

Protocol

An Open-label, Randomized, Crossover Study in Healthy Volunteers to Compare the Pharmacokinetics of Sotorasib Administered as a 240 mg Tablet or 120 mg Tablets

Protocol Status: Final
Protocol Date: 18 February 2022
Protocol Version: 1.0

Investigational Product: Sotorasib (AMG 510)

Amgen Protocol Reference Number: 20210088
Labcorp Drug Development Study Number: 8471134
IND Number: 139023

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

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).

NCT Number: NCT05327491
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staffs and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent.

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 consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; Amgen's general number in the US, 1-805-447-1000.

INVESTIGATOR AGREEMENT

I have read the protocol entitled “An Open-Label, Randomized, Crossover Study in Healthy Volunteers to Compare the Pharmacokinetics of Sotorasib Administered as a 240 mg Tablet or 120 mg Tablets” 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.

Signature

Name of Investigator

Date (DD Month YYYY)

Title and Role of Investigator

Institution Name

Address and Telephone Number of Institution

STUDY IDENTIFICATION

Sponsor	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320
Sponsor's Study Contact	[REDACTED], PhD Director, Clinical Pharmacology Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 Tel: [REDACTED] Email: [REDACTED]
Medical Monitor	[REDACTED], MD, PhD Medical Director Labcorp Drug Development, Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704 Tel (Office): +1 (608) 443-1599 Tel (after hours): [REDACTED] Email: [REDACTED]
Sponsor's Study Manager	[REDACTED] Global Early Clinical Development Manager Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 Tel: [REDACTED] Email: [REDACTED]
Labcorp PM	[REDACTED], MS, CPM Labcorp Drug Development, Inc. 3402 Kinsman Boulevard Madison, Wisconsin 53704 Tel: [REDACTED] Email: [REDACTED]
Statistician	[REDACTED], MS Senior Biostatistician Labcorp Drug Development, Inc. 3301 Kinsman Boulevard Madison, Wisconsin 53704 Tel: [REDACTED] Email: [REDACTED]

SYNOPSIS

<p>Title of study: An Open-label, Randomized, Crossover Study in Healthy Volunteers to Compare the Pharmacokinetics of Sotorasib Administered as a 240 mg Tablet or 120 mg Tablets</p>			
<p>Objectives: The primary objective of the study is:</p> <ul style="list-style-type: none"> to compare the pharmacokinetics (PK) of 240 mg sotorasib administered orally as 1 x 240 mg tablet under fasted conditions to 240 mg sotorasib administered orally as 2 x 120 mg tablets under fasted conditions. <p>The secondary objectives of the study are:</p> <ul style="list-style-type: none"> to evaluate the PK of 240 mg sotorasib administered orally as 1 x 240 mg tablet with a high-fat meal to evaluate the safety and tolerability of 240 mg sotorasib administered orally as 1 x 240 mg tablet and 2 x 120 mg tablets. 			
<p>Study design: This will be an open-label, multi-center (United States), crossover, 3-period study. Groups 1 and 2 will enroll approximately 146 healthy male and healthy female subjects for a duration of at least 2 periods. Approximately 14 out of the 146 (to ensure 12 evaluable subjects) will remain on study for an additional third period. A randomization block will be reserved for Period 3. Periods 1 and 2 will comprise of the bioequivalence portion of the study where subjects will receive a single oral dose of 240 mg sotorasib administered as 1 x 240 mg tablet (test) and a single oral dose of 240 mg sotorasib administered as 2 x 120 mg tablets (reference) under fasted conditions in the order specified by their assigned group. Period 3 will be the fed portion of the study where a subset of subjects will receive an additional 240 mg sotorasib dose administered as 1 x 240 mg tablet with a high-fat meal to evaluate the PK of sotorasib administered as a 240 mg tablet under fed conditions.</p> <p>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 (for subjects enrolled only in Period 1 and Period 2) or Day 9 (for subjects enrolled in all 3 periods). On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive 1 administration of 240 mg sotorasib administered orally under fasted condition as 1 x 240 mg tablet (Treatment A) and 1 administration of 240 mg sotorasib administered orally under fasted condition as 2 x 120 mg tablets (Treatment B) in either Period 1 or Period 2 according to the treatment group below. On Day 7, approximately 14 subjects in either Group 1 or Group 2 will proceed to Period 3 and receive 1 additional administration of 240 mg sotorasib administered orally as 1 x 240 mg tablet with a high-fat meal (Treatment C).</p>			
Group	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
1	Treatment A	Treatment B	Treatment C (14 subjects from Group 1 or Group 2)
2	Treatment B	Treatment A	

