Statistical Analysis Plan

A Phase I, Open-label, Fixed Sequence Crossover Study to Investigate the Effect of Coadministration of Sotorasib on the Pharmacokinetics of Rosuvastatin, a Breast Cancer Resistance Protein Substrate, in Healthy Subjects

SAP Status: Final
SAP Version: 1.0
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Investigational Medicinal Product: Sotorasib (AMG 510)

Protocol Reference: 20200426
Covance Study: 8461525

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NCT Number: NCT05045638
This NCT number has been applied to the document
for the purposes of posting on clinicaltrials.gov

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LIST OF IN-TEXT TABLES AND FIGURES

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
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	AUC from time zero to the last quantifiable concentration
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CL/F	apparent total clearance
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
GLSM	geometric least squares mean
ICF	informed Consent Form
ICH	International Council for/Conference on Harmonisation
LLOQ	lower limit of quantification
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
PE	physical examination
PK	pharmacokinetic(s)
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification

TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 19 May 2021) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), 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. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional 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) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

The primary objective of the study is:

- to determine the effect of sotorasib on the PK of rosuvastatin, and to assess the PK of rosuvastatin when administered alone, in healthy subjects.

The secondary objectives of the study are:

- to assess the safety and tolerability of sotorasib when coadministered with rosuvastatin, and rosuvastatin alone, in healthy subjects
- to assess the PK of sotorasib when coadministered with rosuvastatin.

3. STUDY ENDPOINTS

The primary endpoints of the study are rosuvastatin PK parameters:

- maximum observed concentration (C_{max})

- area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last})
- area under the concentration-time curve from time zero to infinity (AUC_{inf}).

The secondary endpoints of the study are:

- adverse events (AE)
- clinical laboratory tests
- 12-lead electrocardiograms (ECGs)
- vital signs
- sotorasib PK parameters after administration of sotorasib in combination with rosuvastatin, including, but not limited to:
  - C_{max}
  - AUC_{last}
  - AUC_{inf}.

4. STUDY DESIGN

This will be a Phase I, open-label, fixed sequence, crossover study to investigate the effect of coadministration of sotorasib on the PK of rosuvastatin in healthy male subjects and healthy female subjects of nonchildbearing potential. Approximately 14 subjects will be enrolled to ensure that 12 subjects complete the study. All subjects will receive each of the following treatments:

- Day 1: single oral dose of 10 mg rosuvastatin (1 x 10 mg tablet), after an overnight fast of at least 10 hours
- Day 6: single oral dose of 960 mg sotorasib (8 x 120 mg tablets) followed immediately by a single oral dose of 10 mg rosuvastatin (1 x 10 mg tablet), after an overnight fast of at least 10 hours.

Potential subjects will be screened to assess their eligibility to enter the study within 21 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 11.

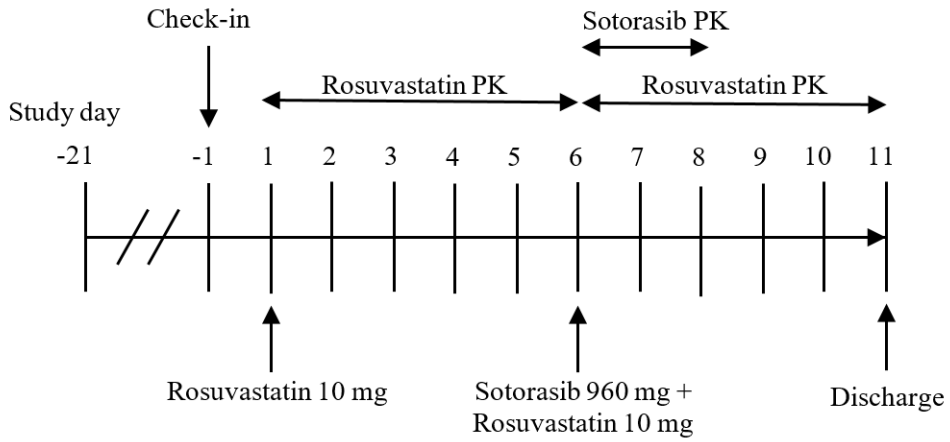
The total duration of study participation for each subject (from Screening through end of study discharge) is anticipated to be approximately 4 and a half weeks.

