Statistical Analysis Plan

Protocol Title:	A Phase I, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to evaluate the safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 890 in subjects with Elevated Plasma Lipoprotein(a)
Short Protocol Title:	Safety and Tolerability of AMG 890 in healthy subjects
Protocol Number:	20170544
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	20MAR2019	
[Amendment 1 (v2.0)]	29OCT2021	Updates based on protocol amendment 6 are as follow: • Section 3.1 updated for two new cohorts: Cohort 8 and 9 and added the table of planned treatment by cohort • Section 3.2 updated based on new cohorts 8 and 9 • Section 4.1 updated for covariates • ECG Baseline value definition updated in section 5 • End of Treatment Date definition updated for Cohorts 8 and 9 • Definition of TEAEs during treatment period updated and new definition added for SAEs during follow-up period in section 5 • Section 7.1 updated as per protocol amendment 6 • Section 7.3 updated for timings of final analysis due to addition of cohorts 8 and 9 • Section 9.4 updated for baseline characteristics and medical history summary table • Section 9.6.1 updated for consideration of PTs for each severity and one new table added for TEAEs by PTs and severity • Section 9.6.5 updated for ECG analysis of both triplicates and single trace values of Cohorts 8-9 • Pharmacodynamics analysis section updated by addition of table/figure of absolute values. • Section 9.7.2 updated • Section 9.7.3 updated to describe the urine sample collection in some cohorts and not necessarily for all cohorts
[Amendment 2 (v3.0)]	08March2023	Updates included in amendment 2 of SAP are as follow: • List of abbreviation updated by adding some more relevant abbreviations

		• Section 1 updated with latest protocol amendment number and date • Section 3.1 updated by removing reference of table 1 from "Protocol" as table 1 is also present in SAP • Section 5 updated for TEAE definition in treatment period and treatment-emergent SAE in follow-up period • Section 7.1 updated for specific details of data disposition for DLRMs • Section 7.2 updated for specific details of data disposition for primary analysis • Section 10 updated for deviation from protocol specified analysis detail • Section 11 updated for latest protocol amendment date

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	**Adverse event**
ApoA1	**apolipoprotein A**
ApoB	**apolipoprotein B**
AUC	area under the concentration-time curve
C_{max}	maximum serum concentration
CPMS	**Clinical Pharmacology, Modeling & Simulation group**
DLRM	Dose Level Review Meeting
DLRT	**Dose level Review Team**
ECG	electrocardiogram
eCRF	electronic case report form
HDL-C	**high-density lipoprotein cholesterol**
LDL-C	**low-density lipoprotein cholesterol**
Lp(a)	Lipoprotein(a)
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate
SC	**subcutaneous**
Source Data	Information from an original record or certified copy of the original record containing information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TEAE	**treatment-emergent adverse event**

[redacted]

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 **7** for study 20170544, AMG 890 dated **07 December 2021**. The scope of this plan includes the primary analysis and final analysis that is 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

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 890 when administered subcutaneously (SC) as single dose to subjects with elevated plasma Lp(a).	• Subject incidence of treatment-emergent adverse events • Safety laboratory analytes, vital signs, and electrocardiograms (ECGs)
Secondary	
• To characterize the pharmacokinetics (PK) of AMG 890 when administered SC as single dose to subjects with elevated plasma Lp(a)	• AMG 890 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC)
• To characterize the pharmacodynamics (PD) effects of AMG 890 on plasma Lp(a)	• Pharmacodynamic parameters: Change and percent change in plasma Lp(a) levels at each scheduled visit up to the end of treatment visit
• To assess the safety, tolerability, and PD effects of AMG 890 when administered in combination with statins	• Primary and secondary endpoints will be reported for subjects receiving statins
[redacted]	
• To assess the effects of AMG 890 on total cholesterol and cholesterol fractions (very-low density lipoprotein	• Change and percent change in total cholesterol and cholesterol fractions (very-low density

cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 (ApoA1) and total apolipoprotein B (ApoB)	lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, apolipoprotein A1 (ApoA1) and total apolipoprotein B (ApoB) at each scheduled visit
• To qualitatively assess AMG 890 urinary excretion following a single SC dose administration	• AMG 890 excretion in urine
[redacted]	

2.2 Hypotheses and/or Estimations

AMG 890 will be safe and well tolerated when administered SC as a single dose in subjects with elevated plasma Lp(a).