<p>Number of subjects: Approximately 146 subjects will be enrolled in order that 132 subjects complete Parts A and B of the study.</p>
<p>Diagnosis and main criteria for inclusion: Healthy male subjects or female subjects, 18 to 60 years of age (inclusive), and body mass index of 18 to 30 kg/m² (inclusive).</p>
<p>Investigational products, dose, and mode of administration: Investigational Medicinal Products (IMP):</p> <ul style="list-style-type: none">• 120 mg tablet of sotorasib• 240 mg tablet of sotorasib <p><u>Treatment A:</u> 240 mg sotorasib administered orally as 1 x 240 mg tablet, after an overnight fast of at least 10 hours <u>Treatment B:</u> 240 mg sotorasib administered orally as 2 x 120 mg tablets, after an overnight fast of at least 10 hours <u>Treatment C:</u> following an overnight fast of at least 10 hours, subjects will consume the entirety of a standard high-fat breakfast within 20 minutes. A 240 mg oral dose of sotorasib (1 x 240 mg tablet) will be given orally 30 minutes after start of the meal.</p>
<p>Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to end of study): approximately 5 weeks.</p>
<p>Primary endpoints: The primary endpoints for this 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 time of last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}).</p> <p>Secondary endpoints: 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}, and AUC_{inf}.</p>
<p>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 mix-effects model will be used to analyze log-transformed primary PK parameters.</p> <p>For the bioequivalence analysis, the model will use PK parameter data from Days 1 and 4 and assumes fixed effect for treatment, period, and group and a random effect for subject. Geometric mean ratios (Treatment A/Treatment B) for C_{max} and AUC values and associated 90% confidence intervals will be estimated.</p> <p>For the food-effect analysis, the model will use PK parameter data from Treatment A and Treatment C and assumes fixed effects for treatment and random effect for subject. Geometric mean ratios (Treatment C/Treatment A) for C_{max} and AUC values and associated 90% confidence intervals will be estimated.</p>

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.

TABLE OF CONTENTS

TITLE PAGE	1
INVESTIGATOR AGREEMENT.....	3
STUDY IDENTIFICATION	4
SYNOPSIS.....	5
TABLE OF CONTENTS.....	8
LIST OF TABLES AND FIGURES.....	11
LIST OF ABBREVIATIONS.....	12
1. INTRODUCTION	13
1.1. Background.....	13
1.2. Pharmacokinetics	15
1.3. Study Rationale.....	16
1.4. Benefit-risk Assessment.....	17
1.4.1. Therapeutic Context.....	17
1.4.1.1. Key Benefits.....	17
1.4.1.2. Risks.....	17
2. OBJECTIVES AND ENDPOINTS	18
2.1. Objectives	18
2.2. Endpoints	18
2.2.1. Primary Endpoints	18
2.2.2. Secondary Endpoints	19
3. INVESTIGATIONAL PLAN.....	19
3.1. Overall Study Design and Plan.....	19
3.2. Discussion of Study Design	21
3.3. Selection of Doses in the Study	21
4. SELECTION OF STUDY POPULATION	21
4.1. Inclusion Criteria	21
4.2. Exclusion Criteria	22
4.3. Screen Failures and Rescreening	24
4.4. Subject Number and Identification.....	24
4.5. Subject Withdrawal and Replacement	25
4.6. Study Termination	26
4.7. Discontinuation of Study Treatment.....	26
5. STUDY TREATMENTS.....	27
5.1. Investigational Product	27
5.2. Investigational Product Administration	28

5.2.1.	Standard High-fat Meal.....	29
5.3.	Treatment of Overdose	29
5.4.	Medical Devices.....	29
5.5.	Product Complaints.....	29
5.6.	Randomization	30
5.7.	Blinding.....	30
5.8.	Treatment Compliance.....	30
5.9.	Drug Accountability.....	30
6.	CONCOMITANT THERAPIES AND OTHER RESTRICTIONS	30
6.1.	Concomitant Therapies	30
6.2.	Diet.....	31
6.3.	Smoking	31
6.4.	Exercise.....	31
6.5.	Blood Donation.....	31
7.	STUDY ASSESSMENTS AND PROCEDURES.....	31
7.1.	Pharmacokinetic Assessments	32
7.1.1.	Pharmacokinetic Blood Sample Collection and Processing.....	32
7.1.2.	Analytical Methodology	32
7.2.	Safety and Tolerability Assessments	32
7.2.1.	Adverse Events and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information.....	32
7.2.2.	Clinical Laboratory Evaluations	35
7.2.3.	Vital Signs.....	36
7.2.4.	12-lead Electrocardiogram.....	36
7.2.5.	Physical Examination.....	36
8.	SAMPLE SIZE AND DATA ANALYSIS.....	36
8.1.	Determination of Sample Size	36
8.2.	Analysis Populations.....	37
8.2.1.	Pharmacokinetic Population	37
8.2.2.	Safety Population	37
8.3.	Pharmacokinetic Analyses	37
8.4.	Safety Analysis	37
8.5.	Interim Analysis.....	38
9.	REFERENCES	38
10.	APPENDICES	39

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events.....	40
Appendix 2: Clinical Laboratory Evaluations	48
Appendix 3: Total Blood Volume.....	49
Appendix 4: Contraception Requirements.....	50
Appendix 5: Collection of Pregnancy and Lactation Information.....	52
Appendix 6: Regulatory, Ethical, and Study Oversight Considerations.....	56
Appendix 7: Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments	61
Appendix 8: Schedule of Assessments	65

LIST OF TABLES AND FIGURES

Table 1: Treatment Group.....20
Table 2: Investigational Product28
Table 3: Conditions for Withholding and/or Permanent Discontinuation of Amgen
Investigational Product and Other Protocol-required Therapies Due to Potential
Hepatotoxicity.....62

Figure 1: Study Schematic.....20
Figure 2: Sample Serious Adverse Event Report Form45
Figure 3: Pregnancy Notification Form.....54
Figure 4: Lactation Notification Form55

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC _{0-24h}	area under the plasma concentration-time curve from time zero to 24 hours postdose
AUC _{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC _{last}	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BDC	bile duct cannulated
CFR	Code of Federal Regulations
C _{max}	maximum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
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
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual

