Statistical Analysis Plan

Protocol Title:	A Double-blind, Randomized, Placebo-controlled Phase 2 Study to Evaluate Efficacy, Safety, and Tolerability of Olpasiran (AMG 890) (a GalNAc-conjugated Small Interfering RNA [siRNA]) in Subjects With Elevated Lipoprotein(a)
Short Protocol Title:	Olpasiran trials of Cardiovascular Events And LipoproteiN(a) reduction – DOSE Finding Study (OCEAN[a]-DOSE)
Protocol Number:	20180109
NCT Number:	NCT04270760
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Sponsor:	Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320, USA
SAP Date:	**Document Version** — **Date** Original (v1.0) — 14 Oct 2020 Amendment 1 (v2.0) — 25 Aug 2021 **Amendment 2 (v2.1)** — **10 May 2022**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	14OCT2020	
Amendment 1 (v2.0)	25AUG2021	**Changes** 1. Change one of the authors from [redacted] Rationale: Study lead statistician role had been transitioned from [redacted] 2. Update statistical analysis plan (SAP) version and date throughout this SAP Rationale: Statistical analysis plan was amended 3. Change the product name from AMG 890 to olpasiran throughout this SAP Rationale: To align with the Protocol Amendment 2 4. Update the explanation for “AUC” in the list of abbreviations Rationale: To correct the typo 5. Remove the abbreviations of “CHD”, “NCEP ATP III”, “PT”, “SOC” and “TEAE” from the list of abbreviations Rationale: These abbreviations are no longer relevant to this SAP 6. Add the explanation for “UC” in the list of abbreviations Rationale: To explain the abbreviation of a new definition added in section 5.3 7. Add a level of achievement of Lp(a) $<$ 125 nmol/L in the section 2.1 Rationale: To align with the Protocol Amendment 2 8. Update the levels of achievement of Lp(a) $\leq$ 100 nmol/L to $<$ 100 nmol/L, Lp(a) $\leq$ 75 nmol/L to $<$ 75 nmol/L, Lp(a) $\leq$ 50 nmol/L to $<$ 50 nmol/L in the section 2.1 Rationale: To align with the Protocol Amendment 2 9. Specify the event types of interests in “adjudicated events” in section 2.1 Rationale: To align with the Protocol Amendment 2 10. Remove the supplement statement of “with or without a history of myocardial infarction or stroke” from

		atherosclerotic cardiovascular disease in section 2.2 and 3.1 Rationale: To align with the Protocol Amendment 2 11. Update the descriptions of interim analysis in section 3.1 Rationale: To align with the Protocol Amendment 2 12. Update the descriptions of sample size in section 3.2 Rationale: To align with the Protocol Amendment 2 13. Update the grouping approach for region in section 4.1 Rationale: To follow the comment from TIMI and have the grouping consistent in section 4.1 and 4.2 14. Add a definition for reflexive approach in section 5.3 Rationale: To clarify that how to derive the variables of LDL-C and VLDL-C by using reflexive approach 15. Add the definition for CAS in section 6.2 Rationale: To clarify the analysis set used in sensitivity analysis 16. Update the descriptions of interim analysis in section 7.1 Rationale: To align with the Protocol Amendment 2 17. Update the wordings from “36-week” to “week 36” and from “locked” to “processed” in section 7.2 Rationale: To align with the Protocol Amendment 2 18. Update the wordings from “48-week” to “week 48” and from “locked” to “processed” in section 7.3 Rationale: To align with the Protocol Amendment 2 19. Add the approach and analysis set for sensitivity analysis in section 9.1 Rationale: To clarify what test and analysis set will be used in sensitivity analysis 20. Add the description for study site will be tabulated in section 9.2 Rationale: To align with the standard TFL shells, the number and percent of subjects randomized will be provided

		21. Update section 9.2 and 9.3 to include COVID-19 impact related descriptive analysis to measure COVID impact Rationale: To describe that the COVID-19 related PD will also be summarized and listed 22. Add a sentence for primary in section 9.5.1 Rationale: To clarify the sensitivity analysis that the primary analysis will be performed by completer analysis set as well 23. Update the wording from "treatment" to "treatment group" in section 9.5.1 Rationale: To provide more accurate wording in the description 24. Remove the sentence for log transformation in section 9.5.1 Rationale: Multiple imputation is assuming normal distribution, we are changing the sensitivity analysis from log transformation to a non-parametric method 25. Update the descriptions of additional analysis in section 9.5.1 Rationale: To provide more accurate descriptions for MCP-Mod analysis 26. Add the descriptions for following lipid parameters will be provided in section 9.5.3 Rationale: Per the suggestions from safety team, the descriptive summary for HDL-C, non-HDL-C, Triglycerides and VLDL-C will be provided as well 27. Update the MedDRA version in section 9.6.1 Rationale: Per the suggestions from safety team and to align with DMP, now the MedDRA version is 24.0 28. Update the descriptions of coding term for treatment-emergent adverse events in section 9.6.1 Rationale: Per safety team's review suggestions, TEAEs will be provided by PT only; TEAEs, serious TEAEs will be tabulated by SOC, HLT and PT; TEAEs leading to discontinuation of IP, fatal TEAEs, treatment-related TEAEs, and treatment-related serious

