**TITLE PAGE**

# Statistical Analysis Plan

## An Open-label Single-dose Study to Evaluate the Pharmacokinetics of Sotorasib in Healthy Subjects and Subjects with Moderate or Severe Hepatic Impairment

SAP Status: Final
SAP Version: 1
SAP Date: 02June2021

Investigational Medicinal Product: Sotorasib (AMG 510)

Protocol Reference: 20200362
Covance Study: 8454975

Sponsor:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320 USA

Principal Investigators:
[redacted], MD

[redacted], MD

[redacted], MD

[redacted], MD

[redacted], MD

Study Sites:
Orlando Clinical Research Center
5055 S. Orange Ave.,
Orlando, FL 32809

Texas Liver Institute
607 Camden Street, Suite 101
San Antonio, TX 78215

Clinical Pharmacology of Miami, LLC.
550 West 84th Street,
Miami, FL 33014

Orange County Research Center
14351 Myford Road, Suite B,
Tustin, CA 92780

Pinnacle Clinical Research
5109 Medical Drive, Suite 200,
San Antonio, TX 78229



NCT Number: NCT04887064
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

**TABLE OF CONTENTS**

**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 plasma concentration-time curve |
| $AUC_{inf}$ | area under the plasma concentration-time curve from time zero to infinity |
| $AUC_{inf,u}$ | unbound $AUC_{inf}$ |
| $AUC_{last}$ | AUC from time zero to the last quantifiable concentration |
| $AUC_{last,u}$ | unbound $AUC_{last}$ |
| BLQ | below the limit of quantification |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | confidence interval |
| $CL_u/F$ | unbound apparent total plasma clearance |
| $C_{max}$ | maximum observed plasma concentration |
| $C_{max,u}$ | unbound $C_{max}$ |
| COVID-19 | coronavirus disease 2019 |
| 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 |
| EOS | end of study |
| ICF | informed Consent Form |
| ICH | International Council for/Conference on Harmonisation |
| IMP | investigational medicinal product |
| LLOQ | lower limit of quantification |
| ln | natural log |
| LSM | least squares mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| 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 |
| $t_{max}$ | time of the maximum observed concentration |
| TFL | table, figure, and listing |
| $V_{z,u}/F$ | unbound 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 dated 09 February 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 evaluate the PK of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function.

The secondary objective of the study is:

- to evaluate the safety and tolerability of sotorasib administered in subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function.

## 3. STUDY ENDPOINTS

The primary endpoints of the study are PK parameters for sotorasib:

- maximum observed plasma concentration ($C_{max}$)

- area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration ($AUC_{last}$)

- area under the plasma concentration-time curve from time zero to infinity ($AUC_{inf}$).

Additional PK parameters may be calculated.

The secondary endpoints of the study are:

- adverse events (AE)
- clinical laboratory evaluations
- 12-lead electrocardiograms (ECGs)
- vital signs
- unbound $C_{max}$ ($C_{max,u}$)
- unbound $AUC_{last}$ ($AUC_{last,u}$)
- unbound $AUC_{inf}$ ($AUC_{inf,u}$)
- unbound apparent total plasma clearance ($CL_u/F$)
- unbound apparent volume of distribution during the terminal phase ($V_{z,u}/F$).

## 4. STUDY DESIGN

This will be a Phase 1, parallel-arm, multi-center (US), open-label, non-randomized study to evaluate the PK of a single oral dose of sotorasib administered in subjects with normal hepatic function (control) and in subjects with moderate or severe hepatic impairment (according to Child-Pugh classification) under fasted conditions. Subjects who meet eligibility requirements will be assigned to 1 of 3 groups as shown in Table 1. The Child-Pugh classification will be based on the Child-Pugh score at Screening.

Attempts will be made to match for age (mean ± 10 years), sex, and body mass index (mean ± 20%) between normal and hepatically impaired groups. Up to 8 subjects can be enrolled in Group 1 to satisfy matching criteria. Up to 8 subjects will be enrolled in Groups 2 and 3 to ensure 6 evaluable subjects. Subjects will maintain the same group assignment throughout the study.

**Table 1: Classification of Hepatic Impairment Groups**

| Group | Degree of Hepatic Impairment | Number of Subjects |
|---|---|---|
| 1 | Normal function (no impairment) | 6 to 8 |
| 2 | Moderate impairment (Child-Pugh Class B) | 6 to 8 |
| 3 | Severe impairment (Child-Pugh Class C) | 6 to 8 |

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the study site on Day -1 and

