

## **Protocol**

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### **An Open-label, Randomized, Two-way Crossover, Bioequivalence Study in Healthy Volunteers to Compare the Pharmacokinetics of Two Different Tablets of Sotorasib**

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This protocol was developed, reviewed, and approved in accordance with Labcorp's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

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This NCT number has been applied to the document for purposes of  
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### INVESTIGATOR AGREEMENT

I have read the protocol entitled “An Open-label, Randomized, Two-way Crossover, Bioequivalence Study in Healthy Volunteers to Compare the Pharmacokinetics of Two Different Tablets of Sotorasib” and agree to conduct the study as described herein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

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Signature

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Name of Investigator

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Date (DD Month YYYY)

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Title and Role of Investigator

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Institution Name

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## SYNOPSIS

**Title of study:** An Open-label, Randomized, Two-way Crossover, Bioequivalence Study in Healthy Volunteers to Compare the Pharmacokinetics of Two Different Tablets of Sotorasib

**Objectives:**

The primary objective of the study is:

- to compare the pharmacokinetics (PK) of 960 mg sotorasib administered orally as 3 x 320 mg tablets (test 1) under fasted conditions to 960 mg sotorasib administered orally as 8 x 120 mg tablets (reference) under fasted conditions.

The secondary objectives of the study are:

- in 14 subjects, to evaluate the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets with a high-fat meal (test 2).
- to assess the safety and tolerability of 960 mg sotorasib administered orally as 3 x 320 mg tablets and 960 mg sotorasib administered orally as 8 x 120 mg tablets.

**Study design:**

This will be an open-label, multi-center (United States), crossover, 3-period bioequivalence study. Period 1 and 2 will enroll approximately 146 subjects and compare the PK of a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1) to a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference) under fasted conditions in healthy male and healthy female subjects. Fourteen out of the 146 subjects will enter Period 3 and receive an additional 960 mg sotorasib administered as 3 x 320 mg tablets with a high-fat meal (test 2). After informed consent is obtained, 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 Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 6 or Day 9.

On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive one administration of 960 mg sotorasib administered orally under fasted condition as 3 x 320 mg tablets (Treatment A: test 1) and one administration of 960 mg sotorasib administered orally under fasted condition as 8 x 120 mg tablets (Treatment B: reference) in either Period 1 or Period 2 according to the treatment sequence below. On Day 7, fourteen subjects in either Group 1 or Group 2 will proceed to Period 3 and receive one additional administration of 960 mg sotorasib administered orally as 3x 320 mg tablets with a high-fat meal (Treatment C: test 2).

Group	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment A	

**Number of subjects:**

Approximately 146 subjects will be enrolled to ensure that at least 132 subjects complete the study.

**Diagnosis and main criteria for inclusion:**

Healthy male subjects or female subjects of nonchildbearing potential, 18 to 60 years of age (inclusive), and body mass index of 18 to 30 kg/m<sup>2</sup> (inclusive).

**Investigational products, dose, and mode of administration:**

Investigational medicinal products:

- 120 mg tablet of sotorasib
- 320 mg tablet of sotorasib

Treatment A: 960 mg sotorasib administered orally as 3 x 320 mg tablets, after an overnight fast of at least 10 hours

Treatment B: 960 mg sotorasib administered orally as 8 x 120 mg tablets, after an overnight fast of at least 10 hours

Treatment C: following an overnight fast of at least 10 hours, subjects will consume the entirety of a standard high-fat breakfast within 20 minutes. A 960 mg oral dose of sotorasib (3 x 320-mg tablets) will be given orally 30 minutes after start of the meal.

**Duration of subject participation in the study:**

Planned Screening duration: approximately 4 weeks.

Planned Study duration (Screening to end of study): approximately 5 weeks.

**Primary endpoints:**

The primary endpoints of the study are sotorasib PK parameters in Period 1 and Period 2: maximum observed plasma concentration ( $C_{max}$ ), area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration ( $AUC_{last}$ ), and AUC from time zero to infinity ( $AUC_{inf}$ ).

**Secondary endpoints:**

The secondary endpoints for this study are: adverse events, clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, and sotorasib PK parameters in Period 3:  $C_{max}$ ,  $AUC_{last}$ ,  $AUC_{inf}$ .

**Statistical methods:**

The primary PK parameters are  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  for sotorasib on Days 1 and 4. All other PK parameters will be regarded as secondary. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment, period, and sequence and a random effect for subject. Geometric mean ratios (test/reference) for  $C_{max}$  and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be Treatment B while the “test 1” treatment will be Treatment A for the bioequivalence analysis. For the food-effect analysis, the model will use 14 subjects’ data and assumes fixed effects for treatment and random effect for subject while test treatment would be fed (test 2; Treatment C) and reference would be fasted (test 1; Treatment A).

The final safety analysis for the study will be performed at the end of the study. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. Endpoints for clinical laboratory tests, ECGs, and vital signs will be summarized.

Additional details will be included in the Statistical Analysis Plan.

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## LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC <sub>inf</sub>	area under the plasma concentration-time curve from time zero to infinity
AUC <sub>last</sub>	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AV	atrioventricular
BIL	bilirubin
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C <sub>max</sub>	maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
<i>KRAS</i>	Kirsten rat sarcoma viral oncogene homolog (gene)
KRAS <sup>G12C</sup>	KRAS protein with a glycine to cysteine amino acid substitution at position 12

<i>KRAS p.G12C</i>	<i>KRAS</i> gene with a mutation resulting in a glycine to cysteine amino acid substitution at position 12
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
TBL	total bilirubin
$t_{\max}$	time to maximum observed plasma concentration
ULN	upper limit of normal
WBC	white blood cell

## 1. INTRODUCTION

Refer to the Investigator's Brochure (IB)<sup>1</sup> for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

### 1.1. Background

The role of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene mutations in human cancers has been known for decades;<sup>2</sup> however, no anticancer therapies targeting *KRAS* mutations have been successfully developed. Thus, an unmet need exists for therapies that can specifically target cancers driven by *KRAS* mutations. Sotorasib is one such small molecule that specifically and irreversibly inhibits the protein product of a mutant *KRAS* gene, which results in a G12C mutation at the protein level (*KRAS p.G12C*). One mutant version of *KRAS*, *KRAS p.G12C*, which encodes the *KRAS*<sup>G12C</sup> protein, might be tractable for small molecule inhibition through a covalent interaction with the mutant cysteine<sup>3,4,5</sup> found in approximately 13% of lung adenocarcinoma (nonsquamous, non-small-cell lung carcinoma), 3% of colorectal cancer, and 1% to 2% of numerous other solid tumors.<sup>6,7,8</sup> Sotorasib forms a specific covalent bond with the mutant cysteine of *KRAS*<sup>G12C</sup>, irreversibly locking the protein in an inactive conformation that cripples oncogenic signaling.<sup>5</sup> As inactivation of *KRAS* has been demonstrated to inhibit cell growth and/or promote apoptosis selectively in tumor cells harboring *KRAS* mutations,<sup>3,4,9,10,11</sup> sotorasib may provide a therapeutic benefit for patients with *KRAS p.G12C*-driven cancers.

The metabolism and excretion of sotorasib were evaluated in bile duct-cannulated male rats after a single intravenous (1 mg/kg) or oral (10 mg/kg) dose of sotorasib. Recovery of sotorasib and M24 was low (< 10%) in the study, consistent with extensive metabolism of sotorasib. Metabolite profiling by liquid chromatography high-resolution mass spectrometry methods identified low amounts of sotorasib and M24 excreted into bile [REDACTED], feces [REDACTED] and urine [REDACTED] following both intravenous and oral administration, with metabolites that included products of oxidative metabolism and glucuronidation (M3, M4, M16), cysteine and N-acetyl cysteine conjugation (M10, M15, M20), reduction (M21), and dealkylation (M24). Refer to the IB<sup>1</sup> for more information.

Four sotorasib clinical studies (20170543, 20190009, 20190135, and 20190147) are currently ongoing in subjects with *KRAS p.G12C*-mutated tumors. In addition, a number of studies in healthy volunteers have explored the pharmacokinetics (PK) of sotorasib, including assessments of mass-balance, food effect, and various drug-drug interactions.

Preliminary data are available for Phase 1 of the Phase 1/2 Study 20170543 that evaluates the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in subjects with *KRAS p.G12C*-mutated advanced solid tumors as monotherapy and in combination with pembrolizumab. As of 01 June 2020, 199 subjects were enrolled in the Phase 1 monotherapy

treatment cohorts; of these, 197 subjects received at least 1 dose of sotorasib (dose range: 180 to 960 mg).

A summary of completed and ongoing clinical studies for sotorasib is provided in the IB (Table 6-1 and Table 6-2).<sup>1</sup>

## 1.2. Pharmacokinetics

Preliminary sotorasib PK data were available as of 20 May 2020 for subjects with a specific *KRAS* mutation with advanced solid tumors in the dose-exploration part of the first-in-human study, with once daily (QD) oral doses ranging from 180 to 960 mg. Dose-related increases in exposure on Day 1 were observed in oral QD doses from 180 through 960 mg; however, the increase in exposure was less than dose-proportional. There was no accumulation with multiple oral QD dosing for 8 days. The increase in exposure from 180 through 960 mg following oral QD dosing was less than dose-proportional on Day 8. Rapid absorption was observed, with time to maximum observed plasma concentration ( $t_{\max}$ ) between 1 to 2 hours after oral administration.

A mass-balance study was conducted to characterize the PK and primary route(s) of elimination of  $^{14}\text{C}$ -sotorasib and drug-related material, and to estimate the overall recovery of radiolabeled material in healthy male subjects after a single oral suspension dose of 720 mg  $^{14}\text{C}$ -sotorasib. Based upon preliminary analysis of interim data, the mean PK parameter estimates are similar to those observed in subjects with advanced solid tumors. The mean cumulative recovery over the collection period (0 to 312 hours) was 80.8%, with 74.6% being excreted in the feces and 6.18% excreted in the urine.

A food-effect study was conducted to evaluate the PK of sotorasib administered in the fasted and fed conditions in healthy subjects. When 360 mg of sotorasib was administered with a high-fat meal, area under the plasma concentration-time curve (AUC) from time zero to infinity ( $\text{AUC}_{\text{inf}}$ ) increased 1.38-fold compared with administration in the fasted condition. The maximum observed plasma concentration ( $C_{\max}$ ) was comparable in fasted and fed conditions. Time to peak was delayed by 1.25 hours under the fed condition. These results support the administration of sotorasib in either the fed or fasted condition.