		TEAEs will be provided by SOC and PT 29. Add an adverse events of interest in section 9.6.1 Rationale: Per safety team's review suggestions, adding the "injection site reactions" as an new adverse events of interest 30. Update the wording in table tile in appendix C Rationale: Per the cross-functional review team's suggestions and follow up the guideline to change the wording from 'guidelines' to 'guideline'
Amendment 2 (v2.1)	20APR2022	**Changes** 1. Add one of the authors [redacted] Rationale: study statistician has been transitioned to [redacted] 2. Update statistical analysis plan (SAP) version and date throughout this SAP Rationale: Statistical analysis plan was amended 3. Edited language in Section 3.1 regarding the extended safety follow-up period. Removed the language of "Only an unblinded team will be unblinded at the end of treatment period analysis. Individuals who will remain involved in the conduct of the study will remain blinded" in Section 7.3. Rationale: to align with protocol amendment 3 that Amgen team will be unblinded after EOT analysis snapshot and extended safety follow up period will be changed to at least 24 weeks after week 48. 4. Add the imputation rule for adverse event and concomitant medication partial end dates in section 8.3.2 Rationale: clarifying imputation rule for partial end dates to provide more clear instruction for programming 5. Removed the wording "after week 36" in section 9.1 Rationale: EOT analysis will be performed including all visits up to week 48.

		6. Update the summary of analyses section for End of Treatment Period analysis in Table 2. Rationale: analyses for primary endpoints will be repeated in EOT analysis as well. 7. Removed the language of biomarker endpoint analysis in the section 9.5.3. Rationale: Per protocol, the results of the exploratory biomarker endpoints will not be included in the final clinical study report unless noteworthy. 8. Update the Appendix A analytical visit window Rationale: 1. add visit window for weight and PROMIS Health endpoint which were missed in previous SAP. 2. Added week 72 derivation for non-lipids/Lp(a) parameters to align with protocol amendment 3 that subjects are expected to have end of study visit on week 72. Changed term "EOS" to "> Week 72" 3. Clarified that all visits for lipids and Lp(a) will be mapped to Q12W windows.

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List of Abbreviations

Abbreviation	Explanation
A1C	Glycated Hemoglobin
ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration Time Curve
BID	Twice Daily
BMI	Body Mass Index
CAS	Completer Analysis Set
CK	Creatine Kinase
C_{max}	Maximum Observed Concentration
CMH	Cochran-Mantel Haenszel
CPMS	Clinical Pharmacology, Modeling and Simulation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DIIR	Data Issue Identification and Resolution
DRT	Data Review Team
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOIP	End of Investigational Product
EOS	End of Study
FAS	Full Analysis Set
HDL-C	High-Density Lipoprotein Cholesterol
hs-CRP	High Sensitivity C-Reactive Protein
hs-IL-6	High Sensitivity Interleukin 6
IARSC	Interim Analysis Review Steering Committee
ID	Identity
IP	Investigational Product
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
Lp(a)	Lipoprotein(a)
LS means	Least Square Means
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical Dictionary for Regulatory Activities
NCEP ATP III	National Cholesterol Education Panel Adult Treatment Panel III
NCT	National Clinical Trials
PK	Pharmacokinetic
PROMIS	Patient-Reported Outcomes Measurement Information System
Q12W	Every 12 Weeks
Q24W	Every 24 Weeks
QD	Once Daily
QoL	Quality of Life
QTc	Corrected QT
SAP	Statistical Analysis Plan
SC	Subcutaneous
SAS	Statistics Analysis System
UC	Ultracentrifugation
ULN	Upper Limit of Normal
VLDL-C	Very Low-Density Lipoprotein Cholesterol
vs.	Versus
WHODrug	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 2 for study 20180109, AMG 890 Olpasiran dated 01 April 2021. The scope of this plan includes the primary analysis, the end of treatment period analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To evaluate the effect of olpasiran administered subcutaneous (SC) every 12 weeks (Q12W) compared with placebo, on percent change from baseline in Lp(a) after 36 weeks of treatment</td><td>• Percent change in Lp(a) from baseline at week 36</td></tr>
<tr><td colspan="2">Primary Estimand</td></tr>
<tr><td colspan="2">The primary estimand consists of:
• The target population, which is adults with atherosclerotic cardiovascular disease and elevated Lp(a)
• The primary variable, which is percent change from baseline in Lp(a) at week 36
• The intercurrent events which are the discontinuation of investigational product and excluded medication(s) taken during study. For the primary estimand, the treatment effect will be estimated in subjects who are randomized and received at least 1 dose of investigational product regardless of the occurrence of these intercurrent events
• The summary measure, which is the difference between olpasiran and placebo in the mean percent change from baseline in Lp(a) at week 36
• The treatments to be compared are each olpasiran group vs. placebo
The primary estimand is the difference between each olpasiran group and placebo in the mean percent change from baseline in Lp(a) at week 36 in adults with atherosclerotic cardiovascular disease and with elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To evaluate the effect of olpasiran administered SC Q12W compared with placebo, on percent change from baseline in:
– Lp(a) after 48 weeks of treatment</td><td>• Percent change from baseline in:
– Lp(a) at week 48
– LDL-C at week 36 and week 48
– ApoB at week 36 and week 48</td></tr>
</table>

