Protocol

An Open-label Study to Evaluate the Impact of Omeprazole, A Proton Pump Inhibitor, on the Pharmacokinetics of Sotorasib Coadministered with an Acidic Beverage in Healthy Volunteers

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

NCT Number: NCT05497557
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

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INVESTIGATOR AGREEMENT

I have read the protocol entitled "An Open-label Study to Evaluate the Impact of Omeprazole, a Proton Pump Inhibitor, on the Pharmacokinetics of Sotorasib Coadministered with an Acidic Beverage in Healthy Volunteers" 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.

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_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

_____

Title and Role of Investigator

_____

Institution Name

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SYNOPSIS

Title of study: An Open-label Study to Evaluate the Impact of Omeprazole, a Proton Pump Inhibitor, on the Pharmacokinetics of Sotorasib Coadministered with an Acidic Beverage in Healthy Volunteers
Objectives: The primary objective of the study is: • to evaluate the effects of omeprazole (a proton-pump inhibitor) and an acidic beverage (Coca-Cola®) on sotorasib pharmacokinetics (PK) when administered orally in healthy volunteers. The secondary objective of the study is: • to evaluate the safety and tolerability of sotorasib when coadministered with omeprazole and an acidic beverage in healthy subjects.
Study design: This will be a Phase 1, single-center (United States), open-label, fixed sequence study to investigate the effect of coadministration of omeprazole with an acidic beverage on the PK of sotorasib in healthy male and female subjects. 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/end of study (EOS) on Day 11. Subjects will receive a single dose of 960 mg sotorasib with 240 mL of water on Day 1, daily doses of 40 mg omeprazole with 240 mL of water on Days 4 to 8, and omeprazole and sotorasib with 240 mL of an acidic beverage on Day 9.
Number of subjects: Up to 14 subjects will be enrolled to ensure that 12 subjects complete the study.
Diagnosis and main criteria for inclusion: Healthy male subjects or female subjects of nonchildbearing potential, 18 to 60 years of age (inclusive), and body mass index of 18 to 30 kg/m^2 (inclusive).
Investigational products, dose, and mode of administration: Amgen Investigational Medicinal Product: 960 mg sotorasib (8 x 120 mg tablets) Amgen Non-Investigational Medicinal Product: 40 mg omeprazole delayed release capsule • Day 1: 960 mg sotorasib administered orally with 240 mL of water after an overnight fast of at least 10 hours • Days 4 to 8: 40 mg omeprazole (delayed release capsule) administered orally with 240 mL of water once daily after an overnight fast of at least 10 hours • Day 9: 40 mg omeprazole (delayed release capsule) followed by 960 mg sotorasib administered orally within 5 minutes with 240 mL of an acidic beverage after an overnight fast of at least 10 hours
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to EOS): approximately 5.5 weeks.

Primary endpoints: The primary endpoints for this study are sotorasib PK parameters on Days 1 and 9: maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}), and area under the plasma concentration-time curve from time zero to time of last quantifiable concentration (AUC_{last}). **Secondary endpoints:** The secondary endpoints for this study are adverse events, clinical laboratory tests, 12-lead electrocardiograms, and vital signs.
Statistical methods: The primary PK parameters are C_{max}, AUC_{last}, and AUC_{inf} for sotorasib on Days 1 and 9. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment and a random effect for subject. Geometric mean ratios for C_{max} and AUC values and associated 90% confidence intervals (Test/Reference) will be estimated. The "Reference" treatment for PK analysis will be sotorasib administered alone with water, while the "Test" treatment will be omeprazole coadministered with sotorasib and an acidic beverage. 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, electrocardiograms, and vital signs will be summarized.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
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
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
IRB	Institutional Review Board

KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (gene)
$KRAS^{G12C}$	KRAS protein with a glycine to cysteine amino acid substitution at position 12
KRAS p.G12C	*KRAS* gene with a mutation resulting in a glycine to cysteine amino acid substitution at position 12
MATE	multidrug and toxic compound extrusion
NSCLC	non-small cell lung cancer
OATP	organic anion transporter
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
QD	once daily
QTcF	QT interval corrected for heart rate based on the Fridericia correction
TBL	total bilirubin
t_{max}	time of the maximum observed concentration
ULN	upper limit of normal
USPI	United States Prescribing Information
V_{ss}	volume of distribution at steady state

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

Investigational Medicinal Product

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, non-small 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 [^{14}C]-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; [^{14}C]-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 [^{14}C]-sotorasib were evaluated in noncannulated male and female dogs after a single oral (500 mg/kg) dose of sotorasib. Overall, [^{14}C]-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.