Multiple drug-drug interaction studies have been conducted with sotorasib. Coadministration of sotorasib with single doses of metformin, rifampin, and multiple doses of itraconazole resulted in no clinically meaningful changes in sotorasib exposure. Results from coadministration of sotorasib with multiple doses of rifampin or omeprazole indicated that exposure of sotorasib may fall to suboptimal levels when administered with a proton-pump inhibitor or strong inducers of cytochrome P450 3A4. Following coadministration with digoxin, systemic exposure of digoxin increased and caution should be used when sotorasib is administered with substrates of P-glycoprotein.

### **1.3. Study Rationale**

The purpose of this study is to compare the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets (test) under fasted condition to 960 mg sotorasib administered as 8 x 120 mg oral tablets (reference) under fasted condition and to compare the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets following a high-fat meal (test 2) to 960 mg sotorasib administered as 3 x 320 mg oral tablets under fasted condition (test 1) in healthy male subjects and healthy female subjects of nonchildbearing potential. Oral dosing is the intended route of administration for sotorasib. The 320 mg tablet formulation of sotorasib would help reduce pill burden for patients requiring sotorasib treatment.

### **1.4. Benefit-risk Assessment**

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB<sup>1</sup> for more information.

#### **1.4.1. Therapeutic Context**

##### **1.4.1.1. Key Benefits**

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

##### **1.4.1.2. Risks**

To limit the risk of excessive exposure to healthy subjects in the current study, each subject will receive a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1, treatment A) and a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference, treatment B) in either Period 1 or Period 2 according to their assigned group, with sufficient washout in between periods (details provided in [Section 3.3](#)). Fourteen healthy subjects in either Groups 1 or 2 will receive a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 2, treatment C) following a high-fat meal (detailed provided in [Section 5.2.1](#)) in Period 3 with sufficient washout in between periods.

Safety monitoring: During the study, subjects will receive all IMP doses by site staff and will be instructed not to crush, chew, or split the sotorasib tablets when taking the dose under the supervision of the site staff. Safety assessments throughout the study include adverse event monitoring, electrocardiograms (ECGs), physical examination, vital signs, and clinical laboratory evaluations.

#### **Risks of Sotorasib**

Based on sotorasib clinical trials experience, adverse drug reactions with sotorasib include diarrhea, nausea, fatigue, vomiting, abdominal pain, and increased liver enzymes. Based on nonclinical toxicity studies of sotorasib, potential safety concerns to be monitored in clinical



studies of sotorasib include renal toxicity, anemia, leukocytosis, thyroid dysfunction, and splenomegaly. Clinical signs and symptoms of these toxicities observed in clinical and nonclinical studies, along with relevant laboratory parameters, will be monitored during the study to ensure subjects' safety.

### **Abnormal Liver Function Tests**

Abnormal liver function tests (increased aspartate aminotransferase [AST] and increased alanine aminotransferase [ALT]) have been observed in oncology subjects receiving sotorasib therapy. The events of abnormal liver function blood tests generally resolved in subjects upon interruption of treatment. The risk mitigation plan consists of monitoring liver enzymes, with regular measurement of AST, ALT, alkaline phosphatase, and bilirubin to be performed. Specific eligibility for sotorasib are provided in [Section 4](#).

As of January 13<sup>th</sup> 2021, no clinically meaningful sotorasib-related renal toxicity, anemia, leukocytosis, thyroid dysfunction or splenomegaly have been observed. More detailed information about the key safety information of sotorasib, including a list of adverse drug reactions, may be found in the sotorasib IB and USPI.<sup>1,12</sup>

## **2. OBJECTIVES AND ENDPOINTS**

### **2.1. Objectives**

The primary objective of the study is:

- to compare the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets (test 1) under fasted condition to 960 mg sotorasib administered orally as 8 x 120 mg tablets (reference) under fasted condition.

The secondary objectives of the study are:

- in 14 subjects, to evaluate the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets with a high-fat meal (test 2).
- to assess the safety and tolerability of 960 mg sotorasib administered orally as 3 x 320 mg tablets and 960 mg sotorasib administered orally as 8 x 120 mg tablets.

### **2.2. Endpoints**

#### **2.2.1. Primary Endpoints**

The primary endpoints of the study are sotorasib PK parameters in Period 1 and Period 2:

- $C_{max}$
- AUC from time zero to the last quantifiable concentration ( $AUC_{last}$ )

- $AUC_{inf}$ .

### 2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- adverse events
- clinical laboratory tests
- 12-lead ECGs
- vital signs
- sotorasib PK parameters in Period 3:  $C_{max}$ ,  $AUC_{last}$ ,  $AUC_{inf}$ .

## 3. INVESTIGATIONAL PLAN

### 3.1. Overall Study Design and Plan

This will be an open-label, multi-center (United States), crossover, 3-period bioequivalence study to compare the PK of a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1) under fasted condition to a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference) under fasted condition and the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets following a high-fat meal (test 2) to 960 mg sotorasib administered as 3 x 320 mg oral tablets under fasted condition (test 1) in healthy male subjects and healthy female subjects. Approximately 146 subjects will be enrolled to ensure that at least 132 subjects complete the study.

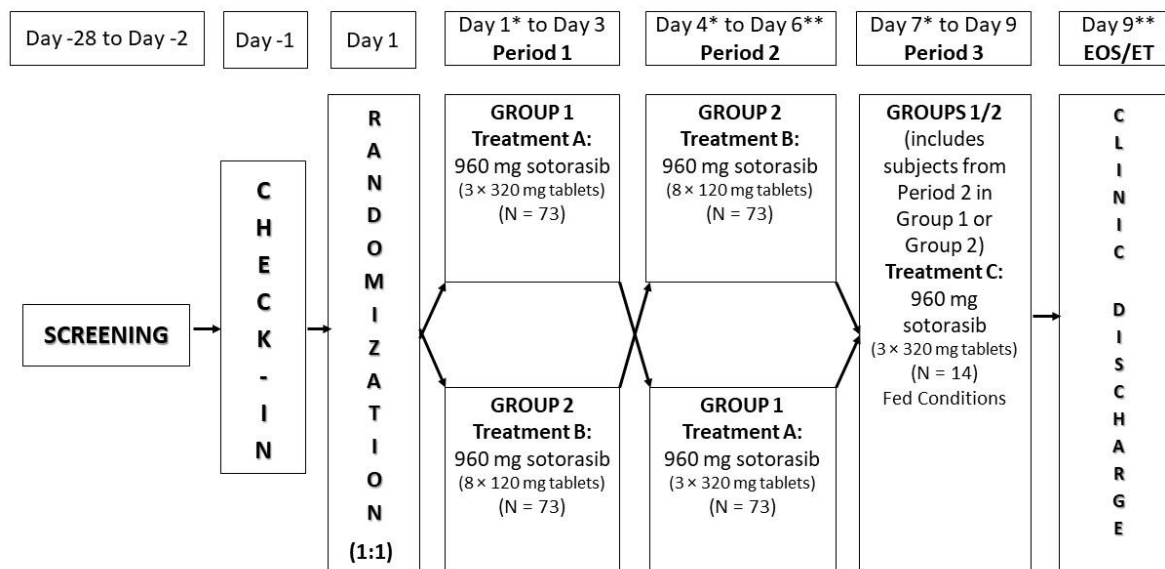
Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 6 or Day 9. On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive one administration of 960 mg sotorasib administered orally as 3 x 320 mg tablets (Treatment A: test 1) and one administration of 960 mg sotorasib administered orally as 8 x 120 mg tablets (Treatment B: reference) in either Period 1 or Period 2 according to their assigned group. Each subject will receive both treatments following an overnight fast according to the treatment sequence in [Table 1](#). On Day 7, 14 subjects in either Group 1 or Group 2 will proceed to Period 3 and receive one additional administration of 960 mg sotorasib administered orally as 3x 320 mg tablets with a high-fat meal (Treatment C: test 2).

**Table 1: Treatment Sequence**

Group	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment A	

An overview of the study design is shown in [Figure 1](#).

**Figure 1: Study Schematic**



Abbreviations: EOS = End of Study; ET = Early Termination; N = number of subjects

\*Subjects will receive a single dose in each treatment period, on Days 1, 4, and 7.

\*\* Subjects will be discharged on Day 6 or Day 9 according to their treatment assignment.

The total duration of study participation for each subject (from Screening through end of study [EOS]) is anticipated to be approximately 5 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 Schedule of Assessments is presented in [Appendix 9](#).

### 3.2. Discussion of Study Design

This is a 3-period crossover study in healthy subjects where all subjects receive at least two treatments. The randomized, crossover design in Period 1 and Period 2 used in this study is typical to evaluate the relative bioavailability of the different treatments. The number of subjects is adequate since the design selected for this study allows intra-subject comparisons and thereby reduces variability. This study will be open-label because the primary endpoints of the study are considered objective.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

### 3.3. Selection of Doses in the Study

The 960 mg dose was selected for the present study because this is the approved dose.<sup>12</sup> There have been 6 clinical studies in healthy subjects where sotorasib has been administered on 2 to 3 occasions at the 960 mg dose, and was well tolerated across all studies.

There have been no dose-limiting toxicities observed with sotorasib monotherapy at 960 mg in subjects with advanced solid tumors with the *KRAS p.G12C* mutation. Please refer to the IB<sup>1</sup> for more information.

## 4. SELECTION OF STUDY POPULATION

### 4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment unless otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male subjects or female subjects, between 18 and 60 years of age (inclusive) at the time of Screening.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [e.g., suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
4. Body mass index between 18 and 30 kg/m<sup>2</sup> (inclusive) at the time of Screening.
5. Females of nonchildbearing potential defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) or postmenopausal (defined as at least 45 years of age with amenorrhea for 12 months without an alternative medical cause and follicle-stimulating hormone [FSH] level  $\geq$  40 mIU/mL).