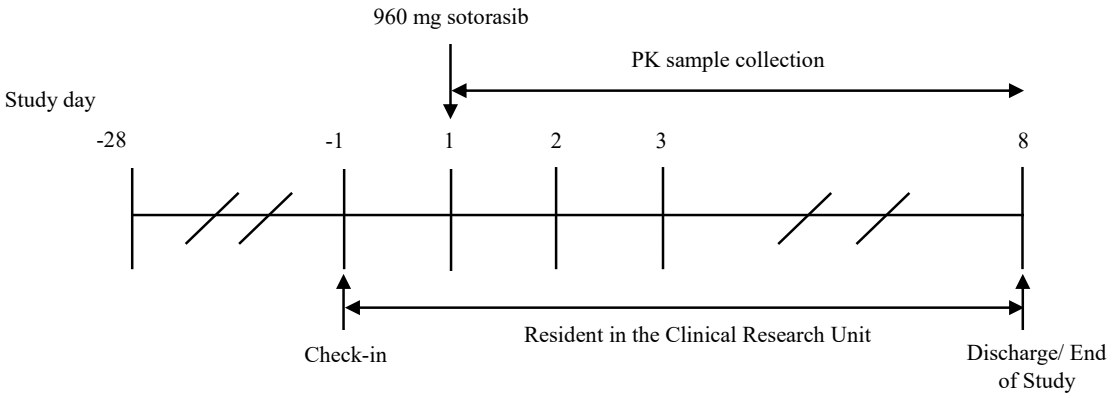
be confined until discharge on Day 8. On Day 1, after at least a 8-hour fast, all subjects will receive a single oral dose of 960 mg sotorasib (8 × 120-mg tablets).

The total duration of study participation for each subject (from Screening through end of study [EOS]) is anticipated to be approximately 4 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).

A schematic of the study design is presented in Figure 1.

**Figure 1: Study Design**




## 5. SAMPLE SIZE JUSTIFICATION

Approximately up to 24 subjects will be enrolled, with a minimum of 6 evaluable subjects and a maximum of up to 8 subjects in Group 1, and a maximum of 16 subjects enrolled in Groups 2 and 3 (8 subjects in each hepatic impairment group to ensure 6 evaluable subjects). The sample size of 6 subjects per hepatic impairment group is based on practical considerations and consistent with regulatory guidance for studies evaluating the effect of hepatic impairment on the PK of an investigational medicinal product (IMP).

## 6. STUDY TREATMENTS

The treatment will be a single oral dose of 960 mg sotorasib (8 × 120-mg tablets).

The hepatic function groups and ordering to be used in the TFLs are presented in Table 2.

**Table 2: Presentation of Hepatic Function Groups in TFLs**

| Hepatic Function Group | Order in TFLs |
|---|---|
| Normal Hepatic Function | 1 |
| Moderate Hepatic Impairment | 2 |
| Severe Hepatic Impairment | 3 |

## 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 sotorasib 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 sotorasib and have evaluable PK data. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration ($t_{max}$) or diarrhea within 24 hours of dosing.

## 8. STATISTICAL METHODOLOGY

### 8.1. General

Listings will be provided for all data captured in the database, including 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 follow-up 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 X.X.X (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. Triplicate Readings

For 12-lead ECG data only, where triplicate readings are taken, the mean of triplicate readings will replace the separate individual triplicate readings in all calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean and/or medians will be calculated, as appropriate, based on the number of readings available.

### 8.1.4. 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 8.1.5) and 12-lead ECG outlier analysis (see Section 8.6.4).

### 8.1.5. Definitions of Baseline, Change from Baseline, and Percentage Change from Baseline

The baseline will be defined as the last value recorded prior to dosing. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the postdose timepoint.

The summary statistics for change from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 8.1.4 for more detail on handling repeat and unscheduled readings in the calculations. See Section 8.1.3 for more detail on handling of triplicate readings in the calculations.

## 8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by hepatic function groups 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 hepatic function groups will be provided, based on the safety population.

## 8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that 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 sotorasib (total and unbound, unbound parameters to be distinguished with a subscripted "u") and metabolites using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

| Parameter | Units[a] | Definition |
|---|---|---|
| $AUC_{last}$[d] | h*ng/mL | area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($t_{last}$)[b] |
| $AUC_{inf}$[d] | h*ng/mL | area under the concentration-time curve from time 0 extrapolated to infinity[c] |
| $C_{max}$[d] | ng/mL | maximum observed concentration |
| $t_{max}$[d] | h | time of the maximum observed concentration |
| $t_{last}$[d] | h | time of the last quantifiable concentration |
| $t_{1/2}$[d] | h | apparent terminal elimination half-life |
| CL/F[d] | L/h | apparent total clearance (parent analyte only) |
| $V_z$/F[d] | L | apparent volume of distribution during the terminal phase (parent analyte only) |
| $f_u$ | NA | fraction of unbound drug in plasma, calculated as the mean from available time points for each individual subject (sotorasib only) |

[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] Area under the concentration-time curve will be calculated using the linear trapezoidal linear interpolation rule.
[c] Based on the last observed quantifiable concentration
[d] PK parameters for unbound sotorosib will be distinguished with a subscripted "u" (i.e., $AUC_{last,u}$; $AUC_{inf,u}$; $C_{max,u}$; $T_{max,u}$; etc.)

