

STATISTICAL ANALYSIS PLAN

Protocol No.: MDCO-PCS-15-01

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.

EuDRACT No.: 2015-003772-74

PROTOCOL VERSION: Amendment 01, 11 Jan 2016

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1. TRIAL DESIGN

1.1. 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 (for example 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)

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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. Following each formal data review, the Sponsor (in consultation with the IDMC and the Executive Committee [EC]) may decide to stop or recommend a modification to study conduct.

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 their second injection of ALN-PCSSC or placebo at the Day 90 visit.

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 then at monthly intervals for 6 months. Any subjects in whom LDL-C levels have not returned to >80% of baseline values will continue to be followed.

1.2. Objective of Trials

Primary:

- To evaluate the effect of ALN-PCSSC treatment on LDL-C levels at Day 180.

Secondary:

- To evaluate the effect of ALN-PCSSC on the following:
 - LDL-C levels at other time points
 - PCSK9 levels over time
 - other lipids, lipoproteins, apolipoproteins
 - the proportion of subjects achieving prespecified global lipid guidelines
 - individual responsiveness to different doses
 - duration of lipid-lowering effect of different doses
 - the safety and tolerability profile of ALN-PCSSC

Exploratory:

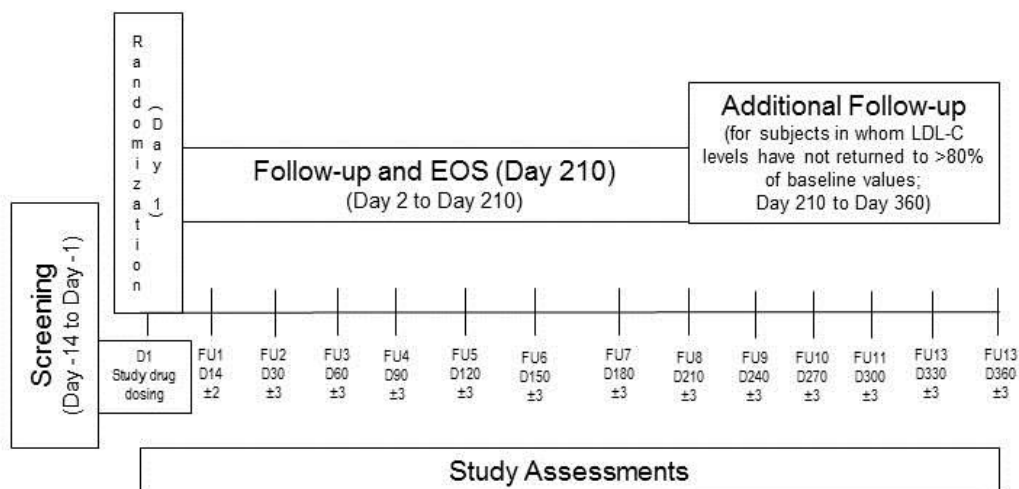
- To collect/evaluate the effect of ALN-PCSSC on the following:
 - Cardiovascular (CV) events such as CV death, non-fatal myocardial infarction (MI), major coronary events (coronary heart disease [CHD] death, resuscitated cardiac arrest, non-fatal MI), ischemic stroke, and hemorrhagic stroke
 - Anti-drug antibodies (ADA) for the investigational product

1.3. Schematic Diagram of Trial Design

➤ One Dose (one or two injections on Day 1)

The study design for one dose is presented in [Figure 1](#) .