### 4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated:

1. History or evidence, at Screening or Check-in, of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or

designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

2. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
3. A QT interval corrected for heart rate (HR) based on the Fridericia method (QTcF) interval >450 msec in male subjects or >470 msec in female subjects or history/evidence of long QT syndrome, at Screening or Check-in, confirmed by calculating the mean of the original value and 2 repeats.
4. PR interval >200 msec, 2nd degree atrioventricular (AV) block or 3rd degree AV block, at Screening or Check-in. An average of the triplicate measurements of the PR interval will be used to evaluate subject's eligibility at Screening and at Check-in.
5. Systolic blood pressure (BP) >140 mmHg or <90 mmHg, or diastolic BP >90 mmHg, or HR >100 bpm, at Screening or Check-in. Subjects with out-of-range values that are not clinically significant (as determined by the Investigator) may have the test repeated once during Screening or Check-in (within 1 hour of original assessment) and the subject may be enrolled if a repeated value is within normal range.
6. History suggestive of esophageal (including esophageal spasm, esophagitis), gastric, or duodenal ulceration or bowel disease (including but not limited to peptic ulceration, gastrointestinal bleeding, ulcerative colitis, Crohn's disease, or irritable bowel syndrome); or a history of gastrointestinal surgery other than uncomplicated appendectomy.
7. Inability to swallow oral medication or history of malabsorption syndrome.
8. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
9. Poor peripheral venous access.
10. Estimated glomerular filtration rate less than 70 mL/min/1.73 m<sup>2</sup> as calculated by the Modification of Diet in Renal Disease equation, at Screening or Check-in. A subject with out-of-range value may have the test repeated once at the discretion of the Investigator.
11. ALT or AST > upper limit of normal (ULN), at Screening or Check-in. ALT and AST should be below ULN at Screening (for these parameters, a subject with out-of-range values may have the tests repeated once and the subject may be enrolled if the repeated values are ≤ULN or if the repeated values above ULN are deemed not clinically significant by the Investigator [eg, ≤1.5 ULN]).
12. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus test, at Screening. Subjects whose results are compatible with prior immunity may be included.

13. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before enrollment.
  - a. Acetaminophen (paracetamol; up to 2 g per day) for analgesia will be allowed.
14. All herbal medicines (e.g., St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to enrollment, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
15. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 30 days prior to dosing.
16. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges within 7 days prior to Check-in.
17. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
18. Alcohol consumption from 48 hours prior to Check-in.
19. Regular alcohol consumption of > 14 units per week for males and > 7 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
20. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
21. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Screening or Check-in.
22. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
23. Female subjects with a positive pregnancy test at Screening or Check-in.
24. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through 7 days after the EOS.
25. Unwilling to adhere to contraceptive requirements through 7 days after the EOS (see [Appendix 4](#)).
26. Unwilling to abstain from sperm donation and ovum donation through 7 days after the EOS (see [Appendix 4](#)).
27. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
28. Male subjects with a pregnant partner or partner planning to become pregnant who are unwilling to practice abstinence (refrain from heterosexual intercourse) or use contraception while the subject is on study through 7 days after the EOS.
29. Subject has received a dose of an investigational drug within the past 30 days or 5 half-lives, whichever is longer, prior to Check-in.
30. Have previously completed or withdrawn from this study or any other study investigating sotorasib or have previously received the investigational product.

31. Donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
32. Receipt of blood products within 2 months prior to Check-in.
33. Unwilling to abide with study restrictions.
34. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
35. Performed strenuous exercise, began a new exercise program, or participated in any unusually strenuous physical exertion within 7 days prior to Check-in.

#### **4.3. Screen Failures and Rescreening**

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once.

#### **4.4. Subject Number and Identification**

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (e.g., Subjects 0101, 0102, 0103). Replacement subjects will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (e.g., Subject 1101 replaces Subject 0101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

#### **4.5. Subject Withdrawal and Replacement**

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) v5 Grade  $\geq 3$  AE

- occurrence of Grade 2 AE considered by the Investigator (or designee) to be at least possibly related to sotorasib and, in the opinion of the Investigator (or designee), warrants subject withdrawal (e.g., neuropathy, chronic diarrhea, etc.)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If two or more subjects are withdrawn from the study due to AEs that are considered by the Investigator to be at least possibly related to sotorasib or if there is one Grade 3 event, dosing would be paused, and the Investigator and Sponsor will convene to review the data and determine the next step.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible ([Appendix 9](#)). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is inhouse-, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their adverse events and serious adverse events, or until the unresolved adverse events and serious adverse events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events/serious adverse events thought to be related to the study drug will generally not be replaced.

#### **4.6. Study Termination**

The Sponsor may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Institutional Review Board (IRB) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply investigational product and by what mechanism, after termination of the study.

In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

#### **4.7. Discontinuation of Study Treatment**

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or study procedures at any time during the study



but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Assessments ([Appendix 9](#)) including different options of follow-up (e.g., in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, serious adverse events and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or study procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to ensure safety surveillance and/or collection of outcome data.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by the Sponsor
- Lost to Follow-up
- Death
- Protocol deviation
- Noncompliance
- Adverse events
- Subject request
- Pregnancy.

## 5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

### 5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in [Table 2](#).

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer's instructions or pharmacy instructions. Until dispensed to the

subjects, the investigational products will be stored at the study site in a location that is locked with restricted access.

## **5.2. Investigational Product Administration**

### **Table 2: Investigational Product**

<b>Study Treatment Name</b>	<b>(Treatment A, C) Investigational Medicinal Product: Sotorasib</b>	<b>(Treatment B) Investigational Medicinal Product: Sotorasib</b>
<b>Unit Strength and Formulation</b>	320 mg tablet	120 mg tablet
<b>Dosage Level</b>	960 mg (3 x 320 mg tablets)	960 mg (8 x 120 mg tablets)
<b>Route of Administration</b>	Oral	Oral
<b>Accountability</b>	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.

<b>Dosing Instructions</b>	<p>Treatment A: The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Three tablets should be taken (the first tablet by itself immediately followed by two tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p> <p>Treatment C: The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Subjects will consume the entirety of a standard high-fat breakfast within 20 minutes. A 960-mg dose of sotorasib will be given orally 30 minutes after start of the meal. Three tablets should be taken (the first tablet by itself immediately followed by two tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p>	<p>The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Eight tablets should be taken (the first tablet by itself immediately followed by seven tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p>
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Except as part of the dose administration, subjects will restrict their consumption of water for 1 hour prior to dosing and for 2 hours after dosing; at all other times during the study, subjects may consume water as desired. Subjects will continue fasting for at least 4 hours postdose.

Subjects will be dosed while standing and will not be permitted to lie supine for 2 hours after administration of IMP, except as necessitated by the occurrence of an adverse event(s) and/or study procedures.

#### **5.2.1. Standard High-fat Meal**

The standardized high-fat meal breakfast should consist of approximately 800 to 1000 calories (including approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories). A typical meal is equivalent to 2 eggs fried in butter, 2 strips of bacon, 2 slices of

buttered toast or bread, 4 ounces of hash brown potatoes (fried with butter), and 8 ounces (240 mL) of whole milk.<sup>13</sup> Substitutions can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has similar meal volume and consistency. Substitutions will apply to all subjects and all subjects will receive an identical meal.

### **5.3. Treatment of Overdose**

The effects of overdose of sotorasib are not known. In case of overdose, consultation with the medical monitor is recommended for prompt reporting of clinically apparent or laboratory adverse events possible related to over dosage, and to discuss further management of the subject.

### **5.4. Medical Devices**

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-Amgen non-investigational medical devices (e.g., syringes, sterile needles), that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

### **5.5. Product Complaints**

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either the Sponsor or by distributors and partners for whom the Sponsor manufactures the material. This includes any investigational product (sotorasib) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an investigational product (sotorasib) supplied by the Sponsor are to be reported according to the instructions provided in the Amgen IPIM.

### **5.6. Randomization**

In Period 1 and Period 2, subjects will be randomized 1:1 into 1 of 2 treatment groups based on the study randomization scheme that will be provided by a biostatistician. Subjects in Period 3 will not be randomized.

### **5.7. Blinding**

This is an open-label study.

### **5.8. Treatment Compliance**

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.

- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

## **5.9. Drug Accountability**

The Investigator (or designee) will maintain an accurate record of the receipt of sotorasib tablets received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

## **6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS**

### **6.1. Concomitant Therapies**

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Acetaminophen (paracetamol; up to 2 g/day) is an acceptable concomitant medication. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment of an adverse event/serious adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

### **6.2. Diet**

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Refer to [Section 5](#) and [Table 2](#) for diet requirements/restrictions on applicable days of study treatment and/or PK assessments.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until EOS.

Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in until EOS.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in until EOS.

### **6.3. Smoking**

Subjects will not be permitted to use tobacco- or nicotine-containing products within 6 months prior to Check-in until the EOS.

### **6.4. Exercise**

Subjects are required to refrain from strenuous exercise from 7 days before Check-in until the EOS. Subjects will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

### **6.5. Blood Donation**

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS.

## **7. STUDY ASSESSMENTS AND PROCEDURES**

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- PK blood samples
- safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, and safety laboratory assessments.

### **7.1. Pharmacokinetic Assessments**

#### **7.1.1. Pharmacokinetic Blood Sample Collection and Processing**

Blood samples (approximately 1 x 4 mL for sotorasib) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in [Appendix 9](#). Procedures for



collection, processing, and shipping of PK blood samples will be detailed in a separate document.

Any blood sample collected according to the Schedule of Assessments ([Appendix 9](#)) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

#### **7.1.2. Analytical Methodology**

Plasma concentrations of sotorasib will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

### **7.2. Safety and Tolerability Assessments**

#### **7.2.1. Adverse Events and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information**

Adverse event definitions, assignment of severity and causality, and procedures for reporting Adverse Events and Serious Adverse Events are detailed in [Appendix 1](#).

The condition of each subject will be monitored from the time of signing the ICF to EOS. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report Adverse Events and Serious Adverse Events occurring at any other time during the study.

#### **Adverse Events**

The adverse event grading scale to be used in this study is described in [Appendix 1](#).

The Investigator is responsible for ensuring that all non-serious adverse events observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning, or noted on physical examination) from enrollment through the EOS are recorded/reported using the appropriate eCRF.

#### **Serious Adverse Events**

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment or the EOS visit (whichever is later) are reported using the

appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in [Appendix 1](#)).

All serious adverse events will be collected, recorded, and reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

The criteria for grade 4 in the Common Terminology Criteria for Adverse Events grading scale differs from the regulatory criteria for serious adverse events. It is left to the Investigator's judgment to report these grade 4 abnormalities as serious adverse events.

### **Serious Adverse Events After the Protocol-Required Reporting Period**

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events should be reported to Amgen (regardless of causality) if the Investigator becomes aware of them. Per local requirements in some countries, Investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge/awareness of the event using the paper-based Serious Adverse Event Report Form.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

### **Method of Detecting Adverse Events and Serious Adverse Events**

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

### **Follow-up of Adverse Events and Serious Adverse Events**

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is Lost to Follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the eCRF.

### **Regulatory Reporting Requirements for Serious Adverse Events**

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/independent ethics committees, and Investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the IRB, if appropriate according to local requirements.

### **Safety Monitoring Plan**

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

### **Pregnancy and Lactation**

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 7 days after EOS. Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment until 7 days after EOS.

If a pregnancy is reported, the Investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in [Appendix 5](#). Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in [Appendix 5](#).

