follow-Up					
Study Day:			FU1	FU2	FU3	FU4		FU6	FU7	FU8	FU9	
<b>One Dose</b>	<b>-14 to -1</b>	<b>1</b>	14 (± 2)	30 (± 3)	60 (± 3)	90 (± 3)	NA	120 (± 3)	150 (± 3)	180 (± 3)	210 (± 3)	FU10 (Day 240) (± 3) FU11 (Day 270) (± 3) FU12 (Day 300) (± 3) FU13 (Day 330) (± 3) FU14 (Day 360) (± 3)
<b>Two Doses</b>	<b>-14 to -1</b>	<b>1</b>	14 (± 2)	30 (± 3)	60 (± 3)	90 (± 3)	104 (± 3) <sup>a</sup>	120 (± 3)	150 (± 3)	180 (± 3)	210 (± 3)	FU10 (Day 240) (± 3) FU11 (Day 270) (± 3) FU12 (Day 300) (± 3) FU13 (Day 330) (± 3) FU14 (Day 360) (± 3)
Fasting lipids and lipoproteins (local)	X											
Urinalysis (local)	X <sup>f</sup>	X <sup>h</sup>									X	
Pregnancy test (local)	X <sup>i</sup>	X <sup>i</sup>	X	X	X	X	X	X	X	X	X	X <sup>j</sup>
Anti-ALN-PCSSC (ADA) antibodies <sup>k</sup>		X <sup>l</sup>		X	X <sup>m</sup>	X <sup>m</sup>		X	X <sup>a,m</sup>	X <sup>a,m</sup>	X	X <sup>n</sup>
Efficacy parameters (LDL-C, lipids, PCSK9) <sup>o</sup>	X	X	X	X	X	X	X	X	X	X	X <sup>k</sup>	X <sup>p</sup>
Study drug administration		X				X						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
AE reporting		X	X	X	X	X	X	X	X	X	X	X
SAE reporting		X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies; AE = adverse event; ECG = electrocardiogram; FU= follow-up; EOS = end of study; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; PCSK9 = proprotein convertase subtilisin/kexin type 9; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

<sup>a</sup> Subjects who receive a second dose of study drug on Day 90 only. <sup>b</sup> Physical examination at Screening includes recording of height and weight.

<sup>c</sup> Vital signs: blood pressure, heart rate, temperature, and respiration will be measured. On Day 1 and Day 90 (subjects who receive a second dose of study drug only), vital signs will be measured prior to injection and at 4 hours after injection.

<sup>d</sup> ECG is performed prior to the injection on Day 1.

<sup>e</sup> Hematology, chemistry (including glucose, liver and renal function), and coagulation testing to be performed by local laboratory at screening. Hematology, chemistry (including glucose, liver and renal function, hsCRP, IL6, IFN- $\gamma$ , and TNF- $\alpha$ ), and coagulation testing to be performed by central laboratory from randomization onwards. Blood samples for determination laboratory values will be performed prior to study drug injection where relevant. All laboratory testing will be performed with subjects in a fasted state. See [Appendix C](#) for a list of laboratory parameters.

<sup>f</sup> Lab tests performed in participating institution's laboratory. Results must be available before the start of study drug injection on Day 1 to confirm subjects meet eligibility criteria.

<sup>g</sup> Lab tests performed by study's designated Central Lab facility from randomization to EOS. In addition, subjects in whom LDL-C levels have not returned to >80% of baseline values by Day 210 will continue to be followed on a monthly visit schedule as part of this study either until this level has been reached or until Day 360 at which point they will be given the opportunity to enroll in the long-term extension study.

<sup>h</sup> Urinalysis collection is prior to the injection on Day 1.

<sup>i</sup> Women of childbearing potential only. Urine pregnancy test performed and results available prior to the injection on Day 1 and Day 90 (for subjects randomized to receive injections on two days).

<sup>j</sup> Women of childbearing potential will have a pregnancy test at each additional follow-up visit until lipids return to >80% of baseline values.

<sup>k</sup> Additional aliquots of plasma and serum will be collected at each time point and stored for future analyses.

<sup>l</sup> Two ADA samples will be drawn on Day 1: one before the injection and one 4 hours after the injection.