IRB	Institutional Review Board
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
<i>KRAS</i>	Kirsten rat sarcoma viral oncogene homolog (gene)
KRAS ^{G12C}	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
MATE	multidrug and toxic compound extrusion
NSCLC	nonsquamous nonsmall cell lung cancer
OATP	organic anion transporter
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's method
TBL	total bilirubin
t _{max}	time of the maximum observed concentration
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)¹ 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;² 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. Recent progress in the field suggests that 1 mutant version of *KRAS*, *KRAS p.G12C*, which encodes the KRAS^{G12C} protein, might be tractable for small-molecule inhibition through a covalent interaction with the cysteine.^{3,4,5} *KRAS p.G12C* mutation is a frequent mutation found in approximately 13% of lung adenocarcinoma (nonsquamous, nonsmall cell lung cancer [NSCLC]), 3% of colorectal cancer, and 1% to 2% of numerous other solid tumors.^{6,7,8} Sotorasib forms a specific covalent bond with the cysteine of KRAS^{G12C}, irreversibly locking the protein in an inactive conformation that cripples oncogenic signaling.⁵ As inactivation of KRAS has been demonstrated to inhibit cell growth and/or promote apoptosis selectively in tumor cells expressing *KRAS* mutations^{9,10,11,3,4}, sotorasib may provide a therapeutic benefit for patients with *KRAS p.G12C*-driven cancers.

The metabolism and excretion of [¹⁴C]-sotorasib were evaluated in noncannulated male or female rats as well as in bile duct cannulated (BDC) male rats after a single oral dose of sotorasib (60 mg/kg). Overall, the data indicated that sotorasib was readily absorbed after an oral dose to noncannulated male and female rats and BDC male rats, underwent extensive biotransformation, and was eliminated primarily by nonenzymatic conjugation and metabolic clearance; [¹⁴C]-sotorasib-derived radioactivity was excreted primarily through biliary and fecal pathways. Biotransformation of sotorasib was mediated primarily by nonenzymatic glutathione conjugation, oxidation, and to a lesser extent, reduction, and dealkylation. Secondary sotorasib metabolism was substantive and included amide hydrolysis, cysteine-conjugate cleavage, N-acetylation, methylation, glucuronidation, and sulfonation. Biotransformation of sotorasib through primary glutathione conjugation was major and accounted for up to approximately 21% to 33% of the dose from intact male and female rats, respectively, and up to approximately 41% of the dose in male BDC rats. Sotorasib metabolites originating from primary oxidation account for up to approximately 20% of the dose in noncannulated rats and for approximately 10% of the dose in BDC rats. Reduction of the sotorasib acrolein moiety account for up to approximately 10% of the dose in noncannulated male and female rats and approximately 2.7% of the dose in BDC rats, whereas dealkylation at the piperazine moiety accounted for approximately 10% to 13% of the dose in noncannulated rats and for approximately 6% of the dose in BDC rats.

The metabolism and excretion of [¹⁴C]-sotorasib were evaluated in noncannulated male and female dogs after a single oral (500 mg/kg) dose of sotorasib. Overall, [¹⁴C] sotorasib-derived radioactivity was minimally absorbed and was eliminated predominantly as unchanged sotorasib in feces following a single 500 mg/kg dose to male or female dogs.

Seven sotorasib clinical studies (20170543, 20190009, 20190135, 20190147, 20190288, 20190436, and 20190442) 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.

Study 20170543 is an ongoing phase 1/2, open-label, nonrandomized study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in subjects with *KRAS p.G12C*-mutated NSCLC, colorectal cancer, and other solid tumors. As of 01 December 2020, 456 subjects have been treated with sotorasib monotherapy across all doses (dose range: 180 to 960 mg) and tumor types in the ongoing Phase 1 and Phase 2 treatment cohorts. This includes 359 subjects who were treated with the sotorasib dose of 960 mg once daily (QD) (fasted) for all tumor types.

For the combination therapy cohorts, as of the data cutoff date (06 July 2020), a total of 11 subjects with NSCLC were treated with sotorasib in combination with pembrolizumab in Part 1c/2c of Study 20170543. As of the data cutoff date (12 July 2021), a total of 41 subjects with *KRAS p.G12C*-mutated advanced solid tumors were treated with sotorasib in combination with trametinib in Study 20190135 Subprotocol A. As of the data cutoff date (12 July 2021), a total of 33 subjects with *KRAS p.G12C*-mutated advanced NSCLC were treated with sotorasib

in combination with afatinib in Study 20190135 Subprotocol D. As of the data cutoff date (12 July 2021), 44 subjects with KRAS p.G12C-mutated advanced solid tumors were treated with sotorasib and 39 subjects were treated with panitumumab in Study 20190135 Subprotocol H.

A summary of completed and ongoing clinical studies for sotorasib is provided in the IB (Tables 6-1, 6-2, and 6-3).¹

1.2. Pharmacokinetics

The PK of sotorasib have been characterized in healthy subjects and in subjects with *KRAS* pG12C-mutated solid tumors, including NSCLC. Sotorasib exhibited nonlinear, time-dependent, PK over the dose range of 180 to 960 mg (0.19 to 1 times the approved recommended dosage) QD with similar systemic exposure (ie, area under the concentration-time curve from time zero to 24 hours postdose [AUC_{0-24h}] and maximum observed plasma concentration [C_{max}]) across doses at steady state. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predispersed in water administered under fasted conditions. Sotorasib plasma concentrations reached steady state within 22 days. No accumulation was observed after repeat sotorasib dosages with a mean accumulation ratio of 0.56 (coefficient of variation [CV]: 59%).

Absorption

The median time of the maximum observed concentration (t_{max}) is 1 hour.

Effect of Food

When 960 mg sotorasib was administered with a high-fat, high-calorie meal (containing approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively) in patients, sotorasib AUC_{0-24h} increased by 25% compared to administration under fasted conditions.