### **7.2.2. Clinical Laboratory Evaluations**

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in [Appendix 9](#). Clinical laboratory evaluations are listed in [Appendix 2](#).

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. Subjects who develop any lab abnormalities outside the reference range that are deemed clinically meaningful during the study period will have follow-up labs once a week, or more frequently if deemed necessary, until the abnormalities have resolved or returned to within the reference range or to the subject's baseline values.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol test at the times indicated in the Schedule of Assessments in [Appendix 9](#). For all female subjects, a pregnancy test and FSH screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in [Appendix 9](#).

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

### **7.2.3. Vital Signs**

Supine blood pressure, supine heart rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in [Appendix 9](#). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and heart rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

### **7.2.4. 12-Lead Electrocardiogram**

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in [Appendix 9](#). Single 12-lead

ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

### **7.2.5. Physical Examination**

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in [Appendix 9](#).

### **7.3. Subject Questionnaire**

Subjects will be asked to provide feedback on the tablets after each dose. Site staff will administer a brief questionnaire to subjects after dosing has occurred in Periods 1 and 2 only ([Appendix 8](#)).

## **8. SAMPLE SIZE AND DATA ANALYSIS**

### **8.1. Determination of Sample Size**

The study will require at least 132 subjects completing the study to establish equivalence between the 2 groups with 90% power. This test is based on a 2-sided ratio of means test for a 2 x 2 crossover design for continuous data with significance level 5%. The ratio of means between treatment and control groups under the alternative hypothesis is 0.95. This test assumes lower and upper equivalence limits of 0.8 and 1.25, respectively, and root mean squared error of the log ratio equal to 0.472. Assuming approximately 10% drop out rate, approximately 146 subjects (73 subjects per treatment) will be enrolled in this study.

### **8.2. Analysis Populations**

#### **8.2.1. 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 adverse events of vomiting that occurs at or before 2 times median time to maximum concentration or diarrhea within 24 hours of dosing.

### 8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of sotorasib and have at least 1 postdose safety assessment.

### 8.3. Pharmacokinetic Analyses

The plasma PK parameters of sotorasib on Days 1 and 4 will be calculated using standard noncompartmental methods.

The primary PK parameters are  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\text{inf}}$  for sotorasib on Days 1 and 4. All other PK parameters will be regarded as secondary. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment, period, and sequence and a random effect for subject. Geometric mean ratios for  $C_{\max}$  and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be Treatment B while the “test 1” treatment will be Treatment A for the bioequivalence analysis. For the food-effect analysis, the model will use 14 subjects’ data and assumes fixed effects for treatment and random effect for subject while test treatment would be fed (test 2; Treatment C) and reference would be fasted (test 1; Treatment A).

Additional parameters may be calculated. Specific details will be presented in the Statistical Analysis Plan for this study.

### 8.4. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Endpoints for clinical laboratory tests, ECG, and vital signs will be summarized.

### 8.5. Interim Analysis

No interim analyses are planned for this study.

## 9. REFERENCES

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## **10. APPENDICES**



**Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events**

**Definition of Adverse Event**

Adverse Event Definition
<ul style="list-style-type: none"><li>• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.</li><li>• Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure.</li><li>• Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).</li></ul>
Events Meeting the Adverse Event Definition
<ul style="list-style-type: none"><li>• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).</li><li>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li><li>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.</li><li>• “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.</li></ul>

<b>Events NOT Meeting the Adverse Event Definition</b>
<ul style="list-style-type: none"><li>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li><li>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li><li>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.</li></ul>

### Definition of Serious Adverse Event

<b>A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:</b>
<b>Results in death (fatal)</b>
<b>Immediately life-threatening</b> <p>The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.</p>
<b>Requires in-patient hospitalization or prolongation of existing hospitalization</b> <p>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.</p>
<b>Results in persistent or significant disability/incapacity</b> <p>The term “disability” means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.</p>
<b>Is a congenital anomaly/birth defect</b>

**Other medically important serious event**

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**Recording Adverse Events and Serious Adverse Events**

**Adverse Event and Serious Adverse Event Recording**

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the Event electronic Case Report Form (eCRF).
- The Investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures;
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.

- If specifically requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

### Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The Investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on the Common Terminology Criteria for Adverse Events (CTCAE) grading scale. For the CTCAE grading scale version 5.0 or higher, refer to: <a href="https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm">https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm</a> .
Assessment of Causality
<ul style="list-style-type: none"><li>• The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event.</li><li>• Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.</li><li>• The Investigator will use clinical judgment to determine the relationship.</li><li>• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.</li><li>• The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.</li><li>• For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.</li><li>• There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.</li></ul>

<ul style="list-style-type: none"><li>• The Investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.</li><li>• The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.</li></ul>
<b>Follow-up of Adverse Event and Serious Adverse Event</b>
<ul style="list-style-type: none"><li>• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.</li><li>• If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.</li><li>• If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.</li><li>• New or updated information will be recorded in the originally completed eCRF.</li><li>• The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.</li></ul>

### Reporting of Serious Adverse Event

<b>Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form</b>
<ul style="list-style-type: none"><li>• Facsimile transmission of the Serious Adverse Event Report Form (see <a href="#">Figure 2</a>) is the preferred method to transmit this information.</li><li>• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.</li><li>• Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.</li><li>• Once the study has ended, serious event(s) should be reported to Sponsor (regardless of causality) if the Investigator becomes aware of a serious adverse event. The Investigator should use the paper-based Serious Adverse Event Report Form to report the event.</li></ul>

**Figure 2: Sample Serious Adverse Event Report Form**

<b>A</b> <b>20210093</b> Covance Study# 8471128 Sotorasib (AMG 510)	<b>Clinical Trial Serious Adverse Event Report – Phase 1–4</b> <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
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Amgen (Sponsor) Safety US: Email: [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com) or Fax +888-814-8653

<b>1. SITE INFORMATION</b>												
Site Number			Investigator				Country			Date of Report Day Month Year		
Reporter			Phone Number ( ) ( ) ( )				Fax Number ( ) ( ) ( )					
<b>2. SUBJECT INFORMATION</b>												
Subject ID Number			Age at event onset				Sex <input type="checkbox"/> F <input type="checkbox"/> M		Race		If applicable, provide End of Study date	
<b>3. SERIOUS ADVERSE EVENT - Information in this section must also be entered on the Serious Adverse Event Summary CRF</b>												
Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year												
Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event  List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.		Date Started  Day Month Year		Date Ended  Day Month Year		Check only if event occurred before first dose of IP Ever Serious Criteria code (see codes below)		Relationship Is there a reasonable possibility that the event may have been caused by IP or an Amgen device used to administer the IP?  If yes see section 10		Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown  Check only if event is related to study procedure eg, biopsy		
								Sotorasib No Yes No Yes No Yes No Yes No Yes				
Serious Criteria: 01 Fatal 02 Immediately life-threatening		03 Required hospitalization 04 Prolonged hospitalization		05 Persistent or significant disability / incapacity 06 Congenital anomaly / birth defect		07 Other medically important serious event						
<b>4. HOSPITALIZATION</b>												
Was subject hospitalized or was a hospitalization prolonged due to this event? <input type="checkbox"/> No <input type="checkbox"/> Yes, if yes, please complete date(s):						Date Admitted Day Month Year			Date Discharged Day Month Year			
<b>5. INVESTIGATIONAL PRODUCT (IP)</b>												
	Initial Start Date	Prior to, or at time of Event				Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #					
	Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency							
Sotorasib <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label							Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unknown					
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label							Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unknown					
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label							Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unknown					
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label							Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unknown					

<b>A</b> <b>20210093</b> Covance Study# 8471128 Sotorasib (AMG 510)	<b>Clinical Trial Serious Adverse Event Report – Phase 1–4</b> <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
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			Site Number			Subject ID Number														
<b>6. CONCOMITANT MEDICATIONS (eg, chemotherapy)</b>													Any Concomitant Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete:							
Medication Name(s)	Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med						
	Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				No✓	Yes✓					
<b>7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)</b>																				
<b>8. RELEVANT LABORATORY VALUES (include baseline values)</b>																	Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete:			
Date	Test																			
	Unit																			
	Day	Month	Year																	
<b>9. OTHER RELEVANT TESTS (diagnostics and procedures)</b>																	Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete:			
Date				Additional Tests						Results						Units				
Day	Month	Year																		

A <b>20210093</b> Covance Study# 8471128 Sotorasib (AMG 510)	<b>Clinical Trial Serious Adverse Event Report – Phase 1–4</b> <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
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	Site Number	Subject ID Number	
<b>10. CASE DESCRIPTION</b> (Provide narrative details of events listed in section 3) For each event in section 3, where relationship=Yes, please provide rationale.			
Signature of Investigator or Designee          <i>I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.</i>	Title	Date	



**Appendix 2: Clinical Laboratory Evaluations**

<b>Clinical chemistry:</b>	<b>Hematology:</b>	<b>Urinalysis:</b>
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Direct bilirubin <sup>a</sup> Gamma-glutamyl transferase Glucose Indirect bilirubin <sup>a</sup> Inorganic phosphate Potassium Sodium Total bilirubin <sup>a</sup> Total CO <sub>2</sub> (measured as bicarbonate) Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
<b>Serology<sup>b</sup>:</b>	<b>Drug screen<sup>c</sup>:</b>	<b>Hormone panel - females only:</b>
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Alcohol test Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Tricyclic antidepressants	Follicle-stimulating hormone <sup>b</sup> (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin) <sup>d</sup> Urine pregnancy test <sup>d</sup>
		<b>Other tests:</b>
		Thyroid-stimulating hormone <sup>e</sup> International normalized ratio (INR) <sup>f</sup> Estimated glomerular filtration rate (eGFR) <sup>c,g</sup>

<sup>a</sup> Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

<sup>b</sup> Only analyzed at Screening.

<sup>c</sup> Only analyzed at Screening and Check-in.

<sup>d</sup> Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

<sup>e</sup> Only analyzed at Screening, Check-in and at EOS.

<sup>f</sup> International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in [Appendix 7](#).

<sup>g</sup> Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease equation.

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**Appendix 3: Total Blood Volume**

The following blood volumes will be withdrawn for each subject.

	<b>Volume per blood sample (mL)</b>	<b>Maximum number of blood samples</b>	<b>Total amount of blood (mL)</b>
Clinical laboratory evaluations	12.5	5	62.5
Serology	7	1	7
Sotorasib pharmacokinetics	4	34-51	136-204
Total:			205.5-273.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

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## Appendix 4: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment and for 7 days after the end of study (EOS).

