Protocol

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

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INVESTIGATOR AGREEMENT

I have read the protocol entitled "An Open-label Single-dose Study to Evaluate the Pharmacokinetics of Sotorasib in Subjects with Moderate and Severe Hepatic Impairment Compared to Healthy Subjects" and agree to conduct the study as described herein.

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

STUDY IDENTIFICATION

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SYNOPSIS

Title of study: An Open-label Single-dose Study to Evaluate the Pharmacokinetics of Sotorasib in Subjects with Moderate or Severe Hepatic Impairment Compared to Healthy Subjects

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (PK) of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function.

The secondary objective of the study is:

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

Study design:

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

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

The classification is based on Child-Pugh scores as per Figg and Dukes.

Attempts will be made to match for age (mean ± 10 years), sex, and body mass index (mean ± 20%) of the healthy subjects to the combined moderate and severe impairment subjects.

Up to 8 subjects can be enrolled in Group 1 to satisfy matching criteria. Up to 8 subjects will be enrolled in Groups 2 and 3 to ensure 6 evaluable subjects. Subjects will maintain the same group assignment throughout the study.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the study site on Day 1 and be confined until discharge on Day 8. On Day 1, after at least a 10-hour fast, all subjects will receive a single oral dose of 960 mg sotorasib (8 x 120-mg tablets).

Number of subjects:

Approximately up to 24 subjects will be enrolled, with a minimum of 6 evaluable subjects and a maximum of up to 8 subjects in Group 1, and a maximum of 16 subjects enrolled in Groups 2 and 3 (8 subjects in each hepatic impairment group to ensure 6 evaluable subjects).

Diagnosis and main criteria for inclusion: Male subjects or female subjects, aged between 18 and 70 years (inclusive); with a body mass index between 18.0 and 38.0 kg/m^2 (inclusive); with normal hepatic function, moderate hepatic impairment, or severe hepatic impairment. Female subjects will be of nonchildbearing potential.
Investigational products, dose, and mode of administration: 960 mg sotorasib, given orally as 8 x 120-mg tablets, on Day 1 following at least a 10-hour fast.
Duration of subject participation in the study: The total duration of study participation for each subject (from Screening through end of study) is anticipated to be approximately 4 weeks.
Primary Endpoints: The primary endpoints of the study are PK parameters for sotorasib: • maximum observed plasma concentration (C_{max}) • area under the plasma concentration‑time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last}) • AUC from time zero to infinity (AUC_{inf}). Additional PK parameters may be calculated. **Secondary Endpoints:** The secondary endpoints of the study are: • adverse events • clinical laboratory evaluations • 12-lead electrocardiograms • vital signs • unbound C_{max} ($C_{max,u}$) • unbound AUC_{last} ($AUC_{last,u}$) • unbound AUC_{inf} ($AUC_{inf,u}$) • unbound apparent total plasma clearance (CL_u/F) • unbound apparent volume of distribution during the terminal phase ($V_{z,u}/F$).

Statistical methods:
The primary PK parameters are C_{max}, AUC_{last}, and AUC_{inf} for sotorasib. Other PK parameters for sotorasib may include time of maximum observed concentration (t_{max}), apparent plasma terminal elimination half-life ($t_{1/2,z}$), apparent total plasma clearance (CL/F), apparent volume of distribution during the terminal elimination phase (V_z/F), unbound fraction (f_u), $C_{max,u}$, $AUC_{last,u}$, $AUC_{inf,u}$, CL_u/F, and $V_{z,u}$/F. A linear model will be used to analyze log-transformed primary PK parameters. The data from hepatically impaired subjects (Group 2 and 3; tests) and control subjects (normal hepatic function [Group 1]; reference) will be included in the analysis. Geometric mean ratios (Test/Reference) for C_{max} and AUC values and associated 90% confidence intervals will be estimated.

Additional parameters may be calculated, and sotorasib metabolites may be analyzed. Specific details will be presented in the Statistical Analysis Plan for this study.