<sup>m</sup> An additional blood draw for anti-ALN-PCSSC antibodies is not required at these visits; a stored serum sample will be used for ADA testing.

<sup>n</sup> For subjects in whom LDL-C levels have not returned to >80% of baseline values, formation of ADA will be assessed at the last visit.

<sup>o</sup> Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], high sensitivity C-reactive protein (hsCRP), and PCSK9.

<sup>p</sup> Efficacy parameters will include basic lipid panel (LDL-C, HDL-C, total cholesterol, triglycerides) and PCSK9; non-HDL-C and VLDL-C will be derived from the lipid panel.

## 6.2. General Conduct of the Trial

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.

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

The following procedures will be performed within 2 weeks prior to randomization:

- Informed consent
- Medical history
- Physical examination (including height and weight and full neurological examination [see [Appendix A](#)])
- Assessment of inclusion/exclusion criteria
- Vital signs
- 12-lead ECG
- HbA1c (local)
- Local clinical laboratory (hematology, chemistry [including fasting glucose, liver and renal function] and coagulation testing) (see [Appendix C](#))
- Urinalysis (local)
- Pregnancy test (local)
- Fasting lipids/lipoproteins (local)
- Concomitant medications
- Central laboratory for the following efficacy parameters: lipid panel, LDL-C by beta quantification, PCSK9, hsCRP, lipoprotein a [Lp(a)], apolipoprotein A1 [Apo-A1] and apolipoprotein B [Apo-B]) and the following safety parameters: inflammatory biomarkers, hsCRP and inflammatory markers interleukin 6 (IL6), interferon-gamma (IFN- $\gamma$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ )

All local screening laboratory tests will be analyzed in-house at the participating institution's laboratory. Results must be available before the start of study drug injection on Day 1 to confirm subjects meet eligibility criteria (see [Section 4](#)). The results of all local screening laboratory tests should be reviewed prior to randomization. If these results confirm an exclusion criterion or suggest any contraindication to treatment with ALN-PCSSC, the subject must not be randomized. All Central laboratory assessments drawn during screening are not required to be reviewed prior to randomization. Please refer to [Appendix C](#) for details of laboratory tests performed during the screening period.

## 6.4. Randomization

The following procedures will be performed prior to the injection:

- Assessment of inclusion/exclusion criteria

- Randomization
- Vital signs: blood pressure, heart rate, temperature, and respiration will be measured prior to injection
- 12-lead ECG
- HbA1c (central)
- Central clinical laboratory (hematology, chemistry [including fasting glucose, liver and renal function, hsCRP and inflammatory markers (IL6, IFN- $\gamma$ , and TNF- $\alpha$ ), and coagulation testing)
- Urinalysis (local)
- Pregnancy test (local) (women of childbearing potential only)
- Assessment of ADA (central)
- Central laboratory for efficacy parameters (lipid panel, LDL-C by beta quantification, PCSK9, hsCRP, lipoprotein a [Lp(a)], apolipoprotein A1 [Apo-A1] and apolipoprotein B [Apo-B])
- Concomitant medications
- AE reporting
- SAE reporting

The following procedures will be performed after the injection:

- Vital signs: blood pressure, heart rate, temperature, and respiration (4 hours after injection)
- ADA (4 hours after injection) (central)
- Concomitant medications
- AE reporting
- SAE reporting

Randomization should only occur once subject eligibility is confirmed. Randomization via an automated IWRS will be used to assign subjects to study drug. All treatment groups will be studied concurrently. A total of 480 randomized subjects are planned for inclusion in the study: 60 subjects per each of six ALN-PCSSC treatment groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six drug groups).

Study drug administration will occur at this visit for all subjects (only dose for those randomized to receive a single dose and the first of two doses for those randomized to receive two).

**Study drug preparation:** The pharmacist will prepare the study drug under aseptic conditions. The amount (in mL) of study drug to be administered will be determined based on the assigned dose level for the cohort. On study drug dosing days, the pharmacist or designee will withdraw the required amount of study drug into one or more syringes to be administered to the subject on

that day. The procedure for preparing study drug and the volume to be loaded into each syringe is provided in the Pharmacy Manual.