Eight sotorasib clinical studies (20170543, 20190009, 20190135, 20190147, 20190172, 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] In the United States and several other countries, sotorasib (960 mg daily) is currently approved for the treatment of adult patients with KRAS p.G12C-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy.

Non-Investigational Medicinal Product

Omeprazole is a proton pump inhibitor (PPI) indicated for the treatment of duodenal and gastric ulcers, heartburn and other symptoms associated with gastroesophageal reflux disease, maintenance of healing of erosive esophagitis, and long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis). Omeprazole inhibits gastric acid secretion and thereby increases the pH of the gastric environment, which may alter the absorption of some drugs with pH-dependent solubility and cause safety and efficacy concerns. Please refer to the United States Prescribing Information (USPI) for Prilosec® (omeprazole) capsules for additional information.[12]

1.2. Pharmacokinetics

The PK of sotorasib have been characterized in healthy subjects and in subjects with *KRAS p.G12C*-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 plasma concentration-time curve [AUC] 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 m^2), 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. Study 20200326 is currently ongoing to evaluate the PK of sotorasib in subjects with moderate or severe hepatic impairment.

Drug-drug Interaction Studies

Interactions of sotorasib with digoxin (P-glycoprotein [P-gp] 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 (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 (such as omeprazole), 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 evaluate the effects of omeprazole, a PPI, on sotorasib PK when administered orally with an acidic beverage (Coca-Cola®) and to evaluate the safety and tolerability of sotorasib when coadministered with omeprazole and an acidic beverage in healthy subjects.

The concomitant use of sotorasib and acid-reducing agents was shown to decrease sotorasib exposures. Based on results from Study 20190320,[1] geometric least-square mean ratios (test/reference) of sotorasib area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and C_{max} were 0.582 and 0.431, respectively, when comparing sotorasib administered with omeprazole (test) and sotorasib administered alone (reference) in the fasted state. In Study 20200199,[1] geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.622 and 0.654, respectively, when comparing sotorasib coadministered with famotidine (test) and sotorasib alone (reference) under fed conditions. Geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.430 and 0.349, respectively, when comparing sotorasib coadministered with omeprazole (test) and sotorasib alone (reference) under fed conditions. These results suggest that concomitant administration of sotorasib with acid-reducing agents should be avoided.

The rationale for this study is to see if temporarily lowering gastric pH by adding a glass of an acidic beverage could reduce the extent of the interaction between sotorasib and concomitantly administered PPIs. Coca-Cola® is the acidic beverage chosen for this study and has a pH of approximately 2.5 that can alter the acidity in the gastric environment and mitigate the impact of acid-reducing agents on the exposures of several compounds.[13,14,15,16]

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] 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, subjects will receive a single oral dose of 960 mg sotorasib administered as 8 x 120 mg tablets on Day 1, and 960 mg sotorasib in combination with 40 mg omeprazole and an acidic beverage on Day 9 (details provided in Section 3.3).

Safety monitoring: During the study, subjects will be administered all investigational product doses by site staff and will be instructed not to crush, chew, or split the sotorasib tablets or omeprazole 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, increased liver enzymes, and interstitial lung disease (ILD)/pneumonitis. Based on nonclinical toxicity studies of sotorasib, potential safety concerns to be monitored in clinical studies of sotorasib include renal toxicity, anemia, and leukocytosis. 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/pneumonitis has occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy. Incidence of ILD in clinical trials was approximately 0.8%. All events were serious and Grade 3 or 4 at onset, and 2 subjects discontinued sotorasib because of ILD/pneumonitis. During the study, subjects should be monitored 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 USPI.[1,17]

Non-investigational Medicinal Product Risks

Commonly reported adverse events for omeprazole include headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence. Please refer to the package insert for commonly reported adverse events for omeprazole.[12]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the effects of omeprazole (a PPI) and an acidic beverage on sotorasib PK when administered orally in healthy volunteers.