– Low- density lipoprotein cholesterol (LDL-C) after 36 and 48 weeks of treatment – Apolipoprotein(B) (ApoB) after 36 and 48 weeks of treatment	
• To characterize the pharmacokinetic (PK) properties of olpasiran	• PK parameters for olpasiran including, but not limited to, maximum observed concentration (Cmax), and the area under the concentration time curve (AUC)

Estimands for Secondary Endpoints

The estimands for the secondary endpoints in Lp(a), LDL-C, and ApoB are the differences between each olpasiran group and placebo in the mean percent change from baseline in:

- Lp(a) at week 48
- LDL-C at week 36
- LDL-C at week 48
- ApoB at week 36
- ApoB at week 48

For adults with atherosclerotic cardiovascular disease and elevated Lp(a) who are randomized and received at least 1 dose of investigational product, regardless of discontinuation of investigational product and excluded medication(s) taken during the study.

Exploratory	
• To evaluate the effect of olpasiran administered SC Q12W compared with placebo, on: – percent change from baseline in Lp(a) – percent change from baseline in LDL-C – percent change from baseline in ApoB – achievement of Lp(a) < 125 nmol/L – achievement of Lp(a) **<** 100 nmol/L – achievement of Lp(a) **<** 75 nmol/L – achievement of Lp(a) **<** 50 nmol/L	• Percent change from baseline at each scheduled visit, except weeks 36 and 48, in: – Lp(a) – LDL-C – ApoB • Achievement at each scheduled visit of the following: – Lp(a) < 125 nmol/L – Lp(a) **<** 100 nmol/L – Lp(a) **<** 75 nmol/L – Lp(a) **<** 50 nmol/L
• To evaluate the effect of olpasiran administered SC Q24W compared with olpasiran administered SC Q12W and placebo, on: – percent change from baseline in Lp(a) – percent change from baseline in LDL-C – percent change from baseline in ApoB – achievement of Lp(a) < 125 nmol/L	For the olpasiran SC Q24W group: • Percent change from baseline at each scheduled visit, in: – Lp(a) – LDL-C – ApoB • Achievement at each scheduled visit of the following:

– achievement of Lp(a) **<** 100 nmol/L – achievement of Lp(a) **<** 75 nmol/L – achievement of Lp(a) **<** 50 nmol/L	– Lp(a) < 125 nmol/L – Lp(a) **<** 100 nmol/L – Lp(a) **<** 75 nmol/L – Lp(a) **<** 50 nmol/L

Objectives	**Endpoints**
Exploratory	
• To estimate cardiovascular event rates in subjects treated with olpasiran, including aggregated exploratory analyses across the olpasiran program	• Adjudicated events – Death by any cause – Cardiovascular death – Myocardial infarction – Hospitalization for unstable angina – Coronary revascularization – Stroke – Transient ischemic attack – Cerebrovascular revascularization – Acute limb ischemia – Major amputation, or urgent peripheral revascularization for ischemia
• To describe the effect of olpasiran of quality of life (QoL) measures as assessed using the PROMIS Global Health	• Change from baseline in PROMIS Global Health measures at each scheduled visit
• To evaluate the effect of olpasiran administered SC on inflammatory biomarkers	• Change from baseline at week 48 in: – high sensitivity (hs) C-reactive protein (CRP) – hs-Interleukin 6 (IL-6)
• To assess the anti-olpasiran antibody response	• Anti-olpasiran antibody formation, if tested
Safety	
• To evaluate the safety and tolerability of olpasiran administered SC compared with placebo in subjects with elevated Lp(a)	• Treatment emergent adverse events • Clinically significant safety laboratory values and vital signs at each scheduled visit

2.2 Hypotheses and/or Estimations

The null hypothesis is that there is no difference between olpasiran and placebo in percent change from baseline in Lp(a) at week 36 in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

3. Study Overview

3.1 Study Design

This is a phase 2, double-blind, randomized, placebo-controlled, multicenter, dose finding study to evaluate efficacy, safety, and tolerability of olpasiran on Lp(a) compared to placebo in subjects with atherosclerotic cardiovascular disease and with elevated Lp(a).

Subjects will be randomized in a 1:1:1:1:1 ratio to 1 of the following 5 treatment groups (some olpasiran arms will include placebo to maintain blind):

- Group 1: 10 mg Q12W
- Group 2: 75 mg Q12W
- Group 3: 225 mg Q12W
- Group 4: 225 mg Q24W
- Group 5: Placebo Q12W

The randomization will be stratified by screening Lp(a) ≤ 200 vs. > 200 nmol/L and by region (Japan vs. Non-Japan).

The study treatment period is 48 weeks with doses at day 1, week 12, week 24, and week 36. After week 48 there is an extended safety follow-up without further dosing with investigational product for **a minimum of 24 weeks.** Subjects will remain on standard of care (including stable lipid-lowering therapy) per their local guidelines during the treatment period and extended safety follow-up period.