**Study drug administration:** Subjects will be administered placebo or ALN-PCSSC by SC injection(s). Study drug injection will be administered by qualified clinical study site staff under the supervision of the investigator or designee and the injection site will be marked and mapped for later observation. The site of injection is the abdomen. If more than one injection is planned as per randomization, the first should be on one side of the abdomen and the second on the opposite side of the abdomen. Do not inject into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

If a local reaction around the injection site occurs, 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. Injection site reactions must be reported as described in [Section 8.5](#). Detailed instructions for study drug administration are found in the Pharmacy Manual.

## 6.5. Follow-Up Visits 1 to 9 (Day 14 to Day 210)

Subjects will return to the study center 14 days ( $\pm 2$  days) after study drug administration for Follow-Up Visit 1, 30 days ( $\pm 3$  days) after study drug administration for Follow-Up Visit 2, and monthly ( $\pm 3$  days) after that for Follow-Up Visits 3 to 7. The following procedures will be performed at these visits:

- Vital signs: blood pressure, heart rate, temperature, and respiration will be measured at each visit. For subjects who receive a second dose of study drug, vital signs will be measured prior to injection and at 4 hours after injection
- HbA1c: At Day 90 and Day 180 (central)
- Central clinical laboratory (hematology, chemistry [including fasting glucose, liver and renal function, hsCRP and inflammatory markers IL6, IFN- $\gamma$  and TNF- $\alpha$ ], and coagulation testing)
- ADA: at Day 30, Day 60, Day 90, Day 120, Day 150, and Day 180 (Note: Day 150 and Day 180 only in subjects who receive a second dose of study drug. An additional blood draw for ADA testing at Day 60, Day 90, Day 150, and Day 180 is not required; a stored serum sample will be used.) (central)
- Central laboratory for efficacy parameters (lipid panel, LDL-C by beta quantification, PCSK9, hsCRP, lipoprotein a [Lp(a)], apolipoprotein A1 [Apo-A1] and apolipoprotein B [Apo-B])
- Study drug administration: Second dose at Follow-Up Visit 4 (Day 90) for subjects randomized to receive two doses
- Pregnancy test (local; women of childbearing potential only): At Day 14 and monthly beginning at Day 30 through Day 180
- Concomitant medications
- AE reporting
- SAE reporting

## 6.6. End of Study Visit (Day 210 or Withdrawal)

A subject's participation in the study is complete when:

- All ongoing SAEs have been followed to resolution
- The following procedures/assessments have been completed
  - Vital signs
  - Physical examination (including full neurological examination [see [Appendix A](#)])
  - 12-lead ECG
  - Central clinical laboratory (hematology, chemistry [including fasting glucose, liver and renal function, hsCRP and inflammatory markers IL6, IFN- $\gamma$  and TNF- $\alpha$ ], and coagulation testing)
  - Urinalysis (local)
  - Pregnancy test (local)
  - ADA (central)
  - Central laboratory for efficacy parameters (lipid panel, LDL-C by beta quantification, PCSK9, hsCRP, lipoprotein a [Lp(a)], apolipoprotein A1 [Apo-A1] and apolipoprotein B [Apo-B])
  - Concomitant medications
  - AE reporting
  - SAE reporting

## 6.7. Additional Follow-Up Visits (Day 240 to Day 360)

Subjects in whom LDL-C levels have not returned to >80% of baseline values will return monthly ( $\pm 3$  days) for Follow-Up Visits 10 to 14 (Days 240, 270, 300, 330, and 360) either until this level has been reached or until Day 360. The following procedures will be performed at these visits:

- HbA1c: At Day 270 and Day 360 (central)
- Central clinical laboratory (hematology, chemistry [including fasting glucose, liver and renal function, hsCRP and inflammatory markers IL6, IFN- $\gamma$  and TNF- $\alpha$ ], and coagulation testing)
- ADA at the last visit(central)
- Lipids/lipoproteins (LDL-C, HDL-C, total cholesterol, triglycerides) and PCSK9; non-HDL-C and very low-density lipoprotein-cholesterol [VLDL-C] will be derived from the lipid panel (central)
- Pregnancy test (local) at each additional follow-up visit until LDL-C has returned to > 80% of baseline values
- Concomitant medications

- AE reporting
- SAE reporting



## 7. PROTOCOL ASSESSMENTS

### 7.1. Assessment of Safety

#### 7.1.1. Adverse Events

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

#### 7.1.2. Clinical Laboratory Assessments

Specimens will be obtained at the time points in the Schedule of Assessments ([Table 3](#)). Additional aliquots of plasma or serum will be collected at each time point and stored for any clinically indicated efficacy or safety analyses to be conducted at the end of the study.