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters $C_{max}$, $t_{last}$, 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 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 ($\lambda_z$) 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 $\lambda_z$ for their calculation (eg, $AUC_{inf}$, $t_{1/2}$, CL/F, and $V_z$/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 |
|---|---|---|
| $\%AUC_{extrap}$ | % | percentage of AUC due to extrapolation from the last quantifiable concentration to infinity |
| $\lambda_z$ | 1/h | apparent terminal elimination rate constant |
| $\lambda_z$ Upper | h | end of exponential fit |
| $\lambda_z$ Lower | h | start of exponential fit |
| $\lambda_z$ N | NA | number of data points included in the log-linear regression |
| $\lambda_z$ Span Ratio | NA | time period over which $\lambda_z$ was determined as a ratio of $t_{1/2}$ |
| $R^2$-adj | NA | adjusted coefficient for determination of exponential fit |

Where possible, the span of time used in the determination of $\lambda_z$ (ie, the difference between $\lambda_z$ Upper and $\lambda_z$ Lower) should be ≥2 half-lives. If the $\lambda_z$ Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the 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 (LLOQ). If there are only 3 consecutive concentrations, at least 1 should follow $C_{max}$. An exception may be made for metabolites, where $C_{max}$ may be the last timepoint.

If the extrapolated area is >20%, $AUC_{inf}$ (and derived parameters) will be listed but flagged and excluded from statistics.

If $AUC_{inf}$ cannot be determined reliably for all subjects, an alternative AUC measure, such as AUC to a fixed timepoint or $AUC_{0\text{-}tlast}$, may be used in the statistical analysis of hepatic impairment.

#### 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 BLQs will be treated as missing. The following rules apply with special 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 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 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 and set to missing for the PK analysis.

### 8.5.2. Presentation of Pharmacokinetic Data

All PK concentrations and parameters will be listed.

Summary tables, arithmetic 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-linear and linear-logarithmic scales, with the exception of figures across all days, which will be produced on the linear-linear scale only. The +SD bars will only be displayed on the linear-linear scale.

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

A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median $t_{max}$.

If the actual time of sample collection deviates from the nominal time by more than ±10%, the concentration will be flagged, but included in the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For PK concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and CV% of geometric mean will be reported as not calculated (NC).

For PK parameters the following rule will apply:

Geometric mean and coefficient of variation (CV) will not be calculated for $t_{last}$ or $t_{max}$.

### 8.5.3. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the PK of sotorasib (total and unbound) following a single dose in subjects with moderate hepatic impairment or severe hepatic impairment compared to subjects with normal hepatic function. The natural log (ln)-transformed[4] PK parameters will be analyzed using an analysis of variance (ANOVA) model.[5] The model will include the factor "hepatic impairment" (ie, moderate, severe, or none) as a fixed effect. Geometric mean ratios (test/reference) and the corresponding 90% confidence intervals (CIs) of $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ of sotorasib between the groups of hepatically impaired subjects (test) and subjects with normal hepatic function (reference) will be calculated.

### 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, their changes from baseline, 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 and boxplots by treatment and timepoint will be provided by hepatic function group for clinical chemistry, hematology, and coagulation parameters, their changes from baseline, as applicable.

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, their changes from baseline, 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 hepatic function group for all vital signs parameters, their changes from baseline, as applicable.

### 8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters, their changes from baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided by hepatic function group for all 12-lead ECG parameters, their changes from baseline.

### 8.6.5. Other Assessments

Medical history will 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. Figg WD, Dukes GE, Lesesne HR et al. Comparison of quantitative methods to assess hepatic function: Pugh's classification, indocyanine green, antipyrine, and dextromethorphan. *Pharmacotherapy* 1995; 15:693-700.

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

## 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:** | 20200362 | **Covance Study ID:** | 8454975 |
| **SAP text filename:** | Amgen510_20200362_SAP_Final.pdf | **TFL shells filename:** | Amgen510_20200362_TFL_Final.pdf |
| **Version:** | 1 | **Date:** | 02June2021 |

**Covance Approval(s):**

Lead Statistician

| | |
|---|---|
| Approval Signature<br>Print Name<br>Job Title<br>Date | [redacted] [redacted]<br>Biostatistician<br>I approved this document<br>09 Jun 2021 10:43 AM -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<br>Print Name<br>Job Title<br>Date | [redacted]<br>Biostatistics Senior Manager<br>09June2021 |

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. | Healthy Matches (n = 6 to 8)<br>Moderate (n = 6 to 8)<br>Severe (n = 6 to 8) |

# Approval Signatures

**Document Name:** 161-09-csr-20200362-statistical-met

**Document Number:** CLIN-000300020

**Document Version:** 1

| Document Approvals | |
|---|---|
| Reason for Signing: Management | Name: [redacted]<br>Date of Signature: 05-Oct-2022 21:10:18 GMT+0000 |