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation.

The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

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

Figure 1: Study Design



5. SAMPLE SIZE JUSTIFICATION

Approximately 14 subjects will be enrolled in order that approximately 12 subjects complete the study. The sample size for this study is based on studies of similar design and considered adequate for evaluation of the study objectives.

6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in **Error! Not a valid bookmark self-reference.**.

Table 1: Presentation of Study Treatments in TFLs

Treatments	Abbreviation	Order in TFLs
single oral dose of 10 mg rosuvastatin (1 x 10 mg tablet), after an overnight fast of at least 10 hours	10 mg rosuvastatin	1
single oral dose of 960 mg sotorasib (8 x 120 mg tablets) followed immediately by a single oral dose of 10 mg rosuvastatin (1 x 10 mg tablet), after an overnight fast of at least 10 hours	960 mg sotorasib + 10 mg rosuvastatin	2

7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those due to coronavirus disease 2019 (COVID-19) and related restrictions (see Section 8.1.1), will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The All Subjects Population will include all subjects who signed the ICF and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The Safety Population will include all subjects who received at least 1 dose of sotorasib or rosuvastatin and have at least 1 postdose safety assessment.

7.3. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of rosuvastatin or sotorasib and have evaluable PK data. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event of vomiting that occurs at or before 2 times median time to maximum concentration or diarrhea within 24 hours of dosing.

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 assigned to the All Subjects Population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they complete the scheduled end of study visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Enterprise Version 4.2.1 (or higher if a new version is issued during the study) 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 'valid' data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

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

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

8.1.1. Handling of Data Quality Issues Due to Coronavirus Disease 2019 and Related Restrictions

Due to COVID-19 and related restrictions, there is a high risk for impact to data integrity, with the recognized potential for:

- Missed visits, caused by, for example:
  - Subject unable to travel to site due to restrictions, the need to quarantine, or COVID-19 infection
  - Subject unwilling to go to site due to fear of COVID-19 infection
  - Site postponing subject's visit due to investigator not being available (eg, if they have been dispatched to hospital handling COVID-19 infections)
- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Outstanding source document verification (SDV) due to sponsor or country restrictions on remote SDV, or no or limited access to site(s) for on-site visits
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to COVID-19 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (eg, data might be categorized into 2 analysis groups, with and without COVID-19 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Amgen Inc. in advance and identified in the CSR.

8.1.2. 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 the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.
- Missing values will not be imputed, 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.

8.1.3. Repeat and Unscheduled Readings

For vital signs and 12-lead 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, with the exception of the 12-lead ECG outlier analysis (see Section 8.6.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section **Error! Reference source not found.**) and 12-lead ECG outlier analysis (see Section 8.6.4).

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the safety population.

8.3. Screening Demographics and Baseline Characteristics

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

A summary table by treatment will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that starts within 30 days prior to enrollment and ends prior to dosing. Concomitant medication will be defined as medication that starts during or 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 September 2020 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of rosuvastatin on Days 1 and 6 and sotorasib on Day 6 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{last}	h*ng/mL	area under the plasma concentration-time curve from time zero to the last quantifiable concentration[b]
AUC_{inf}	h*ng/mL	area under the plasma concentration-time curve from time zero extrapolated to infinity[b,c]
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	h	time of the maximum observed plasma concentration
t_{last}	h	time of the last quantifiable plasma concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
V_z/F	L	apparent volume of distribution during the terminal phase

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule.
[c] Based on the last observed quantifiable concentration

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, nominal times may be used with sponsor's approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

8.5.1.1. Criteria for the Calculation of 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 adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥0.8. Parameters requiring λ_z for their calculation (eg, AUC_{inf}, $t_{1/2}$, CL/F, V_z/F) will only be calculated if the R^2-adj value of the regression line is ≥0.8.

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

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 $t_{1/2}$
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
R^2-adj	NA	adjusted 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 clinical study report (CSR).

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}.