Distribution

The sotorasib mean apparent volume of distribution at steady state (V_{ss}) is 211 L (CV: 135%). In vitro, sotorasib plasma protein binding is 89%.

Elimination

The sotorasib mean terminal elimination half-life is 5 hours (standard deviation: 2). At 960 mg sotorasib QD, the sotorasib steady-state apparent clearance is 26.2 L/hr (CV: 76%).

Metabolism

The main metabolic pathways of sotorasib are nonenzymatic conjugation and oxidative metabolism with cytochrome P450 (CYP)3As.

Excretion

After a single dose of radiolabeled sotorasib, 74% of the dose was recovered in feces (53% unchanged) and 6% in urine (1% unchanged).

Specific Populations

No clinically meaningful differences in the PK of sotorasib were observed based on age (28 to 86 years), sex, race (White, Black, and Asian), body weight (36.8 to 157.9 kg), line of therapy, Eastern Cooperative Oncology Group (0, 1), mild and moderate renal impairment (estimated glomerular filtration rate: ≥ 30 mL/min/1.73 m²), or mild hepatic impairment (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] < 2.5 x upper limit of normal [ULN] or total bilirubin < 1.5 x ULN). The effect of severe renal impairment or moderate to severe hepatic impairment on sotorasib PK has not been studied.

Drug-drug Interaction Studies

Interactions of sotorasib with digoxin (P-glycoprotein substrate), metformin (multidrug and toxic compound extrusion (MATE)1 and MATE2-K substrate), itraconazole (CYP3A4 and P-gp inhibitor), rifampin (organic anion transporter [OATP] 1B1/1B3 inhibitors and CYP3A4 inducer), omeprazole (proton-pump inhibitor [PPI]), famotidine (histamine-2 receptor antagonist), and midazolam (CYP3A4 substrate) are summarized in the IB (Table 6-3).¹ Overall, these results suggest sotorasib may be taken safely with sensitive MATE1/2K substrates, CYP2D6 substrates, strong CYP3A4/P-gp inhibitors, and strong OATP1B1/1B3 inhibitors. However, exposures of P-gp and sensitive CYP3A4 substrates may be altered. Coadministration of PPIs, histamine-2 receptor antagonists, and strong CYP3A4 inducers may lead to decreased sotorasib exposure.

1.3. Study Rationale

The purpose of this study is to compare the PK of 240 mg sotorasib administered as 1 x 240 mg oral tablet (Treatment A) under fasted condition to 240 mg sotorasib administered as 2 x 120 mg oral tablets (Treatment B) under fasted condition and to compare the PK of 240 mg sotorasib administered as 1 x 240 mg oral tablet following a high-fat meal (Treatment C) to 240 mg sotorasib administered as 1 x 240 mg oral tablet under fasted condition (Treatment A) in healthy male subjects and healthy female subjects of nonchildbearing potential. Oral dosing is the intended route of administration for sotorasib. The 240 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 IB¹ 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 240 mg sotorasib administered as 1 x 240 mg tablet (Treatment A) and a single oral dose of 240 mg sotorasib administered as 2 x 120 mg tablets (Treatment B) in either Period 1 or Period 2 according to their assigned group. Approximately 14 healthy subjects in either Group 1 or 2 will receive a single oral dose of 240 mg sotorasib administered as 1 x 240 mg tablet (Treatment C) following a high-fat meal (detailed provided in [Section 5.2.1](#)) in Period 3.

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, anemia, 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, and thyroid dysfunction. 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 AST and increased 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, including baseline liver function, are provided in [Section 4](#).

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy. Three subjects (0.8%) had an adverse event of ILD/pneumonitis. All 3 events were serious and Grade 3 or 4 at onset, and 2 subjects discontinued sotorasib because of ILD/pneumonitis. Monitor patients for new or worsening pulmonary symptoms. At any grade, immediately withhold sotorasib for suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

As of 11 January 2022, no clinically meaningful sotorasib-related renal toxicity, anemia, leukocytosis, thyroid dysfunction, or splenomegaly has 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 United States Prescribing Information.^{1,12}

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to compare the PK of 240 mg sotorasib administered orally as 1 x 240 mg tablet under fasted conditions to 240 mg sotorasib administered orally as 2 x 120 mg tablets under fasted conditions.

The secondary objectives of the study are:

- to evaluate the PK of 240 mg sotorasib administered orally as 1 x 240 mg tablet with a high-fat meal
- to evaluate the safety and tolerability of 240 mg sotorasib administered orally as 1 x 240 mg tablet and 2 x 120 mg tablets.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints for Periods 1 and 2 of the study are:

- C_{max}
- area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last})
- area under the plasma concentration-time curve from time zero to infinity (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 study. Groups 1 and 2 will enroll approximately 146 healthy male and healthy female subjects for a duration of at least 2 periods. Approximately 14 out of the 146 (to ensure 12 evaluable subjects) will remain on study for an additional third period. Periods 1 and 2 will comprise the bioequivalence portion of the study where subjects will receive a single oral dose of 240 mg sotorasib administered as 1 x 240 mg tablet (test) and a single oral dose of 240 mg sotorasib administered as 2 x 120 mg tablets (reference) under fasted conditions in the order specified by their assigned group. Period 3 will be the fed portion of the study where a subset of subjects will receive an additional 240 mg sotorasib dose administered as 1 x 240 mg tablet with a high-fat meal to evaluate the PK of sotorasib administered as a 240 mg tablet under fed conditions.