AMG 890 PK and/or PD data from this study will support the selection of dose and frequency of AMG 890 administration for future multi-dose trials.

3. Study Overview

3.1 Study Design

This is a FIH randomized, double-blind, placebo-controlled, single ascending dose (SAD) study in subjects with elevated plasma Lp(a). AMG 890 will be evaluated as SC injections in adult subjects. Approximately [redacted] subjects will enroll in 9 SAD cohorts. As described in Table 1, for each cohort, subjects will be randomized to receive AMG 890 or placebo SC in a 3:1 ratio.

As described in Eligibility Criteria (Section 7 of Protocol), cohorts 1 to 5 will enroll subjects with plasma Lp(a) between 70 nmol/L and 199 nmol/L, inclusive. Cohorts 6 to 9 will enroll subjects with plasma Lp(a) equal to or greater than 200 nmol/L. In cohorts 6 to 9, at least 6 subjects in each cohort will be on a stable dose of statin for at least six weeks.

For cohorts 1 to 5, and cohort 9 the first 2 enrolled subjects will be randomized in a 1:1 ratio (sentinel pair) and will be dosed on the same day at the same study site. Within the pair and while maintaining treatment blind, 1 subject will receive AMG 890 and the other subject will receive placebo. If deemed safe by the investigator after review of available safety data, and no less than 24 hours after sentinel pair dosing, the same dose will be administered to the remaining cohort subjects.

Enrollment into cohorts 1 to 5 will be staggered. Subsequent cohorts will be dosed after the dose regimen in the preceding cohort has been found by the Dose Level Review Meeting (DLRM) voting members to be safe and reasonably tolerated based on available safety and laboratory data through study day 15 for all subjects.

Enrollment into cohorts 5 to 7 can be initiated after the dose regimen in cohorts 1 through 4 has been found by the DLRT voting members to be safe and reasonably tolerated based on available safety and laboratory data through study day 15 of cohort 4.

Enrollment into cohort 8 will be initiated upon implementation of protocol amendment 5. Enrollment into cohort 9 can be initiated after the dose regimen in cohort 5 has been found by the DLRT to be safe and reasonably tolerated based on available safety data through at least study day 15.

Based on available PD data, and provided there is no safety and tolerability concerns, cohorts 1 to 5 may be expanded up to [redacted] subjects. The same eligibility criteria and randomization ratio (3:1) of AMG 890 to placebo will apply.

Table 1 below shows the treatment allocation and dose by cohort:

Table 1. Planned Treatment by Cohort

Cohort	Number of Subjects	Investigational Product (SC administration)
1 [a]	6	AMG 890 3 mg
	2	Placebo
2 [a]	6	AMG 890 9 mg
	2	Placebo
3 [a]	6	AMG 890 30 mg
	2	Placebo
4 [a]	6	AMG 890 75 mg
	2	Placebo
5 [a]	6	AMG 890 225 mg
	2	Placebo
6 [b,s]	9	AMG 890 9 mg
	3	Placebo
7 [b,s]	9	AMG 890 75 mg
	3	Placebo
8 [b,s]	6	AMG 890 225 mg
	2	Placebo
9 [b,s]	6	AMG 890 675 mg
	2	Placebo

a = subjects with screening plasma Lp(a) ≥ 70 nmol/L and ≤ 199 nmol/L
b = subjects with screening plasma Lp(a) ≥ 200 nmol/L
s = at least 6 subjects must be on a stable dose of a statin for at least 6 weeks in each of cohorts 6 to 9

3.2 Sample Size

The sample size is based on practical considerations. Approximately [redacted] subjects will be enrolled. With at least 6 subjects receiving AMG 890 in each cohort, there is at least a 74% chance of detecting an adverse event with a true incidence of 20% within each cohort. With at least 10 subjects receiving both AMG 890 and statin, there is at least a 89% chance of detecting an adverse event with a true AE incidence rate of 20%. With [redacted] subjects receiving AMG 890 there is a 95% chance of detecting an adverse event with a true incidence of 5%.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable

4.2 Subgroups

No subgroup analysis is planned.