Subjects will be in a fasted state for all clinical laboratory assessments. Screening lab tests as detailed in the Schedule of Assessments and [Section 6.3](#) will be performed by each participating institution's laboratory ([Appendix C](#)). Results from these screening tests must be available before the start of study drug 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](#).

Laboratory assessments may include:

**Hematology:** hemoglobin, hematocrit, erythrocytes, reticulocytes, platelet counts, mean cell hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count, differential blood count.

**Coagulation:** prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT). Blood samples for determination of coagulation parameters will be performed prior to start of study drug injection on Day 1.

**Biochemistry:** AST, ALT, alkaline phosphatase, gamma glutamyl transferase, uric acid, total bilirubin, sodium, creatine phosphokinase, albumin, total protein urea (BUN), creatinine, potassium, chloride, glucose (fasting), HbA1c, inorganic phosphate, hsCRP (fasting), eGFR, calcium, tryptase (as required), and inflammatory markers IL6, IFN- $\gamma$  and TNF- $\alpha$ .

**Urinalysis:** Urinalysis will be performed at the time points defined in the Schedule of Assessments and evaluated by dipstick analyses at the investigational site local lab (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 lab. The following parameters will be assessed: Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells (WBC)/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities).

**Urine pregnancy:** Urine pregnancy testing will be conducted locally at the visits specified in the Schedule of Assessments.

#### 7.1.3. Electrocardiograms

ECGs will be collected at baseline and at the EOS visit only unless clinically indicated.

#### **7.1.4. Assessment of Cardiovascular Events**

Information on CV events such as CHD death, major coronary events, and stroke will be collected as AE data.

#### **7.1.5. Anti-ALN-PCSSC Antibodies**

Additional sample for analysis of the induction of antibodies will be collected at the time points in the Schedule of Assessments (Table 3).

Aliquots of serum samples will be obtained and frozen, to permit future analysis of the effect of ALN-PCSSC on the expression of these exploratory biomarkers. Biological samples for biomarker research will be retained on behalf of the Sponsor for a maximum of 15 years 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**

Specimens will be obtained at the time points in the Schedule of Assessments (Table 3). Subjects will be in a fasted state for all efficacy laboratory assessments. Parameters to be assessed will include: total cholesterol, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, Apo-B), Lp(a), hsCRP, and PCSK9.

#### **7.2.1. Change from Baseline LDL-C**

The primary efficacy endpoint is the percentage change in LDL-C from baseline to Day 180.

In addition, this study will assess:

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 104, 120, 150, and 210
- Proportion of subjects in each group with LDL-C greater than 80% of the baseline value at Day 180 and Day 210
- Duration of time on treatment for subjects to return to 80% of baseline or greater LDL-C or PCSK9 protein
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, 70 mg/dL, and <100 mg/dL at Days 90, 120, and 180
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at Days 90, 120, and 180

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

### **7.2.2. Change from Baseline in Lipids/Lipoproteins**

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

- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, 180, and 210
- Percentage change in other lipids, and apolipoproteins from baseline at each subsequent visit to Day 210
- Proportion of subjects in each group who attain global lipid modification targets for their level of ASCVD risk

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.

## 8. ADVERSE EVENTS

### 8.1. Definitions

#### 8.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including 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.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the subject was randomized in a clinical study are not to be considered AEs.

Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor/investigator.

##### 8.1.1.1. AE Severity

The severity of an AE will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

Adverse events will be graded on a 3-point scale and reported as indicated on the case report form. The intensity of an AE is defined as follows:

- 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.