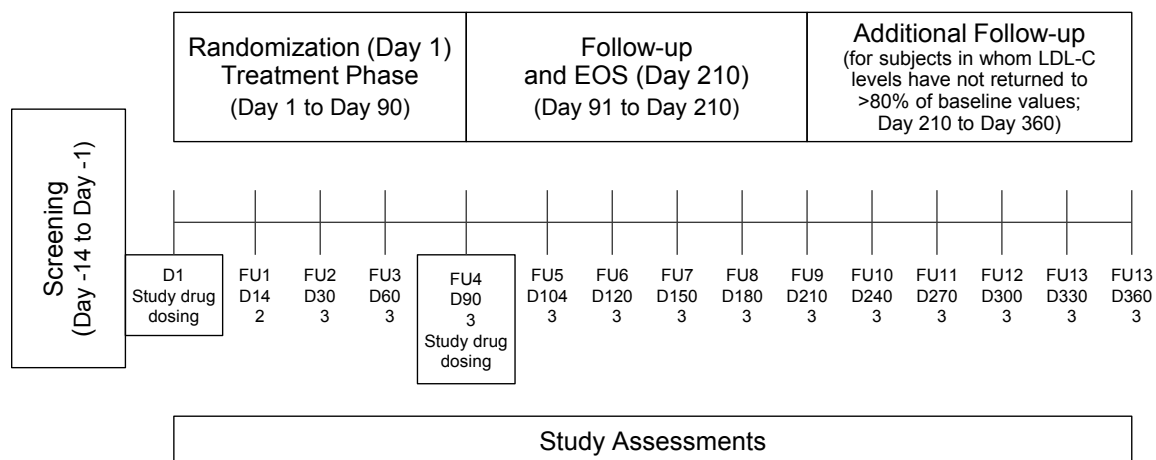
Figure 1: Study Design for One Dose



➤ **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



Note: Any subjects in whom LDL-C levels have not returned to >80% of baseline values will continue to be followed.

1.4. Schedule and Sequence of Procedures

The Schedule of Events/Assessments (Table 2) summarizes the study assessments by time point.

This study consists of 10 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: Days 2 to 210; EOS on Day 210

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: Days 91 to 210; EOS on Day 210

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.

Any subject in whom LDL-C levels have not returned to >80% of baseline values, will continue to be followed.

Schedule of Assessments

Table 2: Study Design and Schedule of Assessments

One Dose:	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)
Two Doses:			Treatment Phase				Follow-Up					
Study Day	-14 to -1	1	FU1 14 (± 2)	FU2 30 (± 3)	FU3 60 (± 3)	FU4 90 (± 3)	FU5 104 (± 3) ^a	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 (including full neurological examination)	X										X	
Inclusion/Exclusion Criteria	X	X										
Randomization		X										
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	
12 Lead ECG ^c	X	X									X	
HbA1c	X	X				X				X		X (day 270 and 360)
Clinical labs ^{d,j}	X ^e	X ^f	X	X	X	X	X	X	X	X	X	X
Urinalysis ^{d,f} (local)	X	X									X	
Pregnancy test ^h (local)	X	X	X	X	X	X	X	X	X	X	X	X ⁱ
Anti-ALN-PCSSC (ADA) antibodies ^j		X ^k		X				X			X	X ⁱ
Efficacy parameters (LDL-C, lipids, PCSK9) ^m	X	X	X	X	X	X	X	X	X	X	X ^l	X ⁿ
Study drug administration		X				X						

One Dose:	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					
Two Doses:			FU1 14 (± 2)	FU2 30 (± 3)	FU3 60 (± 3)	FU4 90 (± 3)	FU5 104 (± 3) ^a	FU6 120 (± 3)	FU7 150 (± 3)	FU8 180 (± 3)	FU9 210 (± 3)	
Study Day	-14 to -1	1										FU10 (Day 240) (± 3) FU11 (Day 270) (± 3) FU12 (Day 300) (± 3) FU13 (Day 330) (± 3) FU14 (Day 360) (± 3)
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; PCSK9 = proprotein convertase subtilisin/kexin type 9; SAE = serious adverse event;TNF-α=tumor necrosis factor alpha.

^a Subjects who receive a second dose of study drug on Day 90 only.

^b Vital signs: blood pressure, heart rate, temperature, and respiration will be measured prior to injection and at 4 hours after injection

^c ECG is performed prior to the injection on Day 1.

^d Hematology, chemistry (including glucose, HbA1c, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing. 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.

^e 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

^f 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 up on a monthly visit schedule until Day 360, or until this level has been reached.

^g Urinalysis collection is prior to the injection on Day 1.

^h 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). Additional urine pregnancy test may be required due to local regulations.

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

^j Two ADA samples will be drawn on Day 1: one before the injection and one 4 hours after the injection.

^k Additional aliquots of plasma and serum will be collected at each time point and stored for future analyses.

^l at final observation

^m Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], C-reactive protein (CRP), and PCSK9.