An administrative interim analysis will be performed when approximately 240 subjects have had the opportunity to complete the week 24 assessments or have early terminated. At that point, approximately 120 subjects may have had the opportunity to complete the week 36 assessments or have early terminated.

The interim analysis results will be used to support dose selection for a phase 3 registrational study and trigger early planning for the phase 3 program. In addition, the safety and efficacy results may be used in company internal discussions and external interactions with regulatory agencies. The study continues regardless of the administrative interim results.

Team members that remain directly involved with the conduct of the study, investigators and subjects will not receive results of the interim analysis and will remain blinded.

The primary analysis will occur when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated. The end of treatment period analysis will occur when all subjects have had the opportunity to complete the week 48 assessments or have early terminated. Final analysis will occur after the last subject either completes the extended safety follow-up and has ended the study or has early terminated from the study.

The overall study design is described by a study schema in Section 1.2. in the protocol. The endpoints are defined in Section 2.1.

3.2 Sample Size

Assuming standard deviation of 30% as observed in phase 1 study, a 5% drop-out rate and with Bonferroni multiplicity adjustment to control family-wise type 1 error rate at 0.05, at least 48 subjects per arm provides at least 90% power to detect a treatment difference of 25% between an active and placebo arm in mean percent change of Lp(a) from baseline. It is expected to have 99% power to detect a treatment effect of -80% vs. -3% between active and placebo arms in mean percent change of Lp(a) from baseline. Considering 5% drop-out rate, at least 48 subjects per arm (at least 192 subjects in the 4 active treatment arms) provides a 95% confidence of detecting 1 case of an adverse event at an incidence of 1/60.

Up to a total of approximately 290 subjects may be enrolled.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Baseline covariates include, but are not limited to:

- Stratification factors
  - Screening Lp(a) (≤ 200 nmol/L vs. >200 nmol/L)
  - Region (Japan vs. Non-Japan)
- Age
- Sex
- Race
- Baseline Lp(a)

- Baseline LDL-C
- Baseline ApoB
- Baseline non-HDL-C
- Lipid Lowering Therapy (high intensity, not high intensity)
- Region (North America, Europe and Australia, other (including Japan))
- Ethnicity (Hispanic vs. Non-Hispanic)

4.2 Subgroups

Subgroups include, but are not limited to the following:

- Stratification factors
  - Screening Lp(a) (≤ 200 nmol/L vs. >200 nmol/L)
  - Region (Japan vs. Non-Japan)
- Age (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race (White, Black, Other)
- Baseline Lp(a) by median
- Baseline LDL-C by median
- Baseline ApoB by median
- Baseline non-HDL-C by median
- Lipid Lowering Therapy (high-intensity, not high-intensity, as defined in Appendix C)
- Region (North America, Europe and Australia, other (including Japan))
- Ethnicity (Hispanic vs. Non-Hispanic)

  If number of subjects in one or more categories is too small (e.g. less than 10%), the subgroup categories may be combined.

5. Definitions

5.1 Study Time Points

Enrollment Date

The enrollment date for each subject is recorded on the Subject Enrollment eCRF.

Randomization Date

Randomization date is defined as the date subject was allocated to a treatment group in the interactive response technology (IRT) as recorded on the Subject Enrollment eCRF.

Study Day 1

For each subject, Study Day 1 is defined as the date of the first dose of investigational product (IP) administration.

Study Day

For each subject, and for a given date of interest, study day is defined as the number of days since Study Day 1:

Study Day = (date of interest – Study Day 1 date) +1.

If the date of interest is prior to the Study Day 1:

Study Day = (date of interest – Study Day 1 date), so that the day prior to Study Day 1 is study day -1.

First Dose Date of Investigational Product

For each subject, the First Dose Date of Investigational Product is defined as the date of the first administration of IP as recorded on the Investigational Product Administration eCRF.

Last Dose Date of Investigational Product

For each subject, the Last Dose Date of Investigational Product is defined as the date of the last administration of IP as recorded on the Investigational Product Administration eCRF.

End of Treatment Period Date

For subjects who have week 48 assessment, the End of Treatment Period Date is the maximum date of all week 48 assessments. For subjects early withdraw study before week 48, the End of Treatment Period Date is the EOS date. ie. End of Treatment Period Date is defined as min (maximum date of all week 48 assessments, EOS date).

Extended Safety Follow-up Period Start Date

Extended Safety Follow-up Period Start Date = End of Treatment Period Date + 1

End of Investigational Product (EOIP) Date

End of Investigational Product Date is defined as the date of decision was made to end investigational product recorded on the End of Investigational Product Administration eCRF.

End of Study (EOS) Date for Individual Subject

End of Study is defined as the date subject ended study recorded on the End of Study eCRF.

Study End Date for the Overall Study

The Study End Date is the last EOS date of all randomized subjects.

5.2 Demographics and Baseline Related Definitions

Age

Age at randomization will be collected as the subject's age in years at enrollment as recorded on the Demographics eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for Lp(a), lipids (total cholesterol, HDL-C, LDL-C, VLDL-C and triglycerides), ApoA1, ApoB, and their derived parameters (eg, ratio between them) are defined as the mean of the two most recent non-missing concentrations measured through central lab prior to or on study day 1. If for any reason only 1 value is available, then that value will be used as baseline.