The secondary objective of the study is:

- to evaluate safety and tolerability of sotorasib when coadministered with omeprazole and an acidic beverage in healthy subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are sotorasib PK parameters on Days 1 and 9:

- C_{max}
- AUC_{inf}
- area under the plasma concentration‑time curve from time zero to time of last quantifiable concentration (AUC_{last})

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

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

3. INVESTIGATIONAL PLAN

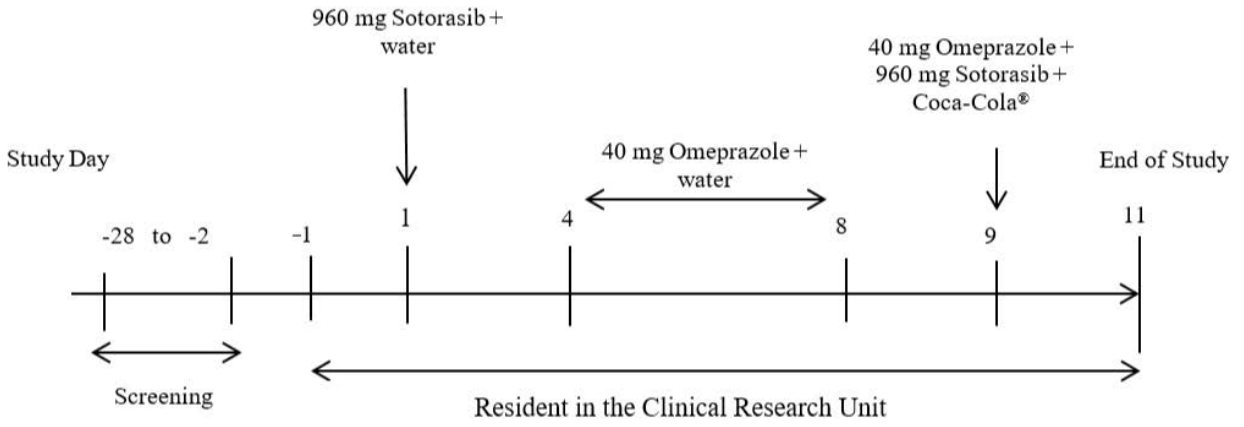
3.1. Overall Study Design and Plan

This will be a Phase 1, single-center (United States), open-label, fixed sequence study to investigate the effect of coadministration of omeprazole with an acidic beverage on the PK of sotorasib in healthy male and healthy female subjects. Up to 14 subjects will be enrolled to ensure that 12 subjects complete the study. All subjects will receive each of the following treatments:

- Day 1: 960 mg sotorasib (8 x 120 mg tablets) administered orally with 240 mL of water after an overnight fast of at least 10 hours
- Days 4 to 8: 40 mg omeprazole (delayed release capsule) administered orally with 240 mL of water QD after an overnight fast of at least 10 hours
- Day 9: 40 mg omeprazole (delayed release capsule) followed by 960 mg sotorasib (8 x 120 mg tablets) administered orally within 5 minutes with 240 mL of an acidic beverageafter an overnight fast of at least 10 hours.

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

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge/end of study (EOS) on Day 11.

The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 5.5 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

The fixed sequence design used in this study is typical for interaction studies where a relatively small number of subjects are required. This study will be open-label because the study endpoints are not considered subjective.

Omeprazole is a well-established PPI and has been used in clinical drug interaction studies.

The proposed regimen for omeprazole in this study is to take omeprazole alone QD for 5 days followed by coadministration of omeprazole and sotorasib plus an acidic beverage. An acidic beverage is expected to temporarily lower gastric pH. The 5-day lead-in period is to maximize the antisecretory effect because the inhibition of acid secretion increases with repeated QD dosing, reaching a plateau after 4 days.[12]

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.[14] 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. Please refer to the IB[1] for more information.

In this study, the 40 mg omeprazole dose will be administered orally. This is a clinically recommended dose level and a dose level used to evaluate clinical drug interactions.