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

### Definitions:

**Women of Childbearing Potential:** premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

### Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone levels of  $\geq 40$  mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

**Fertile male:** a male that is considered fertile after puberty.

**Infertile male:** permanently sterile male via bilateral orchiectomy.

## Contraception Requirements

### Female Subjects:

Female subjects must be of nonchildbearing potential and will not be required to use contraception.

Female subjects should refrain from donation of ova from Check-in (Day -1) until 7 days after the EOS.

### Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 7 days after the EOS. Acceptable methods of contraception for female partners include:

- 
- hormonal injection
  - combined oral contraceptive pill or progestin/progestogen-only pill
  - combined hormonal patch
  - combined hormonal vaginal ring
  - surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
  - hormonal implant
  - hormonal or non-hormonal intrauterine device
  - over-the-counter sponge with spermicide
  - cervical cap with spermicide
  - diaphragm with spermicide.

Male subjects are required to refrain from donation of sperm from Check-in until 7 days after the EOS.

### **Sexual Abstinence**

Subjects who practice true abstinence, because of the subject's lifestyle choice (i.e., the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the Informed Consent Form (ICF) until 7 days after the EOS.

### **Same-sex Relationships**

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

A subject in a same-sex relationships at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 7 days after the EOS.

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## Appendix 5: Collection of Pregnancy and Lactation Information

### Collection of Pregnancy Information

#### Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 7 days after end of study (EOS).
- Information will be recorded on the Pregnancy Notification Form (see
- [Figure 3](#)). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 7 days after EOS. This information will be forwarded to Amgen Global Patient Safety. Generally, infant Follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in [Appendix 1](#). While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see [Section 4.7](#) for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 7 days after EOS, the information will be recorded on the Pregnancy Notification Form. The form (see
- [Figure 3](#)) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant Follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 7 days after EOS.
- Information will be recorded on the Lactation Notification Form ([Figure 4](#)) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.
- With the female subject's signed consent for release of mother and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 7 days after EOS.

**Figure 3: Pregnancy Notification Form**

Amgen Proprietary - Confidential

**AMGEN** Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

**1. Case Administrative Information**

Protocol/Study Number: Amgen protocol number 20210093 Covance study number 8471128

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

Investigator Name \_\_\_\_\_ Site # \_\_\_\_\_

Phone (\_\_\_\_) \_\_\_\_\_ Fax (\_\_\_\_) \_\_\_\_\_ Email \_\_\_\_\_

Institution \_\_\_\_\_

Address \_\_\_\_\_

**3. Subject Information**

Subject ID # \_\_\_\_\_ Subject Gender: ☐ Female ☐ Male Subject age (at onset): \_\_\_\_\_ (in years)

**4. Amgen Product Exposure**

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ____/dd ____/yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm \_\_\_\_/dd \_\_\_\_/yyyy \_\_\_\_

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's last menstrual period (LMP) mm \_\_\_\_/dd \_\_\_\_/yyyy \_\_\_\_ ☐ Unknown ☐ N/A

Estimated date of delivery mm \_\_\_\_/dd \_\_\_\_/yyyy \_\_\_\_

If N/A, date of termination (actual or planned) mm \_\_\_\_/dd \_\_\_\_/yyyy \_\_\_\_

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm \_\_\_\_/dd \_\_\_\_/yyyy \_\_\_\_

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Form Completed by:**

Print Name: \_\_\_\_\_

Title: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Figure 4: Lactation Notification Form**

Amgen Proprietary - Confidential

**AMGEN** Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): [svc-ags-in-us@amgen.com](mailto:svc-ags-in-us@amgen.com)

**1. Case Administrative Information**

Protocol/Study Number: Amgen protocol number 20210093 Covance study number 8471128

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

Investigator Name \_\_\_\_\_ Site # \_\_\_\_\_

Phone (\_\_\_\_) \_\_\_\_\_ Fax (\_\_\_\_) \_\_\_\_\_ Email \_\_\_\_\_

Institution \_\_\_\_\_

Address \_\_\_\_\_

**3. Subject Information**

Subject ID # \_\_\_\_\_ Subject age (at onset): \_\_\_\_\_ (in years)

**4. Amgen Product Exposure**

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm\_\_\_\_/dd\_\_\_\_/yyyy\_\_\_\_

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Breast Feeding Information**

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm\_\_\_\_/dd\_\_\_\_/yyyy\_\_\_\_

Infant date of birth: mm\_\_\_\_/dd\_\_\_\_/yyyy\_\_\_\_

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Form Completed by:**

Print Name: \_\_\_\_\_ Title: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

FORM-115201

Version 1.0

Effective Date: 24-Sept-2018



## **Appendix 6: Regulatory, Ethical, and Study Oversight Considerations**

### **Regulatory and Ethical Considerations**

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### **Finances and Insurance**

Financing and insurance will be addressed in a separate agreement.

### **Informed Consent**

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

The Investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific Screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, and the IRB or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date and the same version of the ICF is in use at the time of rescreening.

### **Subject Data Protection**

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the electronic Case Report Form (eCRF) demographics page, in addition to the unique subject identification number ([Section 4.4](#)), include the age at time of enrollment.

For serious adverse events reported to the Sponsor (or designee), subjects are to be identified by their unique subject identification number ([Section 4.4](#)) (for faxed reports, in accordance with local laws and regulations) and age (in accordance with local laws and regulations).

Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

## **Disclosure**

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subjects will be assigned a unique identifier by the Sponsor (or designee). Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the eCRF demographics page, in addition to the unique subject identification number ([Section 4.4](#)), include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number ([Section 4.4](#)), initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

## **Data Quality Assurance**

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## **Investigator Documentation Responsibilities**

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any Screening procedures, according to the eCRF completion instructions. The Sponsor, or Contract Research Organization, will review the supporting source documentation against the data entered into the eCRFs to

verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

### **Publications**

The policy for publication of data obtained during this study will be documented in the Clinical Study Agreement.

## **Appendix 7: Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments**

Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

### **Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity**

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right-sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomyolysis, hemolysis).

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

**Table 3: Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity**

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	>3x ULN at any time	>2x ULN
INR	--	>1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	>8x ULN at any time	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values
	>5x ULN but <8x ULN for $\geq 2$ weeks	
	>5x ULN but <8x ULN and unable to adhere to enhanced monitoring schedule	
	>3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	>3x ULN (when baseline was < ULN)
	OR	
ALP	>8x ULN at any time	--

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

### Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then OM is to be permanently discontinued.

Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 3) are never to be rechallenged.

## **Drug-induced Liver Injury Reporting and Additional Assessments**

### **Reporting**

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded).
- The appropriate electronic Case Report Form (eCRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 1.

### **Additional Clinical Assessments and Observation**

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 3 or who experience AST or ALT elevations  $>3 \times$  upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL  $>2 \times$  ULN or INR  $> 1.5$ , retesting of liver tests, BIL (total and direct) and INR is to be performed every 24 hours until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:



- Prior and/or concurrent disease or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
  - Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
  - Appropriate blood sampling for pharmacokinetic analysis, if this has not already been collected
  - Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the Investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding eCRFs.

## Appendix 8: Sample Subject Questionnaire

### Medicine Acceptability Questionnaire (administered after each dose by Study Staff)

Please circle the regimen you just took:      8 X 120mg tablets      3 X 320mg tablets

#### 1. How convenient is this medicine?

For each of the following statements, please tick the **ONE** box that best describes your opinion.

This medicine...	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
...is a convenient amount for me to take. (E.g. number of tablets or volume of liquid.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...is easy to fit into my lifestyle.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...is easy to take. (E.g. consider need for taking on an empty stomach or standing upright.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...is suitable to take when not at home. (E.g. consider need for water, or ease of carrying.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tell us overall how happy you are with the convenience of this medicine. Please **CROSS** the number that best describes how you feel (X).

Very unhappy      Neither      Very happy

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

#### 2. How does this medicine taste?

For each of the following statements, please tick the **ONE** box that best describes your opinion.

This medicine...	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
...tastes good.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...has no aftertaste.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tell us overall how happy you are with the **taste and texture** of this medicine. Please **CROSS** the number that best describes how you feel (X).



3. How does this medicine look and how easy is the administration?

For each of the following statements, please tick the **ONE** box that best describes your opinion.

This medicine...	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
...is the size easy to swallow.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...is the number of tablets easy to swallow.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...is easy to see.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
...has a nice color.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tell us overall how happy you are with the **size and number of tablets** of this medicine. Please **CROSS** the number that best describes how you feel (X).



4. Overall acceptability based on convenience, taste and administration?

Please tell us overall how happy you are with the **acceptability** of this medicine. Please **CROSS** the number that best describes how you feel (X).



## **Appendix 9: Schedule of Assessment**

## Schedule of Assessments

Study Procedures	Screening	Check-in	Period 1			Period 2			Period 3		
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 6 or Day 9 (EOS/ET)
Confined to the CRU		X	X	X	X	X	X	X	X	X	X
Outpatient Visit	X										
Inclusion/Exclusion Criteria	X	X									
Informed Consent	X										
Demographics	X										
Serology	X										
Medical History	X	X <sup>a</sup>									
Height and BMI	X										
Weight	X	X									X <sup>l</sup>
Drug Screen	X	X									
Alcohol Test	X	X									
Pregnancy Test (females only) <sup>b</sup>	X	X									X <sup>l</sup>
FSH (postmenopausal females only)	X										
12-lead Electrocardiogram <sup>c</sup>	X	X	X			X			X		X <sup>l</sup>
Vital Signs <sup>d</sup>	X	X	X	X		X	X		X	X	X <sup>l</sup>
Clinical Laboratory Evaluations <sup>e</sup>	X	X			X			X			X <sup>l</sup>
eGFR <sup>f</sup>	X	X									
Physical Examination <sup>g</sup>		X									X <sup>l</sup>
Sotorasib Dose <sup>h</sup>			X			X			X		
Subject Questionnaire			X			X					
Sotorasib PK Blood Samples <sup>i</sup>			X	X	X	X	X	X	X	X	X
Adverse Event Monitoring <sup>j</sup>			X								
Serious Adverse Event Monitoring <sup>j</sup>	X	X									
Prior/Concomitant Medications <sup>k</sup>	X	X									

Abbreviations: BMI = body mass index; CRU = Clinical Research Unit; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination;

FSH = follicle-stimulating hormone; PK = pharmacokinetic.

<sup>a</sup> Interim medical history only.