5. Definitions

Age at time of enrollment

Subject age in years at time of enrollment will be collected in the clinical database.

AUC_{last}

Area under the concentration-time curve from time zero to the last quantifiable concentration.

AUC_{inf}

Area under concentration-time curve from time 0 extrapolated to infinity.

Baseline

Baseline values for Lp(a) are defined as the mean of screening and day 1 predose. If for any reason only 1 value is available, then that value will be used as baseline.

For any other variable, unless otherwise specified, baseline is defined as the last assessment taken prior to administration of AMG 890 or placebo.

ECG Baseline value

Analysis of ECG is applicable to cohorts 1 to 5 and 8 and 9 only.

Baseline ECG for cohorts 1 to 5 is defined as the mean of the triplicate values measured on Day -1. Baseline ECG for cohorts 8 and 9 is defined as the mean of the 3 triplicate values measured at the Day -3 to -1 dosing pre check visit. If there are any missing values, the mean of the non-missing values will be taken as baseline.

Change from Baseline

Change from baseline is the arithmetic difference between post-baseline and baseline.

Enrollment Date

Enrollment date is defined as the date on which subject was enrolled in the study.

End of Study for the Overall Trial

Defined as when the last subject is assessed or receives an intervention for evaluation in the study i.e. last subject last visit, following any additional parts in the study (e.g. Follow-up period, long term follow-up) as applicable.

End of Study for Individual Subject

Defined as the last date recorded on the End of Study form for an individual subject.

End of Treatment Date

End of Treatment Date for cohort 1 and 2 is the date of Day 113 visit, for Cohort 3 to 7 is the date of Day 225 visit and for cohort 8 and 9 is the date of Day 365 visit.

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows:

QTcF=QT/RR^1/3

Investigational Product

The term investigational product is used in reference to AMG 890 or placebo.

Percentage Change from Baseline

Percentage change from baseline is arithmetic difference between post baseline and baseline divided by baseline values times 100.

Randomization Date

Randomization date is defined as the date subject was allocated a unique randomization number and assigned to either AMG 890 or placebo group.

Study Day 1

defined as the first day that investigational product is administered to the subject.

Study Day

Post study day 1: study day= (date of event-study day 1) +1

Pre-study day 1: study day= (date of event-study day 1)

Treatment-emergent Adverse Event during Treatment Period

A treatment-emergent adverse event during treatment period is any adverse event starting on or after the first dose of investigational product (as determined by the flag indicating if the adverse event started prior to the first dose or not on the Adverse Events eCRF) and up to and including the End of Treatment Date, **or EOS date for subjects who early discontinue the study during the treatment period.**

Treatment-emergent Serious Adverse Event during Follow-up Period

Subjects in cohorts 1-7 will be followed up for SAE reporting (every 2 weeks for cohorts 1-2 and monthly for cohorts 3-7) if the Lp(a) level has not returned to ≥80% of baseline by the end of treatment visit. SAEs during the follow-up period are defined as any serious adverse event **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** starting **on or** after the end of treatment date and up to and including the end of study date for an individual subject.

If end of treatment and end of study is same for a subject, then the subject will only have TEAEs for treatment period derived.

For subjects in Cohort 8 and 9 the end of treatment and end of study is same i.e. day 365 so for those cohorts only TEAEs for treatment period will be derived.

6. Analysis Sets

For all analyses, subjects will be analyzed according to the dose and treatment they received, not the dose and treatment to which they were randomized.

