Statistical Analysis Plan

An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of AMG 890 in Chinese Subjects with Elevated Serum Lipoprotein(a)

SAP Version: 2
SAP Status: Final
SAP Date: 06 November 2022

Investigational Product: AMG 890

Protocol Reference: 20190095
Covance Study: 8424665

Sponsor:
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NCT Number: NCT04987320
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ADaM	analysis data model
AE	adverse event
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from time zero to time of last quantifiable concentration (t_{last})
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum serum concentration
CL/F	apparent total body clearance
CSR	clinical study report
ECG	electrocardiogram
EOS	end of study
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
λ_z	elimination rate constant
Lp(a)	Lipoprotein(a)
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
PD	pharmacodynamic
PK	pharmacokinetic(s)
R^2	correlation coefficient of terminal elimination phase
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of maximum serum concentration
V_z/F	apparent volume of distribution during the terminal elimination phase
WHODrug	World Health Organization Drug Dictionary
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity

1. INTRODUCTION

This SAP has been developed in alignment with the clinical study protocol (dated 07 Oct 2020).

This SAP describes the planned analysis of the pharmacokinetic (PK), pharmacodynamic (PD) and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Amgen Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

Significant changes from the protocol-specified analyses are described in section 10 of this SAP. If post-hoc analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Amgen Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- to evaluate the PK of a single dose of AMG 890 in Chinese subjects with elevated serum lipoprotein(a) (Lp(a)).

2.2 Secondary Objective

The secondary objectives of the study are:

- to evaluate the safety and tolerability of a single dose of AMG 890 in Chinese subjects with elevated serum Lp(a).

- to evaluate the pharmacodynamic of a single dose of AMG 890 in Chinese subjects with elevated serum Lp(a).

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoints are:

- maximum serum concentration (C_{max});
- area under the serum concentration-time curve (AUC);
- Additional PK parameters may include, but are not limited to: time to maximum observed concentration (t_{max}), half-life ($t_{1/2}$), apparent volume of distribution during the terminal elimination phase (V_z/F), and apparent total body clearance (CL/F).

3.2. Secondary Endpoints

The secondary endpoints are:

- Treatment-emergent adverse events;
- clinical laboratory tests;
- 12-lead electrocardiograms (ECGs);
- vital signs;
- lipids;
- serum Lp(a).

4. STUDY DESIGN

This study is an open-label, randomized, single-dose, parallel-group study in Chinese subjects with elevated serum Lp(a) to assess the PK, safety and tolerability, and PD of AMG 890. Subjects will be randomized in a 1:1 ratio to receive a single SC dose of AMG 890 at [redacted] mg (Group A) or [redacted] mg (Group B). A total of approximately 24 subjects (12 per group) will be enrolled in this study.

Subjects must be living in mainland China, Hong Kong, or Taiwan, and be of Chinese ancestry with an age of 18 to 60 years old, and have body mass index (BMI) of 18 to 32 kg/m^2 and serum Lp(a) ≥ 70 nmol/L (or approximately ≥ 27 mg/dL).

Subjects will be assigned to 1 of 2 treatment groups shown in Table 1.

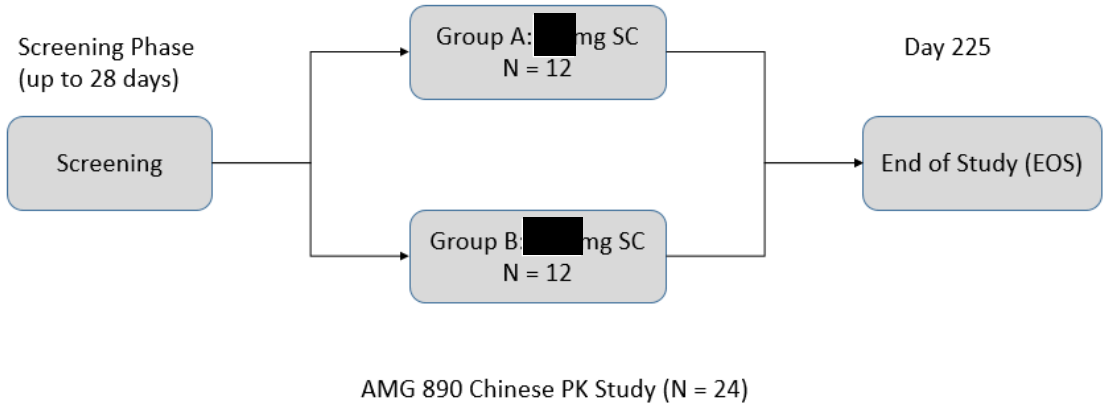
Table 1: Treatment Groups

Group	Number of subjects	Dose

A	12	[redacted] mg SC
B	12	[redacted] mg SC

An overview of the study design is shown in Figure 1 below.