<sup>b</sup> Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

- <sup>c</sup> Electrocardiograms will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; prior to and 0.5, 2, and 4 hours following sotorasib administration on Days 1, 4 and 7; and EOS or ET. The 30-minute postdose ECG measurement will have a collection window of  $\pm 2$  minutes, the 2-hour postdose ECG measurement will have a collection window of  $\pm 5$  minutes, and the 4-hour postdose ECG measurement will have a collection window of  $\pm 10$  minutes.
- <sup>d</sup> Vital signs measurements (supine blood pressure [BP], supine heart rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Screening; Check-in; prior to sotorasib administration on Days 1, 4 and 7; 1 and 24 hours following sotorasib administration on Days 1, 4 and 7; and EOS/ET. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.
- <sup>e</sup> Clinical chemistry (fasted at least 8 hours), hematology, and urinalysis.
- <sup>f</sup> eGFR will be calculated using the Modification of Diet in Renal Disease equation.
- <sup>g</sup> A full physical examination at Check-in and a symptom-directed physical examination at EOS/ET.
- <sup>h</sup> Dose administration of sotorasib is to occur during the mornings of Days 1, 4 and 7 in accordance with the formulation of sotorasib administration specific to their treatment (Treatment A, Treatment B or Treatment C).
- <sup>i</sup> Blood samples for determination of sotorasib plasma concentrations will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on Days 1, 4 and 7. The PK sample collected at 30 minutes postdose will have a sampling window of  $\pm 2$  minutes, samples collected from 1 through 3 hours postdose will have a sampling window of  $\pm 5$  minutes, samples collected from 4 through 10 hours postdose will have a sampling window of  $\pm 10$  minutes, and samples collected from 12 through 48 hours postdose will have a sampling window of  $\pm 20$  minutes. Times of all PK samples will be recorded to the nearest minute.
- <sup>j</sup> Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the ICF through 30 days after the last dose of study treatment or the EOS (whichever is later).
- <sup>k</sup> Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment administration for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (eg, St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic Case Report Form.
- <sup>l</sup> Assessment to be performed at the EOS or if a subject is withdrawn early from the study.

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## Summary of Amended Protocol Changes

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### **An Open-label, Randomized, Two-way Crossover, Bioequivalence Study in Healthy Volunteers to Compare the Pharmacokinetics of Two Different Tablets of Sotorasib**

Protocol Amendment 2 Status: Draft  
Protocol Amendment 2 Date: 10 September 2021  
Protocol Amendment 1 Date: 02 September 2021  
Original Protocol Date: 04 June 2021

Protocol Version 3.0

Amgen Investigational Product: Sotorasib (AMG 510)

Amgen Protocol Reference Number: 20210093  
Labcorp Drug Development Study Number: 8471128  
IND Number: 139023

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

Sponsor Signatory:  
[REDACTED], PhD

Information described herein is confidential and may be disclosed only with the express written permission of the Sponsor.

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**The primary changes in this amendment, along with the rationale for the/each change as appropriate, are:**

1. Based on recommendations from the regulatory agency, the protocol was modified to add additional criteria for subject withdrawal from the study and criteria for pausing dosing.
2. Based on recommendations from the regulatory agency, the protocol was modified to add additional follow-up laboratory evaluations for subjects who develop clinically meaningful abnormalities outside the reference range during the study period.

**Minor changes:**

1. The synopsis was updated according to the changes in the protocol body, as applicable.
2. The amendment/version number and date were updated throughout the protocol.
3. Typographical errors and formatting errors were corrected, as necessary.
4. Abbreviations were added and/or removed, as appropriate.

**A detailed summary of changes is presented below:**

***Section 4.5 Subject Withdrawal and Replacement***

**Previously read:**

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible ([Appendix 9](#)). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their adverse events and serious adverse events, or until the unresolved adverse events and serious adverse events are judged by the Investigator (or designee) to have stabilized.



Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events/serious adverse events thought to be related to the study drug will generally not be replaced.

**Now reads:**

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) v5 Grade  $\geq 3$  AE
- occurrence of Grade 2 AE considered by the Investigator (or designee) to be at least possibly related to sotorasib and, in the opinion of the Investigator (or designee), warrants subject withdrawal (e.g., neuropathy, chronic diarrhea, etc.)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If two or more subjects are withdrawn from the study due to AEs that are considered by the Investigator to be at least possibly related to sotorasib or if there is one Grade 3 event, dosing would be paused, and the Investigator and Sponsor will convene to review the data and determine the next step.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible ([Appendix 9](#)). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their adverse events and serious adverse events, or until the unresolved adverse events and serious adverse events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of adverse events/serious adverse events thought to be related to the study drug will generally not be replaced.

***Section 7.2.2. Clinical Laboratory Evaluations, Paragraph 2***

**Previously read:**

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

**Now reads:**

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in CRF/eCRF. The Investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. Subjects who develop any lab abnormalities outside the reference range that are deemed clinically meaningful during the study period will have follow-up labs once a week, or more frequently if deemed necessary, until the abnormalities have resolved or returned to within the reference range or to the subject's baseline values.

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## Summary of Amended Protocol Changes

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### **An Open-label, Randomized, Two-way Crossover, Bioequivalence Study in Healthy Volunteers to Compare the Pharmacokinetics of Two Different Tablets of Sotorasib**

Protocol Amendment 1 Status: Final  
Protocol Amendment 1 Date: 02 September 2021  
Original Protocol Date: 04 June 2021

Protocol Version 2.0

Amgen Investigational Product: Sotorasib (AMG 510)

Amgen Protocol Reference Number: 20210093  
Labcorp Drug Development Study Number: 8471128  
IND Number: 139023

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

Sponsor Signatory:  
[REDACTED], PhD

Information described herein is confidential and may be disclosed only with the express written permission of the Sponsor.

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**The primary changes in this amendment are:**

1. Based on recommendations from the regulatory agency, the protocol was modified to add a food-effect arm to the study design:
  - Updated applicable sections of the protocol including the objectives, endpoints, study design, investigational product information, randomization, and statistical methods.
  - Updated the study design schema.
  - Added details on the standard high-fat meal for the food-effect arm.
  - Updated the details for the subject questionnaire to clarify that the questionnaire will be administered to subjects in Periods 1 and 2 only.
  - Updated the estimates for the total blood volume collected from each subject.
  - Updated the schedule of assessments.
2. Updated the protocol to clarify that for Exclusion Criterion #4 an average of the triplicate measurement of the PR interval will be used to evaluate subject's eligibility at Screening and at Check-in (previously described in Letter of Administrative Change No. 1).

**Minor changes:**

1. To update the company name from "Covance" to "Labcorp" as Covance is re-branding into the parent company Labcorp (applicable only for business units transitioned on or after 25 Jun 2021).
2. The synopsis was updated according to the changes in the protocol body, as applicable.
3. The version number and date were updated throughout the protocol.
4. Typographical errors and formatting errors were corrected, as necessary.

**A detailed summary of changes is presented below:**

***Title page, Study Identification page, and all headers***

**Previously read:**

Covance

**Now reads:**

Labcorp Drug Development

***Section 1.3 Study Rationale***

**Previously read:**

The purpose of this study is to compare the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets (test) to 960 mg sotorasib administered as 8 x 120 mg oral tablets (reference) in healthy male subjects and healthy female subjects of nonchildbearing potential. Oral dosing is the intended route of administration for sotorasib. The 320 mg tablet formulation of sotorasib would help reduce pill burden for patients requiring sotorasib treatment.

**Now reads:**

The purpose of this study is to compare the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets (test) under fasted condition to 960 mg sotorasib administered as 8 x 120 mg oral tablets (reference) under fasted condition and to compare the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets following a high-fat meal (test 2) to 960 mg sotorasib administered as 3 x 320 mg oral tablets under fasted condition (test 1) in healthy male subjects and healthy female subjects of nonchildbearing potential. Oral dosing is the intended route of administration for sotorasib. The 320 mg tablet formulation of sotorasib would help reduce pill burden for patients requiring sotorasib treatment.

***Section 1.4.1.2 Risks, paragraph 1***

**Previously read:**

To limit the risk of excessive exposure to healthy subjects in the current study, each subject will receive a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1, treatment A) and a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference, treatment B) in either Period 1 or Period 2 according to their assigned group, with sufficient washout in between periods (details provided in Section 3.3).

**Now reads:**

To limit the risk of excessive exposure to healthy subjects in the current study, each subject will receive a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test) and a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference) in either Period 1 or Period 2 according to their assigned group, with sufficient washout in between periods (details provided in Section 3.3). Fourteen healthy subjects in either Groups 1 or 2 will

receive a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 2, treatment C) following a high-fat meal (detailed provided in Section 5.2.1) in Period 3 with sufficient washout in between periods.

### ***Section 2.1 Objectives***

#### **Previously read:**

The primary objective of the study is:

- to compare the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets (test) to 960 mg sotorasib administered orally as 8 x 120 mg tablets (reference).

The secondary objective of the study is:

- to assess the safety and tolerability of 960 mg sotorasib administered orally as 3 x 320 mg tablets and 960 mg sotorasib administered orally as 8 x 120 mg tablets.

#### **Now reads:**

The primary objective of the study is:

- to compare the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets (test 1) under fasted condition to 960 mg sotorasib administered orally as 8 x 120 mg tablets (reference) under fasted condition.

The secondary objectives of the study are:

- in 14 subjects, to evaluate the PK of 960 mg sotorasib administered orally as 3 x 320 mg tablets with a high-fat meal (test 2).
- to assess the safety and tolerability of 960 mg sotorasib administered orally as 3 x 320 mg tablets and 960 mg sotorasib administered orally as 8 x 120 mg tablets.

### ***Section 2.2.1 Primary Endpoints***

#### **Previously read:**

The primary endpoints of the study are:

- $C_{max}$
- AUC from time zero to the last quantifiable concentration ( $AUC_{last}$ )
- $AUC_{inf}$ .

#### **Now reads:**

The primary endpoints of the study are sotorasib PK parameters in Period 1 and Period 2:

- $C_{\max}$
- AUC from time zero to the last quantifiable concentration ( $AUC_{\text{last}}$ )
- $AUC_{\text{inf}}$ .

### ***Section 2.2.2 Secondary Endpoints***

#### **Previously read:**

The secondary endpoints of the study are:

- adverse events
- clinical laboratory tests
- 12-lead ECGs
- vital signs

#### **Now reads:**

The secondary endpoints of the study are:

- adverse events
- clinical laboratory tests
- 12-lead ECGs
- vital signs
- sotorasib PK parameters in Period 3:  $C_{\max}$ ,  $AUC_{\text{last}}$ ,  $AUC_{\text{inf}}$ .

### ***Section 3.1 Overall Study Design and Plan***

#### **Previously read:**

This will be an openlabel, multi-center (United States), randomized two-way crossover, bioequivalence study to compare the PK of a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1) to a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference) in healthy male subjects and healthy female subjects. Approximately 146 subjects will be enrolled to ensure that at least 132 subjects complete the study.