6.1 Safety Analysis Set

The safety analysis set will consist of all study subjects who are randomized and receive at least one dose of AMG 890 or placebo.

Subjects withdrawing prior to any AMG 890 or placebo administration due to adverse events related to study procedure will not be included in the safety analysis set but those adverse events will be listed.

6.2 Pharmacokinetic/Pharmacodynamic Analyses Sets

6.2.1 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all dosed subjects for whom at least one PK parameter or endpoint can be reliably estimated.

6.2.2 Pharmacodynamics (PD) Analysis Set

The PD analysis set will consist of all dosed subjects for whom at least one PD parameter **(Lp(a))** has a baseline value and at least 1 post-baseline measurement available. **Baseline values for Lp(a) are defined as the mean of screening and day 1 predose. If for any reason only 1 value is available, then that value will be used as baseline.**

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study. However, the study will have Dose Level Review Meetings (DLRMs) during the study for each cohort.

All relevant study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed. Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan; however, there is no requirement to resolve outstanding data queries ahead of the snapshot. All available data up to and including the data cut-off date will be included in the analysis based on an "as-is" snapshot of the database without data locking.

For cohorts 1 to 5, and cohort 9, escalation to a higher dose cohort will only proceed when the previous dose regimen has been found to be safe and reasonably tolerated based on available safety data through study day 15 for all subjects and upon unanimous recommendation of the DLRT. Available data from previous cohorts will also be considered. The next cohort will be open for enrollment immediately following the DLRT recommendation and Amgen decision.

Enrollment into cohorts 6 to 8 will be initiated after cohort 4 dose level has been found by the DLRT to be safe and reasonably tolerated based on available safety data through study day 15. Cohorts 5, 6 and 7 may be enrolled in parallel. For cohorts 6 and 7 eligible subjects will be first enrolled into cohort 6 and then into cohort 7. Cohort 8 will be enrolled after implementation of protocol amendment 5 . Enrollment into cohort 9 can be initiated after the preceding dose regimen has been found by DLRT to be safe and reasonably tolerated based on available safety data through at least study day 15 of cohort 5.

7.2 Primary Analysis

The primary analysis will occur after all subjects have completed the end of treatment

visit. At the primary analysis, the primary, secondary, and exploratory endpoints (if applicable) will be analyzed. All data up to each subject's end of treatment visit will be included in the primary analysis.

7.3 Final Analysis

The final analysis will occur after all subjects have completed the study. The follow-up time points will be summarized at the final analysis. The final analysis and primary analysis may be combined if they are scheduled to occur at similar times.

Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the final database lock.

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.

The final analysis specified in this statistical analysis plan will be performed once all subjects have completed the study and the database is locked post the clean snapshot.

Analyses supporting DLRMs will be performed on an ongoing basis throughout the study.

8.3 Handling of Missing and Incomplete Data

The frequency of missing and incomplete data is expected to be low in this study and therefore, missing data will not be imputed.

Laboratory measurements that are below the quantification limits will be considered equal to the lower limit of quantification for the calculation of population averages as a part of the summary tables. Clinical lab values below LLQ will not be imputed for individual subject level data in line listings.

Biomarker data that are below the quantification limits will be considered equal to half of the lower limit of quantification for all analyses unless specified otherwise.

PK concentrations that are below the quantification limits will be set to zero when using non-compartmental methods to compute PK parameters.

For partial dates (such as treatment emergent AE, concomitant medication, drug administration etc.) imputation of dates will be carried out as per Appendix A.

8.4 Detection of Bias

Any source that may introduce bias in the analysis e.g. important protocol deviations, imbalance in baseline characteristics among treatment groups, subject dropout for study or treatment related reasons, nonrandom or informative censoring will be noted in the clinical study report.

8.5 Outliers

Any questionable or outliers will be confirmed with GSO DM. In addition, outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them. Any outliers exclude from the analysis will be discussed in the clinical study report (CSR) including the reasons for exclusion and the impact of their exclusion on the study.