##### 8.1.1.2. Study Drug Causality

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject's clinical condition and medical history

Categorization of causality will be designated by the investigator as stated below:

- **Reasonable possibility** - There are facts (evidence) or arguments to suggest a causal relationship between the event and study drug

- **No reasonable possibility** – There are few to no facts (evidence) or arguments to suggest a causal relationship between the event and study drug

### 8.1.2. Serious Adverse Event

A serious adverse event (SAE) is 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
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse)

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, an MI that may be considered minor could also be an SAE if it prolonged hospitalization.

### 8.1.3. Medication errors

Medication error refers to any unintended error in the dosing and administration of the study product as per instructions in the protocol. Medication Errors generally fall into four categories as follows:

1. Wrong medication
2. Wrong dose (including dosing regimen, strength, form, concentration, amount);
3. Wrong route of administration;
4. Wrong subject (ie, not administered to the intended subject)

Medication Errors include occurrences of underdose of the study product(s).

**Underdose:** Unintentional administration of an insufficient quantity of study drug; ie, incomplete administration of study drug as drawn for injection.

#### 8.1.4. Adverse Events of Special Interest (AESIs)

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor’s product or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. The SAE/AESI form should be utilized for reporting the AESI even if a serious outcome may not apply.

In this study, injection site reactions including individual signs or symptoms at the injection site reported following study drug-administration will be collected as an AESI.

Signs or symptoms of injection site reaction will be evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) criteria of Injection Site Reaction (General disorders and administration site conditions) to determine the event’s grade (severity) (see Table 4).

**TABLE 4: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) OF INJECTION SITE REACTION**

Grade I:	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
Grade II:	Pain; lipodystrophy; edema; phlebitis
Grade III	Ulceration or necrosis; severe tissue damage; operative intervention indicated
Grade IV	Life-threatening consequences; urgent intervention indicated
Grade V	Death

Reference source: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Published 28 May 2009.

As indicated in [Section 6.4](#), if a local reaction around the injection site occurs, photographs should be obtained either by the investigator or another health care professional at first presentation and at each of the follow-up visits until the injection site reaction resolves.

#### 8.1.5. Other Safety Related Information

A comprehensive term that encompasses safety information for which global regulations require collection, evaluation, and/or reporting to Regulatory Authorities. Other safety-related information includes, but is not limited to, reports of the following:

- Abnormal neurological examination, eg, peripheral sensory and motor evaluation, an assessment of gait, pain, position, strength and reflexes ([Appendix A](#))
- Potential anaphylactic reactions assessed by Sampson criteria ([Appendix B](#))
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions
- Occupational exposure

Report the occurrence of suspected transmission via a medicinal product of an infectious agent, drug interactions, or occupational exposure to the Sponsor's GPV department as per [Section 8.3](#), Procedure for Serious Adverse Event Reporting. Note: The Special Situations event does not need to be serious to be reported on the SAE/AESI Report form.

The occurrences of abnormal neurological examination and anaphylactic reaction must be recorded on the source documentation and eCRF, and if the events are serious must be reported to the Sponsor's GPV department using the SAE Report form.

## **8.2. Procedure for Non-Serious Adverse Event Recording**

All nonserious AEs that occur during the designated study period from randomization up to EOS must be assessed and recorded on the source documents and electric case report forms (eCRFs), regardless of causal relationship to the study drug. Note: For subjects in whom LDL-C levels have not returned to >80% of baseline values by Day 210, AEs will continue to be assessed at additional monthly follow-up visits (Day 240, Day 270, Day 300, Day 330, and Day 360) until the final observation.

## **8.3. Procedure for Serious Adverse Event Reporting**

NOTE: This procedure may need to be followed for reporting AESIs or Other Safety Related information as noted in [Section 8.1.5](#) and [Section 8.5](#).

All SAEs that occur during the designated study period (from randomization through the EOS visit) must be reported to the Sponsor's Global Pharmacovigilance Department (GPV) within 24 hours of awareness of the event using the provided study specific SAE/AESI Report Form. The completion and processing of the SAE/AESI Report Form should be per the instructions in the provided SAE/AESI Report Form completion guidelines. In addition to completing the SAE/AESI Report Form, each SAE/AESI must be entered on the appropriate page of the eCRF. Note: For subjects in whom LDL-C levels have not returned to >80% of baseline values by Day 210, SAEs will continue to be assessed at additional monthly follow-up visits (Day 240, Day 270, Day 300, Day 330, and Day 360) until the final observation.