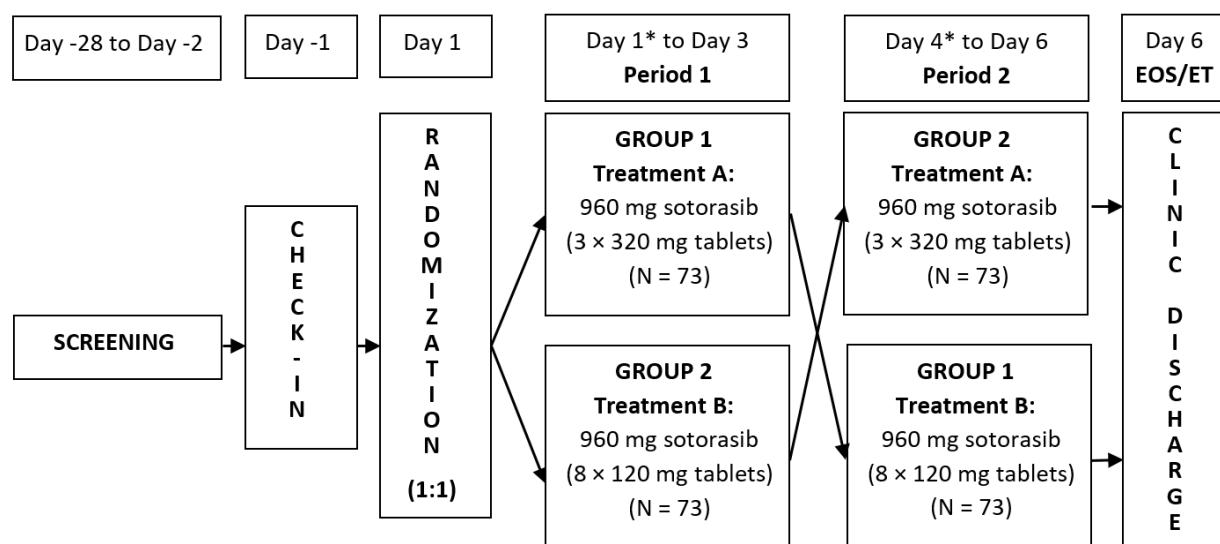
Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day 1 and be confined to the CRU until discharge on Day 6. On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive one administration of 960 mg sotorasib administered orally as 3 x 320 mg tablets (Treatment A: test 1-) and one administration of 960 mg sotorasib administered orally as 8 x 120 mg tablets (Treatment B: reference) in either Period 1 or Period 2 according to their assigned group. Each subject will receive both treatments following an overnight fast according to the treatment sequence in Table 1.

**Table 1: Treatment Sequence**

Group	Period 1 (Day 1)	Period 2 (Day 4)
1	Treatment A	Treatment B
2	Treatment B	Treatment A

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

**Figure 1: Study Schematic**



Abbreviations: EOS = End of Study; ET = Early Termination; N = number of subjects

\*Subjects will receive a single dose in each treatment period, on Day 1 and 4.

The total duration of study participation for each subject (from Screening through end of study [EOS]) is anticipated to be approximately 5 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 Schedule of Assessments is presented in Appendix 9.

### Now reads:

This will be an open-label, multi-center (United States), crossover, 3-period bioequivalence study to compare the PK of a single oral dose of 960 mg sotorasib administered as 3 x 320 mg tablets (test 1) under fasted condition to a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets (reference) under fasted condition and the PK of 960 mg sotorasib administered as 3 x 320 mg oral tablets following a high-fat meal (test 2) to 960 mg sotorasib administered as 3 x 320 mg oral tablets under fasted condition (test 1) in healthy male subjects and healthy female subjects. Approximately 146 subjects will be enrolled to ensure that at least 132 subjects complete the study.



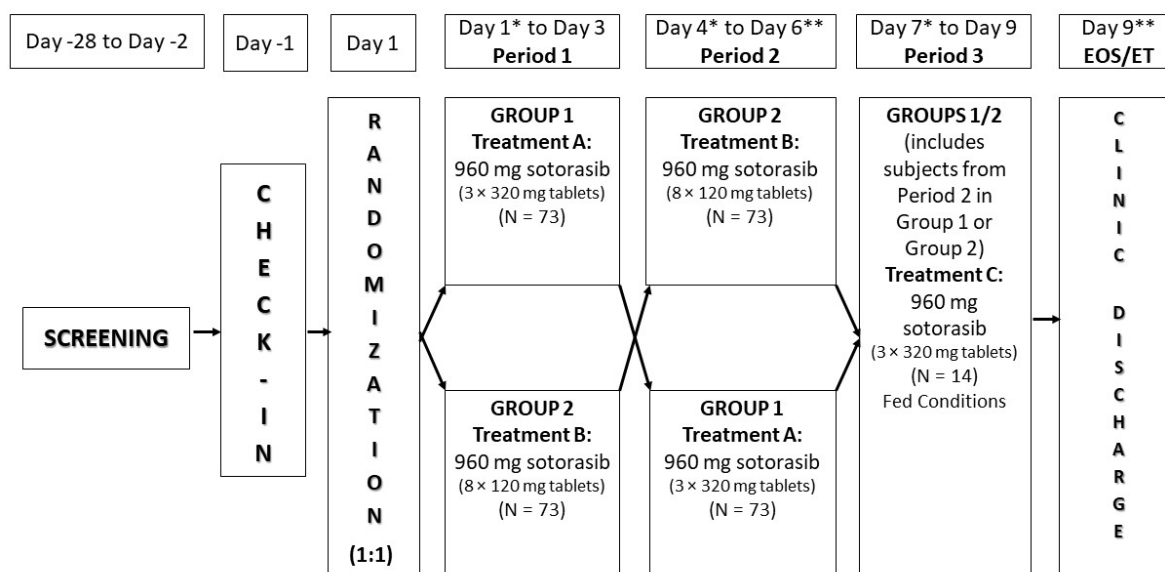
Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day 1 and be confined to the CRU until discharge on Day 6. On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive one administration of 960 mg sotorasib administered orally as 3 x 320 mg tablets (Treatment A: test 1) and one administration of 960 mg sotorasib administered orally as 8 x 120 mg tablets (Treatment B: reference) in either Period 1 or Period 2 according to their assigned group. Each subject will receive both treatments following an overnight fast according to the treatment sequence in Table 1. On Day 7, 14 subjects in either Group 1 or Group 2 will proceed to Period 3 and receive one additional administration of 960 mg sotorasib administered orally as 3 x 320 mg tablets with a high-fat meal (Treatment C: test 2).

**Table 1: Treatment Sequence**

Group	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
1	Treatment A	Treatment B	Treatment C
2	Treatment B	Treatment A	

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

**Figure 1: Study Schematic**



Abbreviations: EOS = End of Study; ET = Early Termination; N = number of subjects

\*Subjects will receive a single dose in each treatment period, on Days 1, 4, and 7.

\*\* Subjects will be discharged on Day 6 or Day 9 according to their treatment assignment.

The total duration of study participation for each subject (from Screening through end of study [EOS]) is anticipated to be approximately 5 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 Schedule of Assessments is presented in Appendix 9.

### ***Section 3.2 Discussion of Study Design, paragraph 1***

#### **Previously read:**

This is a 2-treatment, 2-period crossover study in healthy subjects where all subjects receive both treatments. The randomized, crossover design used in this study is typical to evaluate the relative bioavailability of the different treatments. The number of subjects is adequate since the design selected for this study allows intra-subject comparisons and thereby reduces variability. This study will be open-label because the primary endpoints of the study are considered objective.

#### **Now reads:**

This is a 3-period crossover study in healthy subjects where all subjects receive at least two treatments. The randomized, crossover design in Period 1 and Period 2 used in this study is typical to evaluate the relative bioavailability of the different treatments. The number of subjects is adequate since the design selected for this study allows intra-subject comparisons and thereby reduces variability. This study will be open-label because the primary endpoints of the study are considered objective.

### ***Section 4.2 Exclusion Criteria #4***

#### **Previously read:**

PR interval >200 msec, 2nd degree atrioventricular (AV) block or 3rd degree AV block, at Screening or Check-in.

#### **Now reads:**

PR interval >200 msec, 2nd degree atrioventricular (AV) block or 3rd degree AV block, at Screening or Check-in. An average of the triplicate measurement of the PR interval will be used to evaluate subject's eligibility at Screening and at Check-in.

**Section 5.2 Investigational Product Administration, Table 2**

**Previously read:**

<b>Study Treatment Name</b>	<b>(Treatment A) Investigational Medicinal Product: Sotorasib</b>	<b>(Treatment B) Investigational Medicinal Product: Sotorasib</b>
<b>Unit Strength and Formulation</b>	320 mg tablet	120 mg tablet
<b>Dosage Level</b>	960 mg (3 x 320 mg tablets)	960 mg (8 x 120 mg tablets)
<b>Route of Administration</b>	Oral	Oral
<b>Accountability</b>	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.
<b>Dosing Instructions</b>	The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Three tablets should be taken (the first tablet by itself immediately followed by two tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.  No food will be given for at least 4 hours post administration.	The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Eight tablets should be taken (the first tablet by itself immediately followed by seven tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.  No food will be given for at least 4 hours post administration.

**Now reads:**

<b>Study Treatment Name</b>	<b>(Treatment A, C) Investigational Medicinal Product: Sotorasib</b>	<b>(Treatment B) Investigational Medicinal Product: Sotorasib</b>
<b>Unit Strength and Formulation</b>	320 mg tablet	120 mg tablet
<b>Dosage Level</b>	960 mg (3 x 320 mg tablets)	960 mg (8 x 120 mg tablets)
<b>Route of Administration</b>	Oral	Oral
<b>Accountability</b>	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.
<b>Dosing Instructions</b>	<p>Treatment A: The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Three tablets should be taken (the first tablet by itself immediately followed by two tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p> <p>Treatment C: The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Subjects will consume the entirety of a standard high-fat breakfast within 20 minutes. A 960-mg dose of sotorasib will be given orally 30 minutes after start of the meal. Three tablets should be taken (the first tablet by itself immediately followed by two tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p>	<p>The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Eight tablets should be taken (the first tablet by itself immediately followed by seven tablets) with 8 ounces (240 mL) of water. Additional water may be used during dosing, as required. Tablets should not be broken or chewed.</p> <p>No food will be given for at least 4 hours post administration.</p>

### ***Section 5.2.1 Standard High-fat Meal***

**Previously read:**

Not applicable.