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 ECGs, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
4. Body mass index between 18 and 30 kg/m^2 (inclusive) at the time of Screening.
5. Females must be of nonchildbearing potential, defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, 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 degree atrioventricular (AV) block or third degree AV 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 achlorhydria, 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 mL/min/1.73 m^2 as calculated by the CKD-EPI Creatinine Equation[18], at Screening or Check-in. Subjects with out-of-range values may have the test repeated once at the discretion of the Investigator.
10. ALT or AST should be ≤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 ≤ULN or if the repeated values above ULN are deemed not clinically significant by the Investigator [eg, 1.5 x 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. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges within 7 days prior to Check-in.
15. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.
16. Alcohol consumption from 48 hours prior to Check-in.
17. Regular alcohol consumption of > 14 units per week for males and > 7 units per week for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
18. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
19. Positive test for illicit drugs, cotinine (tobacco or nicotine use) at Screening or Check-in and/or alcohol use at Check-in only.
20. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
21. Female subjects with a positive pregnancy test at Screening or Check-in.
22. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through 7 days after the EOS.
23. Unwilling to adhere to contraceptive requirements through 7 days after the EOS (see).
24. Unwilling to abstain from sperm donation through 7 days after the EOS (see).
25. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
26. 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.
27. 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.
28. Have previously completed or withdrawn from this study or any other study investigating sotorasib or have previously received the investigational product.
29. 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.
30. Receipt of blood products within 2 months prior to Check-in.
31. Unwilling to abide with study restrictions.
32. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

33. Performed strenuous exercise, began a new exercise program, or participated in any unusually strenuous physical exertion within 7 days prior to Check-in.

4.3. Screen Failures and Rescreening

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

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

4.4. Subject Number and Identification

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

will 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, or until the unresolved 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 and Non-Investigational Products

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in Table 1.

The Investigator will commercially source the non-IMP shown in Table 1. The non-IMP will be stored according to the manufacturer's instructions.

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.

Table 1: Investigational Products and Non-Investigational Products

	Amgen Investigational Medicinal Product:	**Non-Amgen Investigational Medicinal Product:**
Study Treatment Name	Sotorasib (AMG 510)	Omeprazole
Unit Strength and Formulation	120 mg tablet	40 mg delayed release capsule
Dosage Level	960 mg (8 x 120 mg tablets)	40 mg (1 x 40 mg capsule)
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 non-investigational product are to be recorded on each subject's electronic Case Report Form.
Dosing Instructions	The Investigator/designee will administer the treatment after the completion of all predose procedures. **Day 1**: Eight tablets will be administered with 8 ounces (240 mL) of water after an overnight fast of at least 10 hours. No food will be given for at least 4 hours postdose. **Day 9**: Omeprazole will be administered followed by 960 mg sotorasib within 5 minutes. Omeprazole and sotorasib will be taken with 8 ounces (240 mL) of an acidic beverage (Coca-Cola®) after an overnight fast of at least 10 hours. No food will be given for at least 4 hours post sotorasib administration.	The Investigator/designee will administer the treatment after the completion of all predose procedures. **Days 4 to 8**: One capsule will be administered with 8 ounces (240 mL) of water after an overnight fast of at least 10 hours. **Day 9**: Omeprazole will be administered followed by 960 mg sotorasib within 5 minutes. Omeprazole and sotorasib will be taken with 8 ounces (240 mL) of an acidic beverage (Coca-Cola®) after an overnight fast of at least 10 hours. No food will be given for at least 4 hours post sotorasib administration.

Note: Only Coca-Cola® will be consumed with omeprazole and sotorasib on Day 9.

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. No food will be given for at least 4 hours post sotorasib administration.

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

5.2. Treatment 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 possibly related to over dosage, and to discuss further management of the subject.

5.3. 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 example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.4. 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 or 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 IMP (sotorasib) and non-IMP (omeprazole) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an IMP supplied by the Sponsor are to be reported according to the instructions provided in the Amgen Investigational Product Information Manual.

5.5. Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

5.6. Blinding

This is an open-label study.

5.7. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses of sotorasib and omeprazole 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 sotorasib and omeprazole will be performed.

5.8. 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.

At the completion of the study, all unused sotorasib tablets will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

Omeprazole will also be subject to accountability procedures, and the CRU staff will destroy unused supplies of omeprazole per the Sponsor's written instructions.