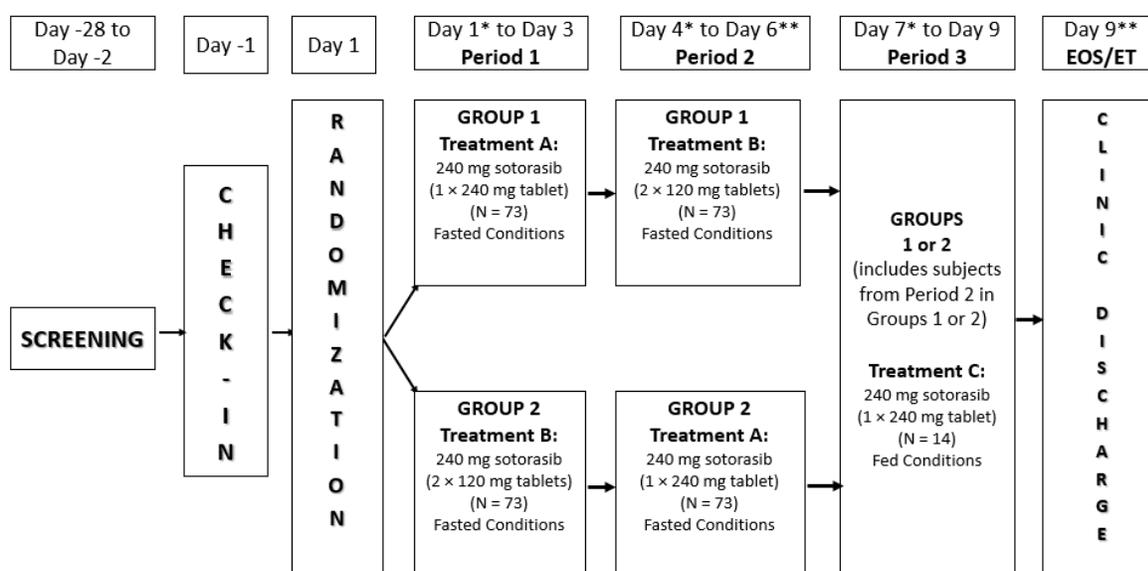
After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 6 (for subjects enrolled only in Period 1 and Period 2) or Day 9 (for subjects enrolled in all 3 periods). On Day 1, subjects will be randomized to Group 1 or Group 2. Each subject will receive 1 administration of 240 mg sotorasib administered orally under fasted condition as 1 x 240 mg tablet (Treatment A) and 1 administration of 240 mg sotorasib administered orally under fasted condition as 2 x 120 mg tablets (Treatment B) in either Period 1 or Period 2 (see [Table 1](#)). On Day 7, approximately 14 subjects in either Group 1 or Group 2 will proceed to Period 3 and receive 1 additional administration of 240 mg sotorasib administered orally as 1 x 240 mg tablet with a high-fat meal (Treatment C).

Table 1: Treatment Group

Group	Period 1 (Day 1)	Period 2 (Day 4)	Period 3 (Day 7)
1	Treatment A	Treatment B	Treatment C (approximately 14 subjects from Group 1 or Group 2)
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 group.

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 8](#).

3.2. Discussion of Study Design

This is a 3-period crossover study in healthy subjects where all subjects receive at least 2 treatments (Treatment A or B). 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. A single-dose fixed group crossover design is the standard design to compare PK data between drug formulations and fasting/fed conditions. 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 study endpoints are not considered subjective.

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 approved dose level of sotorasib is 960 mg.¹² There have been 6 clinical studies in healthy subjects where sotorasib has been administered at dose levels up to 960 mg and was well tolerated across the studies. In addition, there have been no dose-limiting toxicities observed with sotorasib monotherapy at 960 mg in subjects with advanced tumors with the *KRAS p.G612C* mutation.

Amgen is conducting a dose comparison study (CodeBreak 100, Study 20170543 Phase 2 Part B) aiming to evaluate sotorasib efficacy at 960 mg versus 240 mg. The selected dose of 240 mg in this study will support the potential market application of 240 mg tablets. Please refer to the IB¹ for more information on sotorasib.

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 or nonchildbearing 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/m² (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 ≥ 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 correction (QTcF) interval > 450 msec in male subjects or > 470 msec in female subjects or history/evidence of long QT syndrome, and/or PR interval > 200 msec, second- or third-degree atrioventricular block, at Screening or Check-in. Electrocardiograms will be taken as single ECGs. If parameters are out-of-range, the site will collect 2 more ECGs and then calculate the mean to determine eligibility.
4. Systolic blood pressure > 140 mmHg or < 90 mmHg, or diastolic blood pressure > 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.
5. 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.
6. Inability to swallow oral medication or history of malabsorption syndrome.
7. 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.
8. Poor peripheral venous access.
9. Estimated glomerular filtration rate less than $70 \text{ mL/min/1.73 m}^2$ 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.

10. ALT or AST should be \leq ULN at Screening or Check-in (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 \leq ULN or if the repeated values above ULN are deemed not clinically significant by the Investigator [eg, 1.5 ULN]).
11. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus test at Screening. Subjects whose results are compatible with prior immunity (vaccination or prior infection) may be included.
12. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before enrollment, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
 - a. Acetaminophen [paracetamol] (up to 2 g per day) for analgesia will be allowed.
13. All herbal medicines (eg, 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.
14. Administration of a Coronavirus Disease 2019 (COVID-19) vaccine in the past 30 days prior to the first dosing.
15. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges within 7 days prior to Check-in.
16. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
17. Alcohol consumption from 48 hours prior to Check-in.
18. 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.
19. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
20. Positive test for illicit drugs, cotinine (tobacco or nicotine use) at Screening or Check-in and/or alcohol use at Check-in only.
21. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
22. Female subjects with a positive pregnancy test at Screening or Check-in.
23. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through 7 days after the EOS.
24. Unwilling to adhere to contraceptive requirements through 7 days after the EOS (see [Appendix 4](#)).
25. Unwilling to abstain from sperm donation and ovum donation through 7 days after the EOS (see [Appendix 4](#)).

26. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
27. 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.
28. 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.
29. Have previously completed or withdrawn from this study or any other study investigating sotorasib or have previously received the investigational product.
30. 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.
31. Receipt of blood products within 2 months prior to Check-in.
32. Unwilling to abide with study restrictions.
33. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.
34. Performed strenuous exercise, began a new exercise program, or participated in any unusually strenuous physical exertion within 7 days prior to Check-in.
35. Subjects unable to consume a standard high-fat, high-calorie meal within 20 minutes (for Period 3 only).

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 (eg, Subjects 0101, 0102, 0103). Subjects enrolled in the food-effect arm (Period 3) will be assigned subject numbers from an identified block of numbers prior to the first dosing session (Subjects [redacted] to [redacted]). If a decision is made to not enroll all 146 planned subjects in the study, any remaining subject numbers prior to the block of subject numbers reserved for the food-effect arm will not be considered omitted. Replacement subjects will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, 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) v5.0 Grade ≥ 3 adverse event
- occurrence of Grade 2 adverse event 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 (eg, neuropathy, chronic diarrhea, etc.)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If 2 or more subjects are withdrawn from the study due to adverse events that are considered by the Investigator to be at least possibly related to sotorasib or if there is 1 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 8](#)). 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, serious adverse events, or until the unresolved adverse events, 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 8](#)) including different options of follow-up (eg, 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, combination product, 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 IMP and non-IMP, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual (IPIM), 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

Study Treatment Name	Treatment A, C Investigational Medicinal Product: Sotorasib	Treatment B Investigational Medicinal Product: Sotorasib
Unit Strength and Formulation	240 mg Oral Tablet	120 mg Oral Tablet
Dosage Level	240 mg (1 x 240 mg tablet)	240 mg (2 x 120 mg tablets)
Route of Administration	Oral	Oral
Accountability	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's electronic Case Report Form.	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's electronic Case Report Form.
Dosing Instructions	<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. One tablet should be taken with approximately 8 ounces (240 mL) of water. Tablet should not be broken or chewed. No food will be given for at least 4 hours after 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 240 mg dose of sotorasib will be given orally 30 minutes after start of the meal. One tablet should be taken with approximately 8 ounces (240 mL) of water. Tablet should not be broken or chewed. No food will be given for at least 4 hours after administration.</p>	<p>Treatment B: The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Two tablets should be taken with approximately 8 ounces (240 mL) of water. Tablets should not be broken or chewed. No food will be given for at least 4 hours after administration.</p>

For preparation instructions, refer to the IPIM.

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.¹³ 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

No investigational medical device(s) will be used in this study.

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 (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for eg, 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 (1) Sponsor or (2) distributors and partners for whom the Sponsor manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts. 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

At the start of Period 1, 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 for analgesia) 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 EOS. Subjects will otherwise maintain their normal level of physical activity during this time (ie, 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 90 days 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, assessment of adverse events, serious adverse events.

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 8](#). 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 8](#)) 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 validated analytical procedures. 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 the first dose of study drug through the EOS visit 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 awareness of the event. The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Since the criteria the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to Grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as Grade 4 without manifestation of life-threatening status), it will be left to the Investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

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 (as defined above in the 'Serious Adverse Event' section) or after EOS. However, these serious adverse events suspected to be related to investigational products should be reported to Amgen 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 /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.

If further safety-related data are needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

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 (eg, 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 (eg, 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 8](#). 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 urine or breath test at the times indicated in the Schedule of Assessments in [Appendix 8](#). 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 8](#).

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 8](#). 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 8](#). Single 12-lead ECGs will be repeated twice, and an average (mean) taken of the 3 readings, if either of the following criteria apply:

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

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 8](#).

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

This study will require at least 132 subjects completing Periods 1 and 2 of the study to establish equivalence between 2 treatments 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 test and reference 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. In Period 3, approximately 14 subjects planned for food-effect inferential analysis is based on common practice for studies of similar nature and not based on power calculations.

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, 4, and 7 will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max} , AUC_{last} , and AUC_{inf} for sotorasib on Days 1 and 4. Subjects who have evaluable PK parameters on Days 1 and 4 will be included in the primary endpoint analysis. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. A linear mix-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment, period, and group, 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 will be Treatment B while the test treatment will be Treatment A for the bioequivalence analysis. For the food-effect analysis, the model will use up to 14 subjects' data and assumes fixed effects for treatment and random effect for subject while test treatment would be fed (Treatment C) and reference would be fasted (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