Other Baseline Values

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

BMI

Subject's BMI will be derived in kg/m^2 in the clinical database on the Physical Measurement eCRF.

Change (absolute change) from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point:

Change from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

[(value at a given post-baseline time point – baseline value) / baseline value] x 100%

5.3 Other Study Related Definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameter measurements to study weeks. The algorithm is provided in Appendix A.

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives treatment throughout the study that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

Olpasiran SC 10 mg Q12W, 75 mg Q12W, 225 mg Q12W, 225 mg Q24W and placebo SC Q12W.

Study Exposure Period in Months

For each randomized subject, Study Exposure Period = (EOS date – Randomization Date +1) / 365.25 * 12

IP Exposure Period in Months

IP Exposure Period = [min (Last IP Dose Date + 84 days, EOS Date) – First IP Dose Date + 1] / 365.25 * 12

Treatment Emergent Adverse Event in Treatment Period

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to No or missing on the Events eCRF and up to the End of Treatment Period date, or EOS date for subjects who early discontinue the study during the treatment period.

Treatment Emergent Adverse Event in Extended Safety Follow-up Period

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product (as determined by "Did event start before first dose of

investigational product" equal to No or missing on the Events eCRF) and on or after the Extended Safety Follow-up Period Start Date, and up to the EOS date.

Reflexive Approach for LDL-C and VLDL-C

Reflexive approach for LDL-C and VLDL-C is only applicable for the central lab data. For all analyses related to LDL-C and VLDL-C, unless specified otherwise, the following reflexive approach will be used.

When calculated LDL-C is less than 40 mg/dL or triglycerides are > 400 mg/dL, the ultracentrifugation (UC) LDL-C value from the same blood sample will be used instead of calculated LDL-C and the UC VLDL-C value from the same blood sample will be used instead of calculated VLDL-C, if available.

6. Analysis Sets

6.1 Full Analysis Set

Full analysis set (FAS) includes all randomized subjects who received at least one dose of investigational product.

FAS will be used to perform the efficacy analysis based on randomized treatment group, and the safety analysis based on actual treatment group (defined in section 5.3).

6.2 Completer Analysis Set

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP regimen, and have observed value for the primary endpoint. The completer analysis set will be used in sensitivity analysis of the primary endpoint.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

An administrative interim analysis will be performed when approximately 240 subjects have had the opportunity to complete week 24 assessments or have early terminated. At that point, approximately 120 subjects may have had the opportunity to complete week 36 assessments or have early terminated**.** The study continues per protocol as planned regardless of the data from the administrative interim results.

Interim analysis results will be reviewed by an Interim Analysis Review Steering Committee (IARSC) which consists of internal experts, who are or will thereafter be independent of the study team. Further detail regarding the interim analysis process in protecting trial integrity is provided in the IARSC Charter.

In addition to routine pharmacovigilance monitoring by Amgen, a Data Review Team (DRT) has been established to review the accumulating data from this study to ensure there is no avoidable increased risk for harm to subjects. The DRT is internal to Amgen but external to olpasiran teams. In order to maintain the trial integrity, the unblinded data reviewed by the DRT will be restricted and not accessible by the olpasiran team. Further detail regarding the DRT is provided in the DRT Charter.

7.2 Primary Analysis

Primary analysis will be performed when all randomized subjects have had the opportunity to complete the week 36 assessments or have early terminated. At that time, the database related to the primary analyses will be cleaned, processed and a snapshot will be taken.

Only an unblinded team will be unblinded at the primary analysis. Individuals who will remain involved in the conduct of the study will remain blinded.

7.3 End of Treatment Period Analysis

The end of treatment period analysis will be performed when all randomized subjects have had the opportunity to complete week 48 assessments or have early terminated. At that time, the database related to the end of treatment analyses will be cleaned, processed and a snapshot will be taken.

7.4 Final Analysis

Final analysis will be performed when all randomized subjects either complete the extended safety follow-up and ended the study or early terminate from the study. At that time, the database related to the final analysis will be cleaned, processed and the database will be locked. All efficacy and safety analyses during the extended follow-up period will be performed.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. Final PK data for all randomized subjects will be transferred

from statistical programming to Amgen's CPMS group. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

8.3 Handling of Missing and Incomplete Data

8.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. In the Data Issue Identification and Resolution (DIIR) processes, queries will be made to the sites to distinguish true missing values from other unknown values (eg, due to measurement of sample processing error).

All attempts will be made to capture missing or partial data for this trial prior to the data lock. The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

8.3.2 Handling of Incomplete Dates

Adverse event and concomitant medication with completely or partially missing start **and stop** dates will be queried.

After the issue is queried, if the date is still incomplete with year only or year and month only, the start **or stop** date will be imputed as described in Table 1 below.

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant medication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day/Month	1-Jan	Default to Study Day 1 if an event started the same year as Day 1
End date (AE and concomitant medication)	**Day**	**Last day of the month**	
	Day/Month	**31-Dec**	

If the stop date is entirely missing, assume the event or medication is ongoing.