If the extrapolated area is >20%, AUC_{inf} (and derived parameters) will be flagged and may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or pharmacokineticist.

If AUC_{inf} cannot be determined reliably for all subjects and/or treatments, an alternative AUC measure, such as AUC to a fixed timepoint may be included in the statistical analysis upon sponsor approval.

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

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- 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 plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin.

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 the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value will be considered anomalous for rosuvastatin on Day 1 and will be set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

If the predose concentration is >5% of C_{max} in the second treatment period for rosuvastatin, all PK concentration and parameter data will be excluded from the summary statistics and statistical analysis for that period.

8.5.2. Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the plasma concentration will be flagged and excluded from the summary statistics.

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- If the embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, 0 and the geometric mean and geometric coefficient of variation (CV%) will be denoted as NC.
- Arithmetic mean or median values that are BLQ will be presented as 0, and the geometric mean and geometric CV% will be denoted as NC.

For PK parameters the following rule will apply:

- For the calculation of summary statistics of PK parameters, all non-reportable and NC values in a data series will be set to missing.
- AUC_{inf} and AUC_{last} will be set to NC if they were calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.
- Geometric mean and coefficient of variation will not be calculated for t_{last} or 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 and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales.

Summary tables by treatment will be provided for all PK parameters, with the exception of regression-related PK parameters.

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of rosuvastatin by comparing 960 mg sotorasib + 10 mg rosuvastatin (test treatment) to 10 mg rosuvastatin (reference treatment) for AUC_{last}, AUC_{inf}, and C_{max}.

The natural log (ln)-transformed[4] PK parameters will be analyzed using a mixed model.[5] The model will include treatment as fixed effect and subject as a random effect.

For AUC_{last}, AUC_{inf}, and C_{max} separately, the least squares mean (LSM) for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% confidence interval (CI) will be calculated; these values will then be back-transformed to give the geometric least square mean (GLSM), ratio of GLSMs, and corresponding 90% CI.

Additionally, the pooled estimate (across all treatments) of the within-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 pkday paramn param;
  class trtan usubjid;
  model ln_pk = trtan / cl residual ddfm = kr;
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random usubjid;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
run;
```

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 a new version is issued during the study; see the DMP for more details). All AEs will be assigned a severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (or higher if a new version is issued during the study; see the protocol for more details).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing, or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE with a relationship 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 frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

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

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

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

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to not be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started after dosing.
- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to not be a treatment-related TEAE.
- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE 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 dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE 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). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.
- For the derivation of duration (applicable to all AEs): 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 AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as

duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.
- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, will be listed, as applicable; 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 will be provided for clinical chemistry and hematology parameters.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, <x and ≤x values will be set to 0, whereas >x and ≥x values will be set to x.

8.6.3. Vital Signs Parameters

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

Summary tables and boxplots by treatment and timepoint will be provided by treatment group for all vital signs parameters as applicable.

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 will be provided for all 12-lead ECG parameters.

8.6.5. Other Assessments

Medical history will not be listed.

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

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

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: Structure and content of clinical study reports (E3). 30 November 1995.

2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.

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

4. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.

5. Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester: John Wiley & Sons, 1999.

12. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

Statistical Analysis Plan (SAP) Approval Form

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

Sponsor Name:	Amgen, Inc.		
Sponsor Protocol/CIP ID:	20200426	**Covance Study ID:**	8461525
SAP text filename:	Amgen510_20200426_SAP_Final.pdf	**TFL shells filename:**	Amgen510_20200426_TFL_Final.pdf
Version:	1	**Date:**	26Sep2021

Covance Approval(s):

Lead Statistician

Approval Signature Print Name Job Title Date	[redacted] [redacted] Biostatistician I approved this document 27 Sep 2021 3:51 PM -05:00

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	[redacted] 27 September 2020

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

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

16.1.9.2. Quality Tolerance Limit Definitions

Parameter	Justification for Parameter	Unit Tolerance
Minimum number of evaluable subjects needed.	A shortfall in the overall number of subjects could have had a significant impact on interpretation of the primary endpoint because of limited/insufficient exposure.	N: 12