1. Amgen. AMG 510 – Investigator’s Brochure. (Version 6.1). 11 January 2022.
2. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. *J Cell Sci.* 2016;129(7):1287-1292.
3. Ostrem JM, Shokat KM. Direct small-molecule inhibitors of KRAS; from structural insights to mechanism-based design. *Nat Rev Drug Discov.* 2016;15(11):771-785.
4. Patricelli MP, Janes MR, Li LS, et al. Selective inhibition of oncogenic KRAS output with small molecules targeting the inactive state. *Cancer Discov.* 2016;6:316-329.
5. Canon J, Rex K, Saiki AY, et al. The clinical KRAS (G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature.* 2019;575:217-223.
6. The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through an International Consortium. *Cancer Discov.* 2017;7(8):818-831.
7. Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. *Cancer Genet.* 2016;209(5):195-198.
8. Neumann J, Zeindl-Eberhart E, Kirchner T, Jung A. Frequency and type of KRAS mutations in routine diagnostic analysis of metastatic colorectal cancer. *Pathol Res Pract.* 2009;205(12):858-862.
9. Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. *Cell.* 2018;172(3):578-589.
10. McDonald ER, de Weck A, Schlabach MR, et al. Project DRIVE: A compendium of cancer dependencies and synthetic lethal relationships uncovered by large-scale deep RNAi screening. *Cell.* 2017;170(3):577-592.
11. Xie C, Li Y, Li LL, et al. Identification of a new potent inhibitor targeting KRAS in non-small cell lung cancer cells. *Front Pharmacol.* 2017;8:823.

12. Food and Drug Administration LUMAKRAS™ (sotorasib) tablets prescribing information. Revised May 2021. Amgen. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf.
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.

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">• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.• 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.• Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan.
Events Meeting the Adverse Event Definition
<ul style="list-style-type: none">• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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 (ie, not related to progression of underlying disease).• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.• 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.• 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.
Events NOT Meeting the Adverse Event Definition
<ul style="list-style-type: none">• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- 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.

Definition of Serious Adverse Event

A serious adverse event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening 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.
Requires in-patient hospitalization or prolongation of existing hospitalization 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.
Results in persistent or significant disability/incapacity 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
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 (eg, 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;
 - Assessment of seriousness;
 - Severity (or toxicity defined below);
 - Assessment of relatedness to the investigational product(s) and/or study-mandated activity and/or 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, refer to:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The Investigator is obligated to assess the relationship between investigational product(s), protocol-required therapy and/or study-mandated activity and/or procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The Investigator will use clinical judgment to determine the relationship.
- 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.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- 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.
- 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.
- 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.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- 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.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
- 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.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form

- Facsimile transmission of the Serious Adverse Event Report Form (see [Figure 2](#)) is the preferred method to transmit this information.
- 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.
- 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.
- Once the study has ended, serious event(s) should be reported to the 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.

Figure 2: Sample Serious Adverse Event Report Form

A 20210088 Labcorp Study# 8471134 Sotorasib (AMG 510)	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up	
Amgen (Sponsor) Safety US: Email: svc-ags-in-us@amgen.com or Fax +888-814-8653			
1. SITE INFORMATION			
Site Number	Investigator	Country	
Reporter	Phone Number ()	Date of Report Day Month Year	
Fax Number ()			
2. SUBJECT INFORMATION			
Subject ID Number	Age at event onset	Sex <input type="checkbox"/> F <input type="checkbox"/> M	
		Race	
If applicable, provide End of Study date			
3. SERIOUS ADVERSE EVENT - Information in this section must also be entered on the Serious Adverse Event Summary CRF			
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 Enter 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		
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	Sotorasib <Device> <Device> <Device> <Device> <Device> No/ Yes No/ Yes No/ Yes No/ Yes No/ Yes		
4. HOSPITALIZATION			
Date Admitted Day Month Year		Date Discharged Day Month Year	
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):			
5. INVESTIGATIONAL PRODUCT (IP)			
Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year Dose Route Frequency		
Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld		Lot # and Serial # Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unknown	
Sotorasib <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label			
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label			
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label			
<<IP/Device>> <input type="checkbox"/> Blinded <input type="checkbox"/> Open Label			

A 20210088 Labcorp Study# 8471134 Sotorasib (AMG 510)	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	<input type="checkbox"/> New <input type="checkbox"/> Follow-up
---	---	--

	Site Number	Subject ID Number														
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) 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	
7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)																
8. RELEVANT LABORATORY VALUES (include baseline values) Any Relevant Laboratory values? <input type="checkbox"/> No <input type="checkbox"/> Yes, if yes, please complete:																
Date	Test															
	Unit															
Day	Month	Year														
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes, if yes, please complete:																
Date	Additional Tests					Results					Units					
Day	Month	Year														

<p>A 20210088 Labcorp Study# 8471134 Sotorasib (AMG 510)</p>	<p>Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i></p>	<p><input type="checkbox"/> New <input type="checkbox"/> Follow-up</p>
--	--	---

	Site Number	Subject ID Number
--	-------------	-------------------

10. CASE DESCRIPTION (Provide narrative details of events listed in section 3) For each event in section 3, where relationship=Yes, please provide rationale.

<p>Signature of Investigator or Designee</p> <p><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></p>	<p>Title</p>	<p>Date</p>
---	--------------	-------------

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Direct bilirubin ^a Gamma-glutamyl transferase Glucose Indirect bilirubin ^a Inorganic phosphate Potassium Sodium Total bilirubin ^a Total CO ₂ (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)
Serology^b:	Drug screen^c:	Hormone panel - females only:
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Alcohol test ^h Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Tricyclic antidepressants	Follicle-stimulating hormone ^b (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin) ^d Urine pregnancy test ^d
		Other Tests:
		Thyroid-stimulating hormone ^e International normalized ratio (INR) ^f Estimated glomerular filtration rate (eGFR) ^{c,g}

^a Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

^b Only analyzed at Screening.

^c Only analyzed at Screening and Check-in.

^d 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.

^e Only analyzed at Screening, Check-in, and at end of study.

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

^g Estimated glomerular filtration rate will be calculated by the Modified Renal Disease equation.