Pharmacokinetic (PK) Serum concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. Data distribution will be explored, if required, data transformations or alternative non-parametric methods of analyses will be utilized.

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; which is the SAS System version 9.4 or higher.

9. Statistical Methods of Analysis

9.1 General Considerations

Descriptive statistics will be provided for selected demographics, adverse events, vital signs, ECG and selected laboratory measurements. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment group and cohort at each scheduled time point. Graphical summaries of the data may also be presented.

Data for subjects receiving placebo will be combined across cohorts 1 to 5 and separately across cohorts 6 to 9.

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Unless stated otherwise in the statistical analysis plan, the data analysis will be conducted using subjects in the safety analysis set. For statistical analyses comparing change from baseline, only subjects with both baseline and at least one post-baseline assessment will be included.

9.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product, completed study, discontinued the study (including reason for discontinuing) will be summarized by treatment group and cohort.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A subject listing and summary noting inclusion in each analysis set will be reviewed for all subjects enrolled. A subject listing noting reason for discontinuation of treatment and reason for discontinuing the study will be reviewed. A list of subjects screened but not enrolled (screen failures) will be reviewed.

A subject listing will be provided for randomization information, randomized treatment and actual treatments.

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 final list of important protocol deviations (IPDs) will be used to produce the listing of subjects with IPDs in addition, a separate listing of all inclusion and exclusion deviations will be provided.

9.4 Demographic and Baseline Characteristics

Demographic data (i.e. Sex, Ethnicity, Race, Age (Years)) will be summarized using descriptive statistics by treatment group and cohort. If multiple races have been reported for a subject, the subject will be categorized as multiple.

Weight, Height, BMI and Baseline Statin Use (for Cohorts 6 to 9) will be summarized as Baseline Characteristics by treatment group and cohort.

Summary of selected medical history will be provided by system organ class and preferred term for cohorts 6 to 9 by treatment group and cohort.

9.5 Efficacy Analyses

Not applicable for this study.

9.6 Safety Analyses

9.6.1 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events and fatal adverse events by treatment group and cohort during the treatment period.

Severity of adverse events are graded as Mild, Moderate and Severe.

If a subject experienced multiple TEAEs with the same preferred term, this will be counted as separate TEAEs for that treatment under each specific severity recorded.

Summaries of treatment-emergent adverse events, serious adverse events and fatal adverse events during the treatment period will also be tabulated by system organ class, preferred term.

Summary of treatment-emergent adverse events by preferred term and by severity will be tabulated.

SAEs during the follow-up- period will be tabulated by system organ class and preferred term for each treatment group and cohort (cohorts 1-7 only).

Details of each adverse event will be reviewed. Listings of any on-study deaths, serious adverse events (SAE), and events leading to withdrawals of IP or other protocol-required therapies will be reviewed.

9.6.2 Laboratory Test Results

For screening purposes, chemistry, hematology, coagulation, and triglycerides will be analyzed by the local laboratory. For eligibility determination on day -3 to -1, only ALT, AST, and TBIL in the chemistry panel will be performed at the local laboratory. On-study laboratory assessments, unless specifically noted in contrary, will be assessed by a central laboratory.

Results from the laboratory will be included in the reporting of study for Hematology, Chemistry, Coagulation and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol.

Laboratory assessments will be summarized by treatment group and scheduled time points during the treatment period using descriptive statistics for each cohort. Change and percentage change from baseline over time, shift from baseline to maximum post baseline, and shift from baseline to minimum post baseline may also be provided if applicable.

9.6.3 Vital Signs

The summary statistics over time and/or changes and percentage changes from baseline over time for scheduled time points will be produced for the following parameters:

Systolic Blood Pressure (mmHg)
Diastolic Blood Pressure (mmHg)
Heart Rate (beats/min)
Temperature (^{0}C or ^{0}F as per available data)

Subject level data listing will be reviewed.

9.6.4 Physical Measurements

Physical measurement data (I.e. Weight and BMI (kg/m2)) will be summarized descriptively at scheduled time points.