When death occurs with an SAE, the cause of death must be reported as an SAE. "Fatal" will be reported as the outcome for these events.

### **The investigator must assess the causality for each SAE/AESI.**

The Sponsor will contact the investigator, if necessary, to clarify any of the event information. The investigator should provide any follow-up information for the event to the Sponsor on an updated SAE/AESI report form as soon as it becomes available.

If the investigator is notified of a SAE/AESI that occurs post-study period, that he or she wishes to report to the Sponsor (eg, an event suspected to be causally related to study drug), 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. Procedure for Medication Error Reporting**

Medication errors (with or without an associated AE) need to be recorded as medication errors in the eCRF as described in [Section 8.2](#).

Medication errors with an associated SAE need to be recorded as medication errors in the eCRF and reported to the Sponsor's GPV department as described in [Section 8.3](#).

A mis-dosing protocol deviation (refer to [Section 12.3](#)) would need to be reported as a medication error if it was an "unintended error" as defined in [Section 8.1.3](#).

### **8.5. Procedure For Reporting Adverse Events Of Special Interest (AESIs)**

The AESI of Injection Site Reaction has been identified for the study product(s) in this protocol as per [Section 8.1.4](#). Nonserious AESIs should be reported to The Medicines Company (MDCO) GPV within 72 hours and serious AESIs should be reported to MDCO GPV within 24 hours. In both instances, the reporting procedure provided in [Section 8.3](#) should be followed. The SAE/AESI form should be utilized for reporting the AESI even if a serious outcome may not apply.

### **8.6. Procedure For Reporting Pregnancies/Lactation Exposure**

Occurrences of pregnancy/lactation exposure in a study subject or study subject's partner should be reported within 24 hours using the Pregnancy/Lactation Exposure Reporting form. In cases where a pregnancy/lactation exposure occurs with a SAE, the SAE reporting form should be used to report the SAE/AESI and the Pregnancy Reporting form should be used to report the pregnancy. When a pregnancy occurs without any concurrent SAE, the Pregnancy Reporting form may be submitted alone. The pregnancy must be followed through to outcome of pregnancy. Any pregnancy discovered after consent to follow-up need to be reported.



## **9. DATA COLLECTION**

An electronic data capture (EDC) system will be used for this trial. 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 trial. If there is a reason for a site to do so, it must be approved by MDCO 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 corresponding to the blinded pages and the appropriate unblinded designee will similarly address the unblinded section of the 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 trial, 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.

## **10. STATISTICAL PLAN**

### **10.1. Sample Size**

The sample size calculation was performed with the assumption (which was based on the observed results from a Phase I trial) that the difference in change from baseline between the active dose groups and the placebo group for LDL-C will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL, using a Dunnett multiple t-test procedure for six comparisons.

Assuming about a 15% drop out rate, the sample size will be approximately 100 evaluable subjects total across the placebo groups and approximately 50 subjects in each of six ALN-PCSSC treatment groups. This sample size of at least 400 evaluable subjects will provide more than 90% power to detect a 30% reduction of LDL-C levels in at least one ALN-PCSSC dose group.

### **10.2. Randomization**

Subjects will be screened and 480 eligible subjects will be randomized by the IWRS system: 60 subjects per each of six ALN-PCSSC treatment groups plus 120 subjects total across the placebo groups (20 subjects each to match each of the six drug groups). Treatment will be stratified by country and by current use of statins or other lipid-modifying therapies. Each subject will either receive either one or two injections on Day 1 only or a single injection on Day 1 and a second injection on Day 90 of blinded ALN-PCSSC or placebo.

### **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. Categorical variables will be summarized using counts and percentages. Percentages are based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including changes from baseline, will be summarized using descriptive statistics (n, mean, standard deviation, median and interquartile range [first and third quartiles], minimum and maximum).

A Statistical Analysis Plan will be written after finalizing of the eCRF and before database lock. The specifications in this document will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

Statistical analyses will be carried out using SAS statistical analysis software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina, US).