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the clinic on Day -1 and be confined to the clinic until discharge on Day 4. Subjects will return to the clinic for outpatient visits on Days 7, 15, 29, 57, 85, 113, 155, and 183, and at the End of Study (EOS) visit on Day 225. A telephone visit will be scheduled for TEAE assessments on Day 211. The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 253 days (36 weeks).

The start of the study is defined as the date the first subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject randomization number allocation. The enrollment date is the same as the randomization date. The EOS for overall study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

5. SAMPLE SIZE JUSTIFICATION

Approximately 24 subjects (12 per group) will be enrolled in the study. No formal statistical hypothesis testing will be performed. The sample size of 12 subjects per group is based on studies of similar nature and was not based on power calculations. Considering a 33.3% drop-out rate, 8 subjects per cohort provides an approximately 90% confidence of observing a case of a TEAE in each cohort at an incidence of 25%.

6. STUDY TREATMENTS

The study treatment names and ordering to be used in the TFLs are presented in Table 2 below.

Table 2: Presentation of Study Treatments in TFLs

Study Treatment	Treatment Abbreviation	Order in TFLs
Group A: [redacted] mg administered as a single 1 mL ([redacted] mg/mL) SC injection	[redacted] mg AMG 890	1
Group B: [redacted] mg administered as three 1.0 mL ([redacted] mg/mL) SC injections	[redacted] mg AMG 890	2

All treatments described above are the planned treatments. Subject disposition and baseline will be summarized by randomized treatment group, PK and safety analysis will be summarized by actual treatment received., and dose levels will be displayed in increasing order.

7. DEFINITIONS OF ANALYSIS SETS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to analysis sets.

7.1. All Subjects Analysis Set

The all subjects analysis set will include all randomized subjects.

7.2. Safety Analysis Set

The safety analysis set will include all randomized subjects who received AMG 890.

7.3. Pharmacokinetic Analysis Set

The PK analysis set will include all randomized subjects who received AMG 890 and have evaluable PK data.

7.4. Pharmacodynamic Analysis Set

The PD analysis set will include all randomized subjects who received AMG 890 and have evaluable PD data.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects in the all subjects analysis set and include data up to the point of study completion or discontinuation. Any subject who discontinued the study will be listed in the applicable listing. Summaries and statistical analyses will include the subjects assigned to the relevant analysis sets based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 4.2.1 will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, adverse event [AE] severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations.

8.2. Subject Disposition and Analysis Set Assignment

Subject disposition and analysis set assignment will be listed.

A summary table will be provided, based on the all subjects analysis set.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table will be provided, based on the safety analysis set.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version Month 2020 (or later if upversioned during the study). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic and Pharmacodynamic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the serum concentrations of AMG 890 using non compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1 or higher):

The following parameters for OM will be summarized and listed:

Parameter	Units[a]	Definition
AUC_{last}[b]	h*ng/mL	area under the serum concentration-time curve from time 0 to the time of last quantifiable concentration (t_{last})

AUC_{inf}[b]	h*ng/mL	area under the serum concentration-time curve from time 0 extrapolated to infinity
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time to maximum observed concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total body clearance
V_z/F	L	apparent volume of distribution during the terminal elimination phase
%AUCextrap	%	percentage of AUC due to extrapolation from the last quantifiable concentration to infinity

[a] Units are based on concentration units (provided by bioanalytical lab) and dose units used in the study.
[b] AUCs will be calculated using the linear trapezoidal linear interpolation rule.

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual blood sampling times post dose. If actual times are missing, nominal times may be used with sponsor approval.

$C_{max,}$ and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

8.5.1.1. Criteria for the Calculation of an Apparent Terminal Elimination Rate Constant and Half-Life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the coefficient for determination of exponential fit (R^2) of the regression line is ≥0.8. Parameters requiring λ_z in their calculation (eg, AUC_{inf}, $\%AUC_{extrap,}$ $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2 value of the regression line is ≥ 0.8.