8.4 Detection of Bias

This study has been designed to minimize potential bias by the use of randomization of subjects into treatment groups and the use of blinding. It is not expected that any study conduct procedures or statistical analyses will introduce bias in the study results or conclusions. However, potential sources of bias in this study include:

- Major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Subject level unblinding before final database lock and formal unblinding

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed.

8.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

8.6 Distributional Characteristics

Distributional assumptions for the planned analyses of the primary and secondary endpoints will be assessed. If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Unless specified otherwise, efficacy analyses will be performed on the FAS by randomized treatment group, and safety analyses will be performed on the FAS by actual treatment group.

For the Primary Analysis (as described in Section 7.2), all data up to the primary analysis data cut-off date will be included. Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed. Testing will be performed for endpoints defined up to week 36. Descriptive summary will be provided for all available visits by period (ie. Treatment period and extended safety follow-up period).

For the End of Treatment Period Analysis (as described in Section 7.3), all data up to the end of treatment period analysis cut-off date will be included. Testing will be performed for endpoints defined up to week 48. Descriptive summary will be provided for all available visits by period (ie. Treatment period and extended safety follow-up period).

For the Final analysis (as described in Section 7.4), all efficacy and safety analyses during the extended follow-up period will be performed based on the snapshot for the final analysis.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

All categorical variables will be summarized using the number and percent of subjects and all continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations.

Multiplicity Adjustment Method:

The Hochberg procedure will be used to control the type I error for multiple comparisons between active and placebo groups in the primary endpoint. The primary endpoint includes percent change in Lp(a) from baseline at week 36 for olpasiran SC Q12W groups and placebo. Percent change in Lp(a) from baseline for Q24W group is defined as exploratory endpoint.

A summary of the analyses for each planned analysis can be found in Table 2.

Table 2. Summary of Analyses

Analyses	Primary Analysis (all data up to primary analysis data cut-off date)	End of Treatment Period Analysis (all data up to End of Treatment Period Analysis data cut-off date)	Final Analysis (all data based on final snapshot)
Efficacy	• Repeated measures model for primary endpoint, secondary endpoints defined at week 36, and exploratory endpoints of percent change from baseline in Lp(a), LDL-C and ApoB up to week 36. • Multiplicity adjustment for primary endpoint, as described above in Multiplicity Adjustment Method • Sensitivity analysis for primary endpoint using non-parametric (Quade test) approach based on CAS • Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factors will be used for exploratory endpoints of Lp(a) achievements	• Repeated measures model for **primary endpoint**, secondary endpoints defined at **week 36 and** week 48 and exploratory endpoints of percent change from baseline in Lp(a), LDL-C and ApoB up to week 48. Testing is performed up to **week** 48. • **Multiplicity adjustment for primary endpoint, as described above in Multiplicity Adjustment Method** • **Sensitivity analysis for primary endpoint using non-parametric (Quade test) approach based on CAS** • Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factors will	• Descriptive summary for efficacy endpoints in the extended follow-up period

	(including achievement of Lp(a) < 125nmol/L) up to week 36 •Descriptive summary for all efficacy endpoints by period (ie. Treatment period and extended safety follow-up period)	be used for exploratory endpoints of Lp(a) achievements (including achievement of Lp(a) < 125nmol/L) **up** to week 48 • Descriptive summary for all efficacy endpoints by period (ie. Treatment period and extended safety follow-up period)	
Safety	• Summary by actual treatment group by period (ie. Treatment period and extended safety follow-up period)	• Summary by actual treatment group by period (ie. Treatment period and extended safety follow-up period)	• Summary by actual treatment group in the extended follow-up period

9.2 Subject Accountability

The number of subjects screened, randomized, receiving IP, and completing the study will be summarized by randomized treatment group. Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study will be presented.

Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation, including due to COVID-19 impact if applicable.

The number and percent of subjects randomized will be tabulated by study site, the stratification factors.

The number of subjects included in and excluded from each analysis set and reason for exclusion will also be summarized.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to

database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The number of subjects reporting Protocol Deviations due to COVID-19 impact will be summarized in a table. A Protocol Deviation listing of subjects impacted due to COVID-19 will also be provided.

9.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment group and overall using descriptive statistics. Baseline tables will summarize demographics, baseline characteristics, targeted medical history, and lipid regulating medication. If multiple races have been reported for a subject, the subject will be categorized as multiple race. Difference in stratum assignment between IVRS/IWRS stratum and data-derived stratum will be tabulated.

9.5 Efficacy Analyses

9.5.1 Analyses of Primary Efficacy Endpoint

To assess the primary endpoint of the mean percent change from baseline at week 36 in Lp(a), a repeated measures linear mixed effects model including terms for treatment group, stratification factors, scheduled visit and the interaction of treatment group with scheduled visit will be used. The least squares means (LS means) by treatment group and the treatment difference (olpasiran - placebo) at week 36 based on the model above will be summarized. The Hochberg procedure will be used to control the type I error for multiple comparisons between active and placebo groups.