^h Urine or breath alcohol tests will be performed at Check-in.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	12.5	4 to 5	50 to 62.5
Serology	8	1	8
Sotorasib pharmacokinetics	4	34-51	136-204
Total:			194-274.5

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

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 ≥ 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

Only female subjects who are of nonchildbearing potential will be enrolled in the study and are 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 with nonchildbearing female partners (as defined above) are not required to use contraception.

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, 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 (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation 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 relationship 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.

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 (eg, 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 region's 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 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

1. Case Administrative Information														
Protocol/Study Number: <u>Amgen protocol number 20210088 Labcorp study number 8471134</u>														
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)														
2. Contact Information														
Investigator Name _____		Site # _____												
Phone (____) _____		Fax (____) _____		Email _____										
Institution _____														
Address _____														
3. Subject Information														
Subject ID # _____		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male Subject age (at onset): _____ (in years)												
4. Amgen Product Exposure														
<table border="1"><thead><tr><th>Amgen Product</th><th>Dose at time of conception</th><th>Frequency</th><th>Route</th><th>Start Date</th></tr></thead><tbody><tr><td> </td><td> </td><td> </td><td> </td><td>mm____/dd____/yyyy____</td></tr></tbody></table>					Amgen Product	Dose at time of conception	Frequency	Route	Start Date					mm____/dd____/yyyy____
Amgen Product	Dose at time of conception	Frequency	Route	Start Date										
				mm____/dd____/yyyy____										
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No														
If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____														
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No														
5. Pregnancy Information														
Pregnant female's last menstrual period (LMP) mm____/dd____/yyyy____ <input type="checkbox"/> Unknown <input type="checkbox"/> 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? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A														
If yes, provide date of delivery: mm____/dd____/yyyy____														
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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



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

1. Case Administrative Information				
Protocol/Study Number: <u>Amgen protocol number 20210088 Labcorp study number 8471134</u>				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name _____		Site # _____		
Phone (____) _____		Fax (____) _____		Email _____
Institution _____				
Address _____				
3. Subject Information				
Subject ID # _____		Subject age (at onset): <u> </u> (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? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm ____/dd ____/yyyy ____				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Breast Feeding Information				
Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If No, provide stop date: mm ____/dd ____/yyyy ____				
Infant date of birth: mm ____/dd ____/yyyy ____				
Infant gender: <input type="checkbox"/> Female <input type="checkbox"/> Male				
Is the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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: _____		

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 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 (eg, 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 (eg, 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.

Subject 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 Case Report Form (CRF) 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 (eg, 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 (eg, 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 (ie, 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 (eg, 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 (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis).

If investigational product is 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 >5x ULN but <8x ULN for ≥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)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values >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 sotorasib 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 (ie, 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 $> 3 \times$ 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: Schedule of Assessments

Schedule of Assessments

Study Procedures	Screening	Check-in	Period 1 (All Subjects)			Period 2 (All Subjects)			Period 3 (Subset of Subjects Only)		
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 (EOS/ ET) ^a	Day 7	Day 8	Day 9 (EOS/ ET) ^b
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 ^c									
Height and BMI	X										
Weight	X	X						X ⁿ			X ⁿ
Drug Screen	X	X									
Urine or Breathalyzer Alcohol Test		X									
Pregnancy Test (females only)^d	X	X						X ⁿ			X ⁿ
FSH (postmenopausal females only)	X										
12-lead Electrocardiogram^e	X	X	X			X		X ⁿ	X		X ⁿ
Vital Signs^f	X	X	X	X		X	X	X ⁿ	X	X	X ⁿ
Clinical Laboratory Evaluations^g	X	X			X			X ⁿ			X ⁿ
eGFR^h	X	X									
Physical Examinationⁱ		X						X ⁿ			X ⁿ
Sotorasib Dose^j			X			X			X		
Sotorasib PK Blood Samples^k			X	X	X	X	X	X ⁿ	X	X	X ⁿ
Adverse Event Monitoring^l							X				
Serious Adverse Event Monitoring^l	X						X				
Prior/Concomitant Medications^m	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.

^a Day 6 will be the EOS for all subjects except those designated to proceed to Period 3.

^b Day 9 will be the EOS only for the subjects designated to proceed to Period 3.

^c Interim medical history only.

^d 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.

- ^e 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; predose and 0.5, 2, and 4 hours following sotorasib administration on Days 1, 4, and 7; and EOS or ET. Triplicate ECGs will only be collected at Screening and Check-in if needed to verify eligibility criteria. The 30-minute postdose ECG measurement will have a collection window of ± 5 minutes, the 2-hour postdose ECG measurement will have a collection window of ± 5 minutes, and the 4-hour postdose ECG measurement will have a collection window of ± 10 minutes.
- ^f 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.
- ^g Clinical chemistry (fasted at least 8 hours), hematology, and urinalysis.
- ^h eGFR will be calculated using the Modification of Diet in Renal Disease equation.
- ⁱ A full physical examination at Check-in and a symptom-directed physical examination at EOS/ET.
- ^j 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).
- ^k 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 ± 2 minutes, samples collected from 1 through 3.5 hours postdose will have a sampling window of ± 5 minutes, samples collected from 4 through 10 hours postdose will have a sampling window of ± 10 minutes, and samples collected from 12 through 48 hours postdose will have a sampling window of ± 20 minutes. Times of all PK samples will be recorded to the nearest minute.
- ^l 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).
- ^m 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 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.
- ⁿ Assessment to be performed at the EOS or if a subject is withdrawn early from the study.