Safety analysis:
The number and percentage of subjects reporting any treatment-emergent 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.
Observed values for clinical laboratory data, 12-lead electrocardiograms, and vital signs will be summarized. There will be no formal statistical analysis for safety.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
$AUC_{inf,u}$	unbound 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
CFR	Code of Federal Regulations
CL_u/F	unbound apparent total plasma clearance
C_{max}	maximum observed plasma concentration
$C_{max,u}$	unbound maximum observed plasma concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
KRAS	Kirsten rat sarcoma viral oncogene homolog
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
QD	once daily

QTcF	QT interval corrected for heart rate using Fridericia's method
RBC	red blood cell
$t_{1/2,z}$	apparent plasma terminal elimination half-life
TBL	total bilirubin
t_{max}	time of the maximum observed plasma concentration
ULN	upper limit of normal
$V_{z,u}/F$	unbound apparent volume of distribution during the terminal phase
WBC	white blood cell

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. Sotorasib is one such small molecule that specifically and irreversibly inhibits the protein product of a mutant *KRAS* gene, which results in a G12C mutation at the protein level (*KRAS p.G12C*). One mutant version of *KRAS*, *KRAS p.G12C*, which encodes the $KRAS^{G12C}$ protein, might be tractable for small molecule inhibition through a covalent interaction with the mutant cysteine[3,4,5] found in approximately 13% of lung adenocarcinoma (nonsquamous, non-small---cell lung carcinoma), 3% of colorectal cancer, and 1% to 2% of numerous other solid tumors.[6,7,8] Sotorasib forms a specific covalent bond with the mutant 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 harboring *KRAS* mutations,[3,4,9,10,11] sotorasib may provide a therapeutic benefit for patients with *KRAS p.G12C*-driven cancers.

The metabolism and excretion of sotorasib were evaluated in bile duct-cannulated male rats after a single intravenous (1 mg/kg) or oral (10 mg/kg) dose of sotorasib. Recovery of sotorasib and metabolites was low (< 10%) in the study, consistent with extensive metabolism of sotorasib. Metabolite profiling by liquid chromatography high-resolution mass spectrometry (LC-HRMS) methods identified low amounts of sotorasib and metabolites excreted into bile (approximately 0.4% to 3.4% of dose), feces (approximately 1.0% to 2.2% of dose), and urine (0.4% to 1.7% of dose) following both intravenous and oral administration, with metabolites that included products of oxidative metabolism and glucuronidation (M3, M4, M16), cysteine and N-acetyl cysteine conjugation (M10, M15, M20), reduction (M21), and dealkylation (M24). Refer to the IB[1] for more information.

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

Preliminary data are available for phase 1 of the phase 1/2 Study 20170543 that evaluates the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in subjects with *KRAS p.G12C*-mutated advanced solid tumors as monotherapy and in combination with

pembrolizumab. As of 01 June 2020, 199 subjects were enrolled in the phase 1 monotherapy treatment cohorts; of these, 197 subjects received at least 1 dose of sotorasib (dose range: 180 to 960 mg).

1.2. Pharmacokinetics

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

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

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

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

More details of these studies are available in the IB.[1]

1.3. Study Rationale

The liver plays a significant role in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretions. Alterations of these excretory and metabolic activities by hepatic impairment can lead to increased drug exposure and toxicity. As outlined in the Food and Drug Administration (FDA) Guidance for Industry,[12] PK studies are recommended in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for >20% of the elimination of a parent drug or active metabolite.

Results from this study will provide information on the safety, tolerability, and PK of sotorasib and guide dosing in subjects with normal hepatic function and in subjects with moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C).

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

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

Risks of Sotorasib

Based on clinical and nonclinical toxicity studies of sotorasib, the key safety information to be monitored in clinical studies of sotorasib include abnormal liver function tests, renal toxicity, anemia, leukocytosis, thyroid abnormalities, and splenomegaly. Clinical signs and symptoms of these toxicities observed in clinical and nonclinical studies, along with relevant laboratory parameters, will be monitored during the study to ensure subjects' safety.

Abnormal Liver Function Tests

Abnormal liver function tests (increased aspartate aminotransferase [AST] and increased alanine aminotransferase [ALT]) have been observed in oncology subjects receiving both sotorasib monotherapy and combination therapy with sotorasib and anti-programmed cell death protein 1 (PD-1) antibody. 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 criteria and dose-modification guidelines for sotorasib are provided in Section 4.