To evaluate the robustness of the analysis results, sensitivity analyses will be performed as follow:

- The primary analysis will be repeated using CAS**.**
- Non-parametric analyses (Quade test) will be performed based on CAS
- To evaluate the impact of missing data, multiple imputation for subjects who discontinue IP with missing endpoint data:
    - It will be assumed that the missing percent change values will be normally distributed with a mean zero and a variance-covariance matrix the same as the observed variance-covariance matrix from subjects in the placebo group who did not discontinue IP with missing endpoint data.
    - If there is sufficient number of subjects in each treatment group who discontinue IP but have non-missing endpoint data, an additional multiple imputation will be carried out utilizing the information from these subjects to impute the missing data for subjects who discontinue IP and have missing endpoint data.

Additional analysis for percent change in Lp(a) from baseline at week 36 of all dose groups (Q12W and Q24W) will be performed using Multiple Comparison Procedure - Modelling (MCP-Mod) methodology (Bretz et al, 2005). MCP-Mod is a hybrid approach that combines hypothesis testing and modeling in a structured manner to analyze phase 2 dose-ranging studies with the purpose of finding target dose(s) of interest and provide guidance for suitable dose(s) entering the confirmatory phase 3 trials. The first step of the procedure (MCP-step) is used to assess presence of a dose response signal using a trend test deducted from a set of prespecified candidate models. The prespecified candidate

dose response models will be selected based on the known pharmacology and Lp(a) reduction of Olpasiran from phase I trials. The second step (Mod-step) relies on parametric modeling or model averaging to find the “optimal” dose for confirmatory trials. MCP-Mod method is found more effective than pairwise comparison due to its ability to utilize all available data from the continuum of active doses and placebo to estimate a parametric dose response curve which allows for interpolation and extrapolation of effect across a range of doses (Dinko Rekic et al, 2015).

Covariate analyses of the primary endpoint will be performed. Baseline covariates listed in Section 4.1 in their original format, will be included one at a time, in the repeated measures model used in the primary analysis.

Subgroup analyses on the primary efficacy endpoint will be conducted using the subgroups specified in Section 4.2. Treatment effect differences among subgroups, which represent subgroup by treatment interactions, will be estimated and tested based on statistics from the subgroup repeated measures models.

For covariate and subgroup analyses, the data-derived stratification factors will be used.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

Analysis of the secondary endpoints (including percent change from baseline at week 36 in ApoB and LDL-C, and percent change from baseline at week 48 in ApoB, Lp(a) and LDL-C) will be performed similarly to the analysis of the primary endpoint. There will be no multiplicity adjustment for the secondary efficacy endpoints.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Exploratory endpoints of percent change from baseline at scheduled visits in Lp(a), LDL-C and ApoB will be analyzed using repeated measures linear effects model including terms for treatment group, stratification factors, scheduled visit and the interaction of treatment group with scheduled visit will be used; and achievements of Lp(a) at scheduled visits (including achievement of Lp(a) < 125nmol/L) will be analyzed using CMH test as specified in Table 2. Subject incidence of positively adjudicated events (overall and by event type as defined in protocol) and change from baseline in PROMIS Global Health measures at scheduled visits will be summarized by treatment group using descriptive statistics.

Descriptive summary for non-HDL-C, HDL-C, VLDL-C and Triglycerides will be provided by scheduled visits.

9.6 Safety Analyses

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. All adverse event tables will be summarized by actual treatment group. All adverse event summaries will include all treatment-emergent events reported on the Event eCRF, including CEC reviewed events.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events.

Subject incidence of all treatment-emergent adverse events will be provided by preferred term in descending order of frequency. Treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated by system organ class, high level term, and preferred term in descending order of frequency. Treatment-emergent adverse events leading to discontinuation of investigational product, treatment-emergent fatal adverse events, treatment-related treatment-emergent adverse events, and treatment-related treatment-emergent serious adverse events will be provided by system organ class, and preferred term in descending order of frequency.

Subject incidence of adverse events of interest (peripheral neuropathy, myopathy, hypersensitivity reactions, effects on renal and liver function, hyperglycemia (including new onset diabetes), thrombocytopenia, coagulation parameters, immune-inflammatory and injection site reactions) will be summarized by category and preferred term.

9.6.2 Laboratory Test Results

Selected laboratory parameters will be summarized using descriptive statistics at scheduled visits. Laboratory shift tables using the CTCAE v5.0 or later grading will be used for analytes of interest, when applicable. The results will be based on the maximum (e.g., worst) shift from baseline to the EOS.

In addition, creatine kinase (CK) and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visits of the following categories:

- CK > 5 x ULN
- CK > 10 x ULN
- ALT or AST > 3 x ULN
- ALT or AST > 5 x ULN

- Total bilirubin > 2 x ULN
- (ALT or AST > 3 x ULN) and Total bilirubin > 2 x ULN and Alkaline Phosphatase <2 x ULN

9.6.3 Vital Signs

Vital signs will be summarized using descriptive statistics at each scheduled visit by actual treatment group.

9.6.4 Physical Measurements

Physical measurements will be summarized using descriptive statistics at each scheduled visit by actual treatment groups.

9.6.5 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.6 Antibody Formation

Anti-olpasiran binding antibodies will be summarized descriptively, if applicable. Subject level listing may be provided instead of summary if there is a small number of subjects that are tested for anti-olpasiran antibodies.