#### **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 trial. Treatment classification will be based on the randomized treatment. This population will be used to assess the randomness of treatment allocation.

#### **10.3.2.2. Modified Intent-to-Treat (mITT) Population**

All randomized subjects who receive at least one dose of study drug and have both the baseline and the 180 day follow-up LDL-C assessment. Treatment classification will be based on the randomized treatment. This will be the primary population for analysis of the primary and secondary endpoints.

#### **10.3.2.3. Per-Protocol (PP) Population**

All mITT subjects who received all randomized treatments and the 180 day follow-up LDL-C assessment. The PP population will be finalized during a data review before database lock. This will be the supportive population for analysis of the primary and secondary endpoints.

#### **10.3.2.4. Safety Population**

All subjects who received at least one dose of study drug. 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 each subject includes the screening period (from Day -14 to Day -1), the EOS visit (Day 210 or withdrawal date). The time at which LDL-C levels have returned to >80% of baseline values will be the last observation. Any lab results collected after the last observation will not be included in the planned efficacy analysis. Safety events after the last observation, even if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

Unless otherwise specified, for evaluations that are collected at multiple occasions prior to initiation of study drug, the last evaluation will be considered the "Baseline" evaluation for analysis.

Two samples for lipids and PCSK9 will be taken prior to initiation of study drug (one at screening and one prior to randomization on Day 1). The average value of the two samples will be used as the baseline evaluation.

#### **10.3.4. Missing Data Handling**

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

## **10.4. Statistical Analyses**

### **10.4.1. Demographic and Background Characteristics**

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

### **10.4.2. Study Drug and Concomitant Medications**

Summaries of 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 WHO drug dictionary. Subjects will be counted only once within each period by medication.

### **10.4.3. Efficacy Analysis**

#### **10.4.3.1. Primary Efficacy Endpoints**

The primary endpoint is the percentage change in LDL-C from baseline to Day 180.

Two sample t-tests will be performed to test the superiority of any dosing group over placebo. A Dunnett multiple t-test procedure will be applied to adjust for multiple comparisons with six different dosing regimens.

#### **10.4.3.2. Secondary Efficacy Endpoints**

The secondary objectives of this study are to evaluate the effect of ALN-PCSSC on the following:

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 104, 120, 150, and 210
- Proportion of subjects in each group with LDL-C greater than 80% of the baseline value at Day 180 and Day 210
- Duration of time on treatment for subjects to return to 80% of baseline or greater LDL-C or PCSK9 protein
- Individual responsiveness defined as the number of subjects reaching on treatment LDL-C levels of <25 mg/dL, <50 mg/dL, 70 mg/dL, and <100 mg/dL at Days 90, 120, and 180
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at Days 90, 120, and 180
- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 104, 120, 150, 180, and 210
- Percentage change in other lipids, lipoproteins, and apolipoproteins from baseline at each subsequent visit to Day 210
- Proportion of subjects in each group who attain global lipid modification targets for their level of ASCVD risk

#### **10.4.3.3. Interim Analysis**

An interim analysis of lipids and PCSK9, unblinded by dose cohort only, will be prepared upon completion of Day 90 by the Statistical Reporting Organization. The interim analysis will be performed for all subjects completing Day 90 and these data will be used to help select the ALN-PCSSC dose for subsequent clinical trials.

#### **10.4.4. Safety Analysis**

The safety objectives of this study are to evaluate the safety and tolerability profile of ALN-PCSSC.

##### **10.4.4.1. Adverse Events**

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified as preferred term) occurring during the double-blind 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 study drug. 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 study drug, respectively.

Incidences of injection site reactions will also be presented by dose group (see also [Section 8.1.4](#)). Time to first injection site reaction will be analyzed. The severity and duration of injection site reactions, as well as their signs and symptoms, will also be summarized.

##### **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 lab parameter by treatment group for incidence rates of potentially clinical significant values for subjects without potentially clinical significant 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.