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 visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Paracetamol/acetaminophen (2 g/day) are acceptable concomitant medications. 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 1 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 the EOS visit, with the exception of the Day 9 visit (dosing plus an acidic beverage).

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

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 visit.

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, safety laboratory assessments, and assessment of adverse events and 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. If an event is reported as beginning prior to signing of the ICF or occurs prior to initiation of study treatment on Day 1 and is assessed as not related to study procedures by the Investigator (or designee), the event will be recorded as subject medical history. If an event occurs after signing of the ICF but prior to initiation of study drug and the event is considered serious (regardless of causality to procedure), the event will be recorded as a serious adverse event.

Any events occurring after study drug administration on Day 1 through EOS will be reported as adverse events. 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 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 for 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

After EOS, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the Investigator. However, if the Investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to the Sponsor within 24 hours following the Investigator's awareness of the event.

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 the 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 a 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 towards 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, 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 and pregnancies in female partners of male subjects will be collected after the start of the 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 the Case Report Form/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 judgement) 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 laboratory abnormalities outside the reference range that are deemed clinically meaningful during the study period will have follow-up laboratory assessments 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 HR, 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 taken of the 3 readings, if either of the following criteria apply:

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

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

7.2.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 8.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately 14 subjects will be enrolled in order that approximately 12 subjects complete the study. The sample size for this study was based upon precedent set by other PK studies of a similar nature and was 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. The PK population for the primary endpoint analysis will include all subjects who received both sotorasib, and sotorasib in combination with omeprazole and an acidic

beverage, and have evaluable PK data. A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event of vomiting that occurs at or before 2 times median t_{max} or diarrhea within 24 hours of dosing.

8.2.2. Safety Population

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

8.3. Pharmacokinetic Analyses

The plasma PK parameters of sotorasib on Days 1 and 9 will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max}, AUC_{inf}, and AUC_{last} for sotorasib. A linear mixed-effects model will be used to analyze log-transformed primary PK parameters. The model will assume fixed effect for treatment and a random effect for subject. Geometric mean ratios for C_{max} and AUC values and associated 90% confidence intervals (Test/Reference) will be estimated. The "Reference" treatment for PK analysis will be sotorasib administered alone with water, while the "Test" treatment will be omeprazole administered in combination with sotorasib and an acidic beverage.

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.

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10. APPENDICES

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

Definition of Adverse Event

Adverse Event Definition
• 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
• 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 events or serious adverse events if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • 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 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 the 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 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 or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem 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) suspected to be related to investigational product will be reported to Amgen 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 20220024 Labcorp Study# 8493285 *Sotorasib* *(AMG 510)*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑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	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex ❑F ❑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 Sotorasib No Yes / <<Device>> No Yes / <<Device>> No Yes / <<Device>> No Yes / <<Device>> No Yes	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

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑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 #
Sotorasib ❑Blinded ❑Open Label							Lot # _____ ❑ Unknown Serial # _____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot # _____ ❑ Unknown Serial # _____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot # _____ ❑ Unknown Serial # _____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot # _____ ❑ Unknown Serial _____ ❑ Unknown

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A 20220024 Labcorp Study# 8493285 *Sotorasib* *(AMG 510)*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

A 20220024 Labcorp Study# 8493285 *Sotorasib* *(AMG 510)*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	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.

Signature of Investigator or Designee	Title	Date
_____ *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.*		

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 Magnesium Potassium Sodium Total bilirubin[a] Total CO2 (measured as bicarbonate) Total creatine kinase 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 virus (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Cotinine test Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Alcohol urine or alcohol breath test (Check-in only)	Follicle-stimulating hormone[b] (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[d]
		Other tests:
		International normalized ratio (INR)[e] Estimated glomerular filtration rate (eGFR)[c,f] Thyroid-stimulating hormone[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 at Screening, Check-in, and at the end of study or if a subject is withdrawn early from the study. 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] International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in Appendix 7.
[f] Calculated by the Modification of Diet in Renal Disease equation.
[g] Only analyzed at Screening, Check-in, and at end of study.

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	50.0
Serology	7.0	1	7.0
Sotorasib pharmacokinetics	4.0	28	112.0
Total:			169.0

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) visit.