Subject level data listing will be reviewed.

9.6.5 Electrocardiogram

Each ECG will include following measurements: PR, QRS, QT, QTc, RR.

The following summary will be provided for cohorts 1 to 5 and Cohorts 8 and 9 only.

Summaries over time and change and percentage change from baseline over each scheduled time points (including time points with single and triplicate measurements) will be provided for each ECG parameter by treatment group and cohort.

Further subjects' maximum change from baseline in QTcF will be categorized in following categories and the number and percentage of subjects in each treatment group and cohort will be summarized. Unscheduled assessments will be included in the determination of the maximum change.

<=30 msec

>30-60 msec

>60 msec

Subjects' maximum post baseline values in QTcF will also be categorized in the following categories and the number and percentage of subjects in each treatment group and cohort will be summarized. Unscheduled assessments will be included in the determination of the maximum post baseline value.

<=450 msec

>450-480 msec

>480-500 msec

>500 msec

Subject level data listing will be reviewed.

9.6.6 Exposure to Investigational Product

Details of each AMG 890 administration **may** be listed and reviewed for every subject. In addition, a listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

9.6.7 Exposure to Concomitant Medication

The number and proportion of subjects receiving lipid regulating therapies of interest will be summarized by medication category and preferred term by treatment group and cohort as coded by the World Health Organization Drug (WHO Drug) dictionary.

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Endpoints

Pharmacokinetic Analysis

The pharmacokinetic analyses will be performed by the Clinical Pharmacology, Modeling & Simulation group (CPMS).

Serum samples will be analyzed for AMG 890 concentrations using a validated assay.

Individual concentration-time plots for AMG 890 will be presented for each subject as well as mean concentration-time plots for each cohort.

Descriptive statistics for PK concentration data will be provided at each time point for each cohort.

Pharmacokinetic parameters including but not limited to AUC_{last}, AUC_{inf}, C_{max}, and t_{max} will be estimated using non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort using the PK analysis set.

Subject level data listing will be generated for both PK concentration and PK parameter data.

Pharmacodynamic Analysis

Descriptive statistics for absolute value, change and percentage change for plasma Lipoprotein(a) by cohort and at scheduled time points during the treatment period will be presented using PD analysis set.

Figures for absolute value, change and percent change in plasma Lipoprotein(a) t will be generated by cohort and at scheduled time points, including the treatment period and any values collecting during the follow-up period (where applicable).

Descriptive statistics for actual value and change and percentage change from baseline will be provided for total cholesterol, Cholesterol fractions (very-low density lipoprotein cholesterol [VLDL-C], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C], triglycerides, apolipoprotein A1 [ApoA1] and total apolipoprotein B [ApoB]) at each scheduled time points during the treatment period by treatment group and cohort using Safety analysis set.

Subject level data listing will be reviewed.

9.7.2 Qualitative assessment of AMG 890 in Urine

Urine samples will be collected in some cohorts and AMG 890 concentrations in urine may be analyzed so that fractions of dose eliminated unchanged in urine may be determined, if sufficient data are available.

Summary statistics by treatment group and cohort will be presented if appropriate using Safety analysis set.

10. Changes from Protocol-specified Analyses

Protocol specifies the analysis of adverse events leading to withdrawal of IP however as this is single dose study, this will not be a meaningful analysis. As a result it has been removed from the planned analysis.

11. Literature Citations / References

Study Protocol dated **07 December 2021**

12. Appendices

Appendix A. Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Imputation Rules for Partial or Missing Stop Dates:

If the month and year are present, impute the last day of the month.

If only the year is present, impute December 31 of that year.

If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or concomitant medication stopped and the stop date will be imputed, if partial.

Imputation Rules for Partial or Missing Start Dates:

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	
Partial: yyyymm	Equal to 1st Dose yyyymm	2	1	2	1	N/A	1	1
	Not equal to 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	Equal to 1st Dose yyyy	3	1	3	1	N/A	1	1
	Not equal to 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose

2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.
Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.