The following regression-related diagnostic PK parameters will be determined:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2	NA	coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

Per Sponsor request, the half-life calculation is based on the beta phase of the elimination instead of terminal phase elimination. This decision is based on the PK properties of AMG890 where the terminal elimination phase constitutes a very small fraction of the total exposure (AUC) and the concentrations at terminal phase are close to the LLOQ value.

8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

AUC_{inf} values where the percentage extrapolation is less than or equal to 20% will be reported. AUC_{inf} values where the percentage extrapolation is greater than 20% will be listed but flagged and excluded from descriptive statistics.

8.5.1.3. Criteria for Handling Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Serum concentration values that are below the limit of quantification (BLQ) will be set to a value of zero, with the following defined exceptions which will be set to missing:

- Any embedded BLQ value (between 2 quantifiable concentrations).
- BLQ values following the last quantifiable concentration in a profile.
- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.

Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless they are considered to be a true characteristic of the profile of the drug.

If a predose serum concentration is missing, it may be set to zero by default.

8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in CSR.

Quantifiable predose concentration values in the first treatment period (if applicable) will be considered anomalous and set to missing for the PK analysis.

If the predose concentration is >5% of C_{max} in the second treatment period (if applicable), all PK concentration and parameter data may be excluded from the summary statistics and statistical analysis for that period at the discretion of the Pharmacokineticist.

8.5.2. Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ± 20%, the concentration may be flagged and excluded from summary statistics. Individual concentrations that are deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will be applied:

- Values that are BLQ will be set to 0 for calculation of summary statistics.
- Arithmetic mean or median that are BLQ will be presented as 0.

For PK parameters the following rule will be applied:

- Geometric mean and coefficient of variation will not be calculated for t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment group and time post dose will be provided for serum PK concentrations. All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will be only displayed on the linear scale.

Summary tables by treatment group will be provided for all PK parameters, with the exception of regression-related PK parameters. Separate summary tables by treatment group and time interval will be provided for excretion parameters.

8.5.4. Pharmacodynamic Statistical Methodology

Venous blood samples (approximately 6 mL) will be collected for measurement of Lp(a) at scheduled times.

Lipid panel will include triglycerides, very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), total cholesterol, apolipoprotein A1 (ApoA1) and total apolipoprotein B (Apo B). At screening, lipid panel will measure triglycerides only. Venous blood samples (approximately 6 mL) will be collected for measurement of lipid panel at scheduled times. The lipid panel will be analyzed by a central lab of Covance Shanghai.

All PD parameters will be listed.

Summary tables and mean change and percent change from baseline (+ SE) figures by treatment and timepoint will be provided for all PD parameters based on PD analysis set.

Baseline is defined as the mean of last two non-missing values predose. If only 1 predose value is available then that value will be used as the baseline.

Values below the limit of quantification will be set to BLQ for the calculation of summary statistics.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to BLQ , whereas >x and ≥x values will be set to x.

No inferential statistical analyses are planned.

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 (or higher if upversioned during the study).

A treatment-emergent adverse event (TEAE) will be defined as any AE that starts 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 AE electric case report form) and up to EOS.

A treatment related TEAE will be defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The subject incidence of TEAE and the number of TEAEs will be summarized for the following categories based on safety analysis set:

- TEAEs (overall, serious, leading to study discontinuation, and leading to death) by treatment group
- TEAEs by severity and treatment group
- Treatment-related TEAEs (overall, serious, leading to study discontinuation, and leading to death) by treatment group
- Treatment-related TEAEs by severity and treatment group

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs events by the following:

- System organ class, preferred term, and treatment group
- Preferred term and treatment group

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the first dose.

- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, the treatment relationship will be kept as missing.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the last dose is 01MAY2019/08:00 and recorded start date/time of an adverse event is 03MAY2019, then the minimum possible onset time will be calculated by assuming the an adverse event started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an adverse event date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the adverse event ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted as missing severity.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment group, this will be counted as separate TEAEs for that treatment under each specific severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables by timepoint along with change from baseline and percent change from baseline will be provided for clinical chemistry and hematology parameters based on safety analysis set. The baseline is defined as the last reading before dosing.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags and calculation of summary statistics, <x and ≤x values will be set to BLQ, whereas >x and ≥x values will be set to x.