##### **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.

## 11. RECORDS RETENTION

United States Food and Drug Administration (FDA) regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- At least 2 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 European Union (EU) Directives/Regulations and International Conference on Harmonisation (ICH) guidelines collectively require that essential clinical trial documents (including case report forms) other than patient's medical files must be retained for the following time period:

*The sponsor and investigator shall retain the essential documents relating to a clinical trial for at least 5 years after its completion. They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator. Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.*

- For at least 15 years after completion or discontinuation of the trial
- Or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region
- Or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product

Investigators shall retain the documents for a longer period, where so required by applicable local requirements.

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 any data clarification forms received from the Sponsor. 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 trial. 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, drug 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.

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:

- Injection not administered for any reason other than subject safety or withdrawal
- Wrong dose (dose concentration, wrong dose, wrong treatment, wrong regimen, wrong injection site)\*
- Missed assessment as per the Schedule of Events/Assessments (Table 3) at Baseline, Days 90, 180, and 210 (EOS) visit

- Inclusion criteria violation
- Exclusion criteria violation
- Subject not adhering to protocol subject restrictions
- Subject taking any prohibited concomitant medication

\*If the mis-dosing was unintended (ie, a medication error), the error should be reported as per instructions in [Section 8.4](#), Procedure for Medication Error Reporting.



### **13. ETHICS AND RESPONSIBILITY**

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the 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 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 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 (ICF), which shall be approved by the same IRB or EC responsible for approval of this protocol. Each ICF 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 ICF 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 ICF. The subject shall be given a copy of the signed ICF, 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 ICF 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 ICF 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 without written prior permission from the Sponsor. 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, unless otherwise agreed to in writing by the Sponsor.

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.

With respect to the clinical trial data that is received from countries in the European Economic Area and Switzerland, MDCO has certified adherence to the US- EU and the US-Swiss Safe Harbor Principles.

## 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 investigational new drug ALN-PCSSC, 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 Institutional Review Board (IRB) or Ethics Committee (EC) responsible for such matters in the Clinical Study Facility where ALN-PCSSC 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.

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Principal Investigator (Signature)

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Date

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Principal Investigator (Printed Name)

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Institution Name

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## APPENDIX A. 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.

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.

### **SENSORY FUNCTION**

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

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

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

Sensory Tests:

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

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

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

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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 antecubital 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 B. 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 mmHg or >30% decrease from that person's baseline

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

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

**APPENDIX C. CLARIFICATION OF LABORATORY ASSESSMENTS  
TO BE PERFORMED IN THE SCREENING PHASE (DAY  
-14 TO -1)**

<b>Screening Labs</b>	<b>Local / central Lab</b>	<b>Comments</b>
Hematology	Local lab	Standard panel to include Hb, WBC and platelets as a minimum
Chemistry	Local lab	Standard chemistry panel to include BUN and electrolytes, serum creatinine, glucose. (Taken at same time as fasting lipids so glucose measurement is fasting). Liver function tests to include ALT, AST and total bilirubin which are exclusion criteria
Coagulation	Local lab	Standard coagulation panel to include PTT or aPTT, INR and PT (if part of local coagulation panel)
Inflammatory biomarkers	Central lab	hsCRP and inflammatory markers (IL6, IFN- $\gamma$ , and TNF- $\alpha$ ) will be measured only at the central lab
HbA1c	Local lab	HbA1c is an exclusion criteria
Fasting lipids and lipoproteins	Local lab	Standard lipid and lipoprotein panel to include LDL-C and triglyceride which are inclusion criteria
Fasting lipids	Central lab	Sample taken at same time as local lab sample and shipped to Medpace. (With the sample from the randomization visit these two samples will provide the baseline lipid measurements for the study).
PCSK9	Central lab	Sample taken at same time as local lab sample and shipped to Medpace. (With the sample from the randomization visit these two samples will provide the baseline PCSK9 measurements for the study).
Urinalysis	Local lab	Done using dipsticks provided by central lab. Abnormal specimens sent to local lab for further testing.
Urine Pregnancy testing	Local lab	Done using dipsticks provided by central lab. To be conducted for eligible women at all visits.

Note: Local lab assessments for eligibility are not expected to include the full panel measured by Medpace, which are measured for the purpose of the study and the study report.

Laboratory assays beyond the specific inclusion/exclusion criteria during screening are performed to exclude significant medical conditions making the subject unsuitable for the study as per exclusion criteria 10 and 16d.