**Now reads:**

The standardized high-fat meal breakfast should consist of approximately 800 to 1000 calories (including approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories). A typical meal is equivalent to 2 eggs fried in butter, 2 strips of bacon, 2 slices of buttered toast or bread, 4 ounces of hash brown potatoes (fried with butter), and 8 ounces (240 mL) of whole milk.<sup>13</sup> Substitutions can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has similar meal volume and consistency. Substitutions will apply to all subjects and all subjects will receive an identical meal.

### ***Section 5.6 Randomization***

**Previously read:**

This is a randomized, two-way crossover study. Subjects will be randomized 1:1 into 1 of 2 treatment groups based on the study randomization scheme that will be provided by a biostatistician.

**Now reads:**

In Period 1 and Period 2, subjects will be randomized 1:1 into 1 of 2 treatment groups based on the study randomization scheme that will be provided by a biostatistician. Subjects in Period 3 will not be randomized.

### ***Section 7.3 Subject Questionnaire***

**Previously read:**

Subjects will be asked to provide feedback on the tablets after each dose. Site staff will administer a brief questionnaire to subjects after dosing has occurred (Appendix 8).

**Now reads:**

Subjects will be asked to provide feedback on the tablets after each dose. Site staff will administer a brief questionnaire to subjects after dosing has occurred in Periods 1 and 2 only (Appendix 8).

### ***Section 8.3 Pharmacokinetic Analyses, paragraph 2***

#### **Previously read:**

The primary PK parameters are  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\text{inf}}$  for sotorasib on Days 1 and 4. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment, period, and sequence and a random effect for subject. Geometric mean ratios for  $C_{\max}$  and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be Treatment B while the “test” treatment will be Treatment A.

#### **Now reads:**

The primary PK parameters are  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\text{inf}}$  for sotorasib on Days 1 and 4. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment, period, and sequence and a random effect for subject. Geometric mean ratios for  $C_{\max}$  and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be Treatment B while the “test 1” treatment will be Treatment A for the bioequivalence analysis. For the food-effect analysis, the model will use 14 subjects’ data and assumes fixed effects for treatment and random effect for subject while test treatment would be fed (test 2; treatment C) and reference would be fasted (test 1; Treatment A).

### ***Section 9 References, Added Reference #13***

#### **Previously read:**

Not applicable.

#### **Now reads:**

- 13 Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. Rockville (MD): Department of Health and Human Services (US), Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Dec 2002.

### ***Appendix 3 Total Blood Volume***

#### **Previously read:**

The following blood volumes will be withdrawn for each subject.

	<b>Volume per blood sample (mL)</b>	<b>Maximum number of blood samples</b>	<b>Total amount of blood (mL)</b>
Clinical laboratory evaluations	12.5	4	50
Serology	7	1	7
Sotorasib pharmacokinetics	4	34	136
Total:			193

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

**Now reads:**

The following blood volumes will be withdrawn for each subject.

	<b>Volume per blood sample (mL)</b>	<b>Maximum number of blood samples</b>	<b>Total amount of blood (mL)</b>
Clinical laboratory evaluations	12.5	5	62.5
Serology	7	1	7
Sotorasib pharmacokinetics	4	34-51	136-204
Total:			205.5-273.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

## Appendix 9 Schedule of Assessments

Previously read:

### Schedule of Assessments

Study Procedures	Screening	Check-in	Period 1			Period 2		
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 (EOS/ET)
Confined to the CRU		X	X	X	X	X	X	X
Outpatient Visit	X							
Inclusion/Exclusion Criteria	X	X						
Informed Consent	X							
Demographics	X							
Serology	X							
Medical History	X	X <sup>a</sup>						
Height and BMI	X							
Weight	X	X						X <sup>l</sup>
Drug Screen	X	X						
Alcohol Test	X	X						
Pregnancy Test (females only) <sup>b</sup>	X	X						X <sup>l</sup>
FSH (postmenopausal females only)	X							
12-lead Electrocardiogram <sup>c</sup>	X	X	X			X		X <sup>l</sup>
Vital Signs <sup>d</sup>	X	X	X	X		X	X	X <sup>l</sup>
Clinical Laboratory Evaluations <sup>e</sup>	X	X			X			X <sup>l</sup>
eGFR <sup>f</sup>	X	X						
Physical Examination <sup>g</sup>		X						X <sup>l</sup>
Sotorasib Dose <sup>h</sup>			X			X		
Subject Questionnaire			X			X		
Sotorasib PK Blood Samples <sup>i</sup>			X	X	X	X	X	X
Adverse Event Monitoring <sup>j</sup>			X					
Serious Adverse Event Monitoring <sup>j</sup>	X		X					
Prior/Concomitant Medications <sup>k</sup>	X		X					

Abbreviations: BMI = body mass index; CRU = Clinical Research Unit; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination;

FSH = follicle-stimulating hormone; PK = pharmacokinetic.

<sup>a</sup> Interim medical history only.



- <sup>b</sup> Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
- <sup>c</sup> Electrocardiograms will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; prior to and 0.5, 2, and 4 hours following sotorasib administration on Days 1 and 4; and EOS or ET. The 30-minute postdose ECG measurement will have a collection window of  $\pm 2$  minutes, the 2-hour postdose ECG measurement will have a collection window of  $\pm 5$  minutes, and the 4-hour postdose ECG measurement will have a collection window of  $\pm 10$  minutes.
- <sup>d</sup> Vital signs measurements (supine blood pressure [BP], supine heart rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Screening; Check-in; prior to sotorasib administration on Days 1 and 4; 1 and 24 hours following sotorasib administration on Days 1 and 4; and EOS/ET. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.
- <sup>e</sup> Clinical chemistry (fasted at least 8 hours), hematology, and urinalysis.
- <sup>f</sup> eGFR will be calculated using the Modification of Diet in Renal Disease equation.
- <sup>g</sup> A full physical examination at Check-in and a symptom-directed physical examination at EOS/ET.
- <sup>h</sup> Dose administration of sotorasib is to occur during the mornings of Days 1 and 4 in accordance with the formulation of sotorasib administration specific to their treatment (Treatment A or Treatment B).
- <sup>i</sup> Blood samples for determination of sotorasib plasma concentrations will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on Days 1 and 4. The PK sample collected at 30 minutes postdose will have a sampling window of  $\pm 2$  minutes, samples collected from 1 through 3 hours postdose will have a sampling window of  $\pm 5$  minutes, samples collected from 4 through 10 hours postdose will have a sampling window of  $\pm 10$  minutes, and samples collected from 12 through 48 hours postdose will have a sampling window of  $\pm 20$  minutes. Times of all PK samples will be recorded to the nearest minute.
- <sup>j</sup> Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the ICF through 30 days after the last dose of study treatment or the EOS (whichever is later).
- <sup>k</sup> Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment administration for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (eg, St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic Case Report Form.
- <sup>l</sup> Assessment to be performed at the EOS or if a subject is withdrawn early from the study.

Now reads:

### Schedule of Assessments

Study Procedures	Screening	Check-in	Period 1			Period 2			Period 3		
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 6 or Day 9 (EOS/ET)
Confined to the CRU		X	X	X	X	X	X	X	X	X	X
Outpatient Visit	X										
Inclusion/Exclusion Criteria	X	X									
Informed Consent	X										
Demographics	X										
Serology	X										
Medical History	X	X <sup>a</sup>									
Height and BMI	X										
Weight	X	X									X <sup>l</sup>
Drug Screen	X	X									
Alcohol Test	X	X									
Pregnancy Test (females only) <sup>b</sup>	X	X									X <sup>l</sup>
FSH (postmenopausal females only)	X										
12-lead Electrocardiogram <sup>c</sup>	X	X	X			X			X		X <sup>l</sup>
Vital Signs <sup>d</sup>	X	X	X	X		X	X		X	X	X <sup>l</sup>
Clinical Laboratory Evaluations <sup>e</sup>	X	X			X			X			X <sup>l</sup>
eGFR <sup>f</sup>	X	X									
Physical Examination <sup>g</sup>		X									X <sup>l</sup>
Sotorasib Dose <sup>h</sup>			X			X			X		
Subject Questionnaire			X			X					
Sotorasib PK Blood Samples <sup>i</sup>			X	X	X	X	X	X	X	X	X
Adverse Event Monitoring <sup>j</sup>			X								
Serious Adverse Event Monitoring <sup>j</sup>	X	X									
Prior/Concomitant Medications <sup>k</sup>	X	X									

Abbreviations: BMI = body mass index; CRU = Clinical Research Unit; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination;

FSH = follicle-stimulating hormone; PK = pharmacokinetic.

<sup>a</sup> Interim medical history only.

<sup>b</sup> Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

<sup>c</sup> Electrocardiograms will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; prior to and 0.5, 2, and 4 hours following sotorasib administration on Days 1, 4 and 7; and EOS or ET. The 30-minute postdose ECG measurement will have a collection window of  $\pm 2$  minutes, the 2-hour postdose ECG measurement will have a collection window of  $\pm 5$  minutes, and the 4-hour postdose ECG measurement will have a collection window of  $\pm 10$  minutes.

<sup>d</sup> Vital signs measurements (supine blood pressure [BP], supine heart rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Screening; Check-in; prior to sotorasib administration on Days 1, 4 and 7; 1 and 24 hours following sotorasib administration on Days 1, 4 and 7; and EOS/ET. Heart rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

<sup>e</sup> Clinical chemistry (fasted at least 8 hours), hematology, and urinalysis.

<sup>f</sup> eGFR will be calculated using the Modification of Diet in Renal Disease equation.

<sup>g</sup> A full physical examination at Check-in and a symptom-directed physical examination at EOS/ET.

<sup>h</sup> Dose administration of sotorasib is to occur during the mornings of Days 1, 4 and 7 in accordance with the formulation of sotorasib administration specific to their treatment (Treatment A, Treatment B or Treatment C).

<sup>i</sup> Blood samples for determination of sotorasib plasma concentrations will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on Days 1, 4 and 7. The PK sample collected at 30 minutes postdose will have a sampling window of  $\pm 2$  minutes, samples collected from 1 through 3 hours postdose will have a sampling window of  $\pm 5$  minutes, samples collected from 4 through 10 hours postdose will have a sampling window of  $\pm 10$  minutes, and samples collected from 12 through 48 hours postdose will have a sampling window of  $\pm 20$  minutes. Times of all PK samples will be recorded to the nearest minute.

<sup>j</sup> Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the ICF through 30 days after the last dose of study treatment or the EOS (whichever is later).

<sup>k</sup> Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment administration for over-the-counter or prescription medications, and 30 days prior to enrollment for herbal medicines (eg, St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic Case Report Form.

<sup>l</sup> Assessment to be performed at the EOS or if a subject is withdrawn early from the study.