8.6.3. Vital Signs Parameters

All vital signs parameters will be listed; any value outside the clinical reference range will be flagged.

Summary tables along with change from baseline and percent change from baseline will be provided for all vital signs parameters based on safety analysis set. The baseline is defined as the last reading before dosing.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters will be listed; any value outside the clinical reference range will be flagged.

Summary tables by timepoint along with change from baseline and percent change from baseline will be provided for all 12-lead ECG parameters based on safety analysis set. The baseline is defined as the last reading before dosing.

8.6.5. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

Medical history will not be listed.

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned for this study.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

12. APPENDICES

Appendix 1: Document History

Document Version, Status, Date	Change Made By	Date of Change	Change after DB lock?	Client Approval?	Summary/Reason for Changes
Version 1, Final, 11 November 2020					Not applicable; the first version
Version 1, Final, Working Version	WX	12Jan2020	NA	NA	Corrected Typo in the SAP. Change wording from: The following parameters for *OM* will be summarized and listed: To: The following parameters for *AMG 890* will be summarized and listed:
Version 1, Final, Working Version	WX	24Jun2021	NA	NA	Updated the following per Protocol V2.0 Dated 03May2021: 1) Update Globally, Change all AMG 890 in SAP and TFL shells to "Olpasiran" 2) SAP p7: update screening period from "28" to "40" days in both language and figure 1. 3) SAP p8: update [redacted]ng dosage from "three 1.0 mL" to "two 1.5 mL" 4) SAP p7: update duration of study from "253 days (36 weeks)." to "265 days (about 38 weeks)" correspondingly in both language and figure 1;
Version 1, Final, Working Version	WX	27Oct2021	NA	NA	Typo correction, updated MedDRA version to be 24.0 instead of "XX.X" to match the DMP on p14 of the SAP narrative.
Version 1, Final, Working Version	WX	10Jan2022	NA	NA	Corrected Pinnacle 21 version: Change from: Pinnacle 21 Community Validator 4.2.1 To: Pinnacle21 Community Validator 3.1.2
Version 1, Final, Working Version	WX	02Feb2022	NA	NA	Corrected Figure title per sponsor comment: Update the Figure titles from: Figure 14.2.2-1 Arithmetic Mean (+SD) Lp(a) Concentration-time Profiles Figure 14.2.2-2 Arithmetic Mean (+SD) Lp(a) Change from Baseline Concentration-time Profiles Figure 14.2.2-3 Arithmetic Mean (+SD) Lp(a) Percent Change from Baseline Concentration-time Profiles

					To: Figure 14.2.2-1 Arithmetic Mean (+SD) Pharmacodynamic Parameters Concentration-time Profiles Figure 14.2.2-2 Arithmetic Mean (+SD) Pharmacodynamic Parameters Change from Baseline Concentration-time Profiles Figure 14.2.2-3 Arithmetic Mean (+SD) Pharmacodynamic Parameters Percent Change from Baseline Concentration-time Profiles
Version 1, Final, Working Version	WX	24Aug2022	NA	NA	Section 8.5.1.1 Updated PK language typo from: Parameters requiring λz in their calculation (eg, AUCinf, %AUCextrap, t1/2, CL/F, and Vz/F) will only be calculated if the R2 value of the regression line is ≥ 0.7. To: Parameters requiring λz in their calculation (eg, AUCinf, %AUCextrap, t1/2, CL/F, and Vz/F) will only be calculated if the R2 value of the regression line is ≥ 0.8.
Version 2, Final	WX	06Dec2022	NA	Y	Amended the front page study site name, address and PI's name and credential.

Statistical Analysis Plan (SAP) Approval Form

Type of Approval (select one) : ☒ **SAP**

Sponsor Name:	Amgen Inc.		
Sponsor Protocol/CIP ID:	20190095	**Covance Study ID:**	8424665
SAP text filename:	Amgen_890_20190095_SAP_06Dec2022_Final	**TFL shells filename:**	Amgen_890_20190095_TFL_06Dec2022_Final
Version:	2.0	**Date:**	06Dec2022

Covance Approval(s):

Lead Statistician

Approval Signature [redacted] Biostatistician Date	[redacted]

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature Print Name Job Title Date	N/A

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	[redacted] Biostatistician
Email:	[redacted]