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 required to use contraception.

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 visit. 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 visit.

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, postovulation methods) and withdrawal are not acceptable methods of contraception.

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

Same-sex Relationships

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

If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception from the time of signing the ICF until 7 days after the EOS visit.

Appendix 5: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

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

Collection of Lactation Information

- The 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 awareness of the 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 discontinuing protocol-required therapies.

Figure 3: Pregnancy Notification Form

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: Amgen protocol number 20220024 Labcorp study number 8493285

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Figure 4: Lactation Notification Form

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: Amgen protocol number 20220024 Labcorp study number 8493285

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator' 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 21 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), 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 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.

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

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

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

Documents that are not submitted to Amgen (eg, 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, rhabdomylosis, hemolysis).

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

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

Table 2: 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	-- OR	>1.5x ULN (for subjects not on anticoagulation therapy) 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) OR	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values >3x ULN (when baseline was < ULN)
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 2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

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

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

Additional Clinical Assessments and Observation

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

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL >2x ULN or INR > 1.5, retesting of liver tests, bilirubin (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 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 are 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

Study Procedures	Screening	Check-in	Sotorasib (Day 1) and Omeprazole (Day 4-8) Alone					Sotorasib in Combination with Omeprazole and acidic beverage		
	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Days 4 to 7	Day 8	Day 9	Day 10	Day 11 (EOS/ET)
Confined to the CRU		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[a]								
Height and BMI	X									
Weight	X	X								X[b]
Drug Screen	X	X								
Alcohol Test		X								
Pregnancy Test (females only)[c]	X	X								X[b]
FSH (postmenopausal females only)	X									
12-lead Electrocardiogram[d]	X	X	X					X		X[b]
Vital Signs[e]	X	X	X	X	X			X	X	X[b]
Clinical Laboratory Evaluations[f]	X	X					X			X[b]
eGFR[g]	X	X								
Thyroid-stimulating Hormone	X	X								X
Physical Examination[h]	X	X								X[b]
Sotorasib Dose[i]			X					X		
Omeprazole Dose[j]						X	X	X		
Sotorasib PK Blood Samples[k]			X	X	X			X	X	X
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; AT = early termination; FSH = follicle-stimulating hormone; PK = pharmacokinetic.

[a] Interim medical history only.

[b] Assessment to be performed at the EOS or ET.

[c] 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.

[d] Electrocardiograms (ECGs) 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. ECGs will be assessed at Screening, Check-in, at predose on Days 1 and 9, and at 0.5, 2, and 4 hours following sotorasib administration; and at 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.

[e] Vital signs measurements (oral body temperature, respiratory rate, supine blood pressure, and supine heart rate) will be carried out, prior to having blood drawn, at Screening, Check-in, predose, and at 1, 24, and 48 hours after each dose of sotorasib, and at EOS or ET. Blood pressure and heart rate 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.

[f] Clinical chemistry (fasted at least 8 hours), hematology, and urinalysis.

[g] eGFR will be calculated using the Modification of Diet in Renal Disease equation.

[h] A full physical examination at Screening and Check-in and a symptom-directed physical examination at EOS or ET.

[i] Dose administration of sotorasib is to occur during the mornings of Days 1 and 9 following an overnight fast of at least 10 hours. On Day 9, sotorasib administration will occur within 5 minutes after administration of omeprazole with an acidic beverage (Coca-Cola®).

[j] Dose administration of omeprazole is to occur during the mornings of Days 4 through 9 following an overnight fast of at least 10 hours.

[k] Blood samples for determination of sotorasib plasma concentrations and PK parameters will be collected: Predose (Hour 0), 0.5 , 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours postdose following administration of sotorasib on Days 1 and 9. The PK sample collected 30 minutes postdose will have a sampling window of ± 2 minutes, samples collected from 1 through 3 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 or ET. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form through 30 days after the last dose of study treatment or until EOS or ET (whichever is later).

[m] Prior and concomitant medication administration will be recorded from the time the subject signs the Informed Consent Form. In addition, all Investigator-approved medications (prescription or over the counter), all herbal medicines (eg, St. John's wort), vitamins, and supplements taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to enrollment will be recorded on the subject's electronic Case Report Form.