ⁿ 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.

2. GENERAL CONDUCT OF TRIAL

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

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

- Informed consent
- Medical history
- Physical examination
- Assessment of inclusion/exclusion criteria
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical laboratory assessments (hematology, chemistry [including liver and renal function], HbA1c, urinalysis, and coagulation testing)
- Urinalysis (local)
- Pregnancy test (local)
- Assessment of lipids/lipoproteins:
- Concomitant medications
- Central laboratory assessments (lipid panel, BQ LDL-c, PCSK9, hsCRP, Lp(a), Apo AI and Apo B)

2.2. 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
- Clinical laboratory assessments (hematology, chemistry [including liver and renal function], HbA1c, and coagulation testing)
- Urinalysis (local)
- Pregnancy test (local)
- Assessment of ADA
- Assessment of lipids/lipoproteins
- Concomitant medications

- AE reporting
- Serious Adverse Event (SAE) reporting

The following procedures will be performed after the injection:

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

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).

2.3. Follow-Up Visits 1 to 7

Subjects will return to the study center 14 days (± 2 days) after study drug administration for Follow-Up Visit 1, 30 days (± 3 days) after study drug administration for Follow-Up Visit 2, and monthly (± 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 prior to injection and at 4 hours after injection
- Clinical laboratory assessments (hematology, chemistry [including liver and renal function], urinalysis, and coagulation testing)
- Assessment of ADA: At Follow-Up Visit 2 (Day 30) and Follow-Up Visit 5 (Day 120)
- Assessment of lipids/lipoproteins
- Study drug administration: Second dose at Follow-Up Visit 4 (Day 90) for subjects randomized to receive two doses
- Concomitant medications
- AE reporting
- SAE reporting

2.4. End of Study Visit (Follow-Up Visit 8; 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

- 12-lead ECG
 - Clinical laboratory assessments (hematology, chemistry [including liver and renal function], urinalysis, and coagulation testing)
 - Urinalysis (local)
 - Pregnancy test (local)
 - Assessment of ADA
 - Assessment of lipids/lipoproteins
 - Concomitant medications
 - AE reporting
 - SAE reporting
- LDL-C levels have returned to >80% of baseline values.

2.5. 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.

2.6. Assessment of Safety

2.6.1. Adverse Events

Subjects will be carefully monitored for adverse events (AEs) and for adverse events of special interest (injection site reactions) by the investigator during the designated study period.

2.6.2. Clinical Laboratory Assessments

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

Additional aliquots of plasma or serum will be collected at each time point and stored for 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 will be performed by each participating institution's laboratory. Results from these Screening tests must be available before the start of study drug injection on Day 1 to confirm subjects meet eligibility criteria.

Urinalysis will be performed at the time points defined in the Schedule of Assessments and evaluated.

2.6.3. Electrocardiograms

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

2.6.4. Assessment of Cardiovascular Events

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

2.6.5. 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 2](#)).

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.

For the assessment of immunogenicity the following will be performed:

- The incidence of subjects testing ADA positive
- Review of safety data of ADA positive patients (AE, SAE, AESI)
- Determination of clinically relevant differences in safety findings between ADA positive and ADA negative patients who received PCSSC when possible

2.7. Assessment of Efficacy

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

Subjects will be in a fasted state for all efficacy laboratory assessments. Parameters to be assessed will include: total cholesterol (TC), triglycerides, LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein (VLDL), apolipoprotein A1 (Apo-AI), apolipoprotein B (Apo-B), lipoprotein(a) [Lp(a)], C-reactive protein (CRP), and PCSK9.

Blood samples for determination of LDL-C (β -quantification) concentrations will be collected at the time points in the Schedule of Assessments.

Plasma samples will be analyzed using a validated enzyme linked immunosorbent assay to determine PCSK9 protein concentration.

3. ADVERSE EVENTS

3.1. 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 drug was given or 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.

Incidences of injection site reactions will also be presented by dose group. 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.

3.2. 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.

3.3. 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 the IMP.

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

3.4. 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, or
- 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.

3.5. 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 a quantity of the study product given per administration.

3.6. 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).