9.6.7 Exposure to Investigational Product

The exposure to IP will be summarized using descriptive statistics by actual treatment group.

9.6.8 Exposure to Concomitant Medication

Number and proportion of subjects receiving medications of interest will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug (WHODrug) dictionary.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

A PK sub-study will be conducted with a total of approximately 75 subjects (approximately 15 from each treatment cohort). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and

the sponsor. Pharmacokinetic samples will be collected as per the PK sub-study schedule of assessments (see protocol Table 1-1 and Table 1-2).

Individual and summary statistics for PK concentrations will be provided. These analyses will be performed by the CPMS group for the primary analysis, the end of treatment period analysis, and final analysis.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

Bach JP, Riedel O, Pieper L, et al. Health-related quality of life in patients with a history of myocardial infarction and stroke. *Cerebrovasc Dis*. 2011;31:68-76.

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*. 2005;61(3):738-748.

Grundy SM, Stone NJ, Bailey AL, et al.

AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018; 139: e1046-e1081.

Dinko Rekic, Yaning Wang, Vikram Sinha. Request for Qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. 22 April, 2015

12. Prioritization of Analyses

Not applicable.

13. Data Not Covered by This Plan

Not applicable.

14. Appendices

Appendix A. Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following table.

Handling multiple records assigned to an analytical study week:

If there is more than one record in a study week interval, the analytical record for that specific study week will be defined as the record closest to the scheduled visit day of that specific study week (7 x study week + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Analytical Study Week	Scheduled Visit Day	Physical, Neurological, and Muscular Examination, Vital Signs, Urine Pregnancy Test, Anti-Olpasiran-Antibody, **PROMIS General Health**	**Physical measurement (weight only)**	Fasting Lipids and Lp(a)	Glucose, ApoA1, ApoB, VLDL-C, Coagulation, Hematology, Hemoglobin A1C, Chemistry including hs-CRP, eGFR, Urinalysis
Day 2	2			(1, 15]	
Week 4	29			(15, 42]	(1, 56]
Week 8	57			(42, 70]	
Week 12	85	(1, 126]		(70, 98]	(56, 126]
Week 16	113			(98, 126]	
Week 20	141			(126, 154]	
Week 24	169	(126, 210]		(154, 182]	(126, 210]
Week 28	197			(182, 210]	
Week 32	225			(210, 238]	
Week 36	253	(210, 294]		(238, 266]	(210, 294]
Week 40	281			(266, 294]	
Week 44	309			(294, 322]	
Week 48	337	(294, **420**]	**(1, 420]**	(322, 378]	(294, **420**]
Week 60	421			(378, 462]	
Week 72	505	**(420, 546]**	**(420, 546]**	(462, 546]	**(420, 546]**
Week 84	589			(546, 630]	
Q12W[a]	n*7+1			((n-6)*7, (n+6)*7]	
> Week 72	Scheduled **visit day**	**> 546**	**> 546**	**-**[b]	**> 546**

[a] For Q12W scheduled visit, week n can have possible values of 96+12*m, where m=0, 1, 2, 3, … until the subject **has completed study** or subject has discontinued from the study.
[b] **For Lipids and Lp(a), all visits occurred after week 84 will be mapped to Q12W window.**

Appendix B. Common Terminology Criteria for Aes (CTCAE)

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 is modified for laboratory shift table. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. Lipid Modifying Background Therapy

Based on modified ACC/AHA 2018 **guideline**:

	High-Intensity Lipid Lowering Therapy	Moderate-Intensity Lipid Lowering Therapy	Low-Intensity Lipid Lowering Therapy
Atorvastatin	≥ 40 mg QD	10 – < 40 mg QD	< 10 mg QD
Rosuvastatin	≥ 20 mg QD	5 – < 20 mg QD	< 5 mg QD
Simvastatin	≥ 80 mg QD	20 – < 80 mg QD	< 20 mg QD
Pravastatin		≥ 40 mg QD	< 40 mg QD
Lovastatin		≥ 40 mg QD	< 40 mg QD
Fluvastatin XL		80 mg QD	< 80 mg QD
Fluvastatin		40 mg BID	< 40 mg BID
Pitavastatin		1 – 4 mg QD	< 1 mg QD

If a subject is on PCSK9 inhibitor, it will be considered as high intensity.

If a subject is on statin (high or moderate intensity, or at low intensity for Atorvastatin or Rosuvastatin) + Ezetimibe 10mg QD, it will be considered as high intensity.

If a subject is on low intensity statin (for Simvastatin, Pravastatin, Lovastatin, Fluvastatin XL, Fluvastatin, or Pitavastatin) + Ezetimibe 10mg QD, it will be considered as moderate intensity.

If Ezetimibe 10mg QD only, it will be considered as low intensity.

If a subject is on Bempedoic acid 180 mg QD without statin, it will be considered as low intensity.

If a subject is on Bempedoic acid 180 mg QD with statin, it will be considered as high intensity.

If a subject is on Ezetimibe 10mg QD and Bempedoic acid 180 mg QD, it will be considered as moderate intensity.

If a subject is not on any Lipid Lowering Therapy, it will be considered as no lipid lowering therapy.