Table 3: Common Terminology Criteria for Adverse Events (CTCAE) criteria 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

Abbreviations: AE = adverse even

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

4. MEASURES TO MINIMIZE/AVOID BIAS

The study will be conducted using a double-blind design, with placebo matched by volume within each dose and regimen but not between regimens. 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 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.

5. STATISTICAL PLAN

5.1. Sample Size

The sample size calculation was performed with the assumption (which was based on the observed results from a phase 1 trial) that the difference in change from baseline between the active dose groups and the placebo will be no less than 30 mg/dL, with a standard deviation of 20 mg/dL. [REDACTED]

[REDACTED] 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.

5.2. 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). [REDACTED]

[REDACTED] 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.

5.3. General Statistical Considerations and Definitions

5.3.1. 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 [SD], confidence intervals, median and interquartile range [Q1 and Q3], minimum and maximum).

The Statistical Analysis Plan (SAP) will be finalized before database lock.

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

5.3.2. Analysis Population

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

5.3.2.1. 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.

5.3.2.2. 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.

5.3.2.3. 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.

5.3.2.4. 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.

5.3.3. Analysis Windows and Baseline

The observational period for the study includes screening period (from Day -14 to Day -1) to the EOS visit (follow-up Visit 8, 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, if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including safety events that were 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 PD samples for lipids and PCSK9 will be taken prior to initiation of study drug. The average of the two samples will be used as the baseline evaluation. If only one sample was collected, the collected sample will be used as baseline. If more than two samples were taken, then the average of the last two will be used as baseline.

5.3.4. Missing data handling

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

5.4. Statistical Analyses

5.4.1. 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.

5.4.2. Study Drug

For all cohorts including those that receive doses only Day 1 and those that receive a dose on Day 1 and a second dose on Day 90, dose regimen, summary of study drug dose given, number of syringes given and syringe volume, incidences of study drug not prepared, incidences of mis-dosing will be provided.

5.4.3. 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.

5.4.4. Efficacy Analysis

The results of efficacy and safety analysis will be used to help determine the dose(s) for future phase 3 trial(s).

5.4.4.1. 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.

5.4.4.2. Endpoints

The secondary endpoints of this trial are:

➤ **Change from Baseline LDL-C**

- Percentage change in LDL-C from baseline to Day 90
- Percentage change in LDL-C from baseline to Days 14, 30, 60, 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 (if not resolved by Day 210, subjects will continue to be followed until LDL-C returns to within 80% of baseline.
- 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
- Proportion of subjects in each group who attain global lipid modification targets for their level of ASCVD risk

➤ **Change from Baseline 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 (calculated and BQ) HDL-C, non-HDL-C, very low-density lipoprotein (VLDL), Apo-AI, Apo-B, Lp(a), CRP, and PCSK9.

- Percentage change in PCSK9 levels from baseline to Days 14, 30, 60, 90, 120, 150, 180, and 210
- Percentage change in other lipids, lipoproteins, apolipoproteins from baseline at each subsequent visit to Day 210

5.4.4.3. Exploratory Efficacy Endpoints

The exploratory endpoints of this trial are:

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

5.4.5. Safety Analysis

The safety objectives of this study are to evaluate:

- The safety and tolerability profile of ALN-PCSSC.

5.4.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. An AE (classified as preferred term, and AESI) 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.

5.4.5.2. 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.

5.4.5.3. Clinical Laboratory Assessments

Clinical laboratory endpoints include:

Hematology: hemoglobin, hematocrit, erythrocytes, reticulocytes, platelet counts, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), 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 (ALP), gamma glutamyl transferase (GGT), uric acid, TBIL(direct and indirect bilirubin), sodium, creatine phosphokinase, albumin, total protein, urea (BUN), creatinine, potassium, chloride, glucose (fasting), inorganic phosphate, eGFR, calcium

Urinalysis: The following parameters will be assessed: Nitrite, protein, glucose, ketone, urobilinogen, bilirubin, RBC/erythrocytes, WBC/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities)

5.4.5.4. Vital Signs

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

5.4.5.5. Neurological Examinations

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

6. COMPUTER METHODS

Statistical analyses will be performed using SAS (version 9.2 or later version).

7. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

There are no changes to the analyses specified in the protocol.

8. REFERENCES

Protocol MDCO-PCS-15-01