Renal Toxicity

Sotorasib-related degeneration/necrosis of renal tubule epithelium was observed in the rat repeated-dose toxicology studies. The incidence and severity of tubular degeneration/necrosis was dependent on dose/exposure levels and treatment duration. In the 28-day study, 2 of 20 animals at 200 mg/kg (the highest dose tested) had minimal to mild change. In the 3-month study, the same renal change progressed to a chronic change that involved more of the renal tubule, which was attributed to higher exposures and longer study duration (60 mg/kg: 7/20 [6 minimal and 1 mild], 180 mg/kg: 12/19 [5 minimal, 6 mild, and 1 moderate], and 750 mg/kg: 20/20 [4 minimal, 13 mild, 1 moderate, and 2 marked]). Partial recovery was confirmed at the end of the recovery phase; however, marked tubular degeneration/necrosis was also accompanied with interstitial fibrosis and glomerulosclerosis, which are considered irreversible changes. The changes in renal tubular injury biomarkers in urine were observed as early as Day 8, with the largest magnitude of increase for kidney injury molecule (KIM)-1 and clusterin generally occurring at this timepoint, and were observed predominantly in animals at 750 mg/kg.

The risk mitigation plan consists of monitoring of renal function with measurement of the serum creatinine and/or estimated creatinine clearance along with urinalysis examinations. Specific eligibility criteria to only include subjects with adequate renal function are included, as described in Section 4.

Anemia

Sotorasib-related decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) was observed in both rat and dog toxicology studies. In the rat studies, decreased RBC cell mass was observed inconsistently associated with secondary physiologically appropriate increases in reticulocyte counts, and increases in RBC indices and platelets. Increased reticulocytes correlated with minimally increased hematopoiesis in the spleen were seen only in the 28-day rat study. In the dog studies, minimal to mild decreases in RBC mass were seen associated with decreased reticulocytes. Due to the small magnitudes of change, the sotorasib-related effects on hematology parameters were considered non-adverse and were reversible after a 28-day recovery in rats; reversibility was expected based on the normal regenerative capacity of the hematopoietic system and the absence of overt bone-marrow toxicity (eg, hypocellularity).

The risk mitigation plan consists of monitoring hemoglobin, hematocrit, and associated adverse events. Specific eligibility criteria and dose-modification guidelines pertaining to hematology parameters are provided in Section 4.

Leukocytosis

Sotorasib-related increased leukocytes were observed in the rat repeated-dose toxicology studies, including increases in white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and large unstained cells with no light microscopic correlates. Due to the small magnitudes of change, the sotorasib-related effects on hematology parameters were considered non-adverse and were not observed after recovery period. The risk mitigation plan consists of monitoring WBC count and differential and associated adverse events.

Thyroid Dysfunction

In the 3-month dog toxicology study (0, 200, and 1000 mg/kg/day administered as 0, 100 and 500 mg/kg twice daily), there was abnormal content in the gall bladder and microscopic changes in the liver, pituitary, or thyroid that were considered to be either non-severely toxic and/or adaptive or secondary responses to hepatocellular enzyme induction. In the thyroid, mild to moderate follicular cell hypertrophy and moderate to marked colloid depletion were observed accompanied with decreased thyroid weights. A few animals at 1000 mg/kg/day also had marked atrophy of the thyroid. The risk mitigation plan consists of monitoring thyroid function with regular measurement of serum triiodothyronine (T3), free thyroxine (T4), and thyroid-stimulating hormone (TSH), and for any clinical signs or symptoms concerning for thyroid dysfunction.

Splenomegaly

Sotorasib-related increase in spleen weights was observed in males at ≥ 100 mg/kg in a Good Laboratory Practice 28-day rat toxicology study. At 100 and 200 mg/kg, spleen weights were increased up to 21% and these increases were not observed at the end of the 28-day recovery period. Although minimal increased hematopoiesis was observed in the spleen at 200 mg/kg, the degree of increased hematopoiesis was interpreted to be insufficient to account for increased spleen weights. There was no sotorasib-related change in spleen weight in the rat 3-month study. The risk mitigation plan consists of monitoring the size of the spleen (with physical examination) and hematology parameters.

More detailed information about the key safety information of sotorasib, including a list of adverse drug reactions, may be found in the sotorasib IB.[1]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function.

The secondary objective of the study is:

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

2.2. Endpoints

2.2.1. Primary Endpoints

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

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

Additional PK parameters may be calculated.

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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

based on the Child-Pugh score at Screening. The Child-Pugh scores classification is described in Appendix 3.

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

Table 1: Classification of Hepatic Impairment Groups

Group	Degree of Hepatic Impairment	Number of Subjects
1	Normal function (no impairment)	6 to 12
2	Moderate impairment (Child-Pugh Class B)	6 to 8
3	Severe impairment (Child-Pugh Class C)	6 to 8

The classification is based on Child-Pugh- scores as per Figg and Dukes.[13] Child-Pugh scores classification is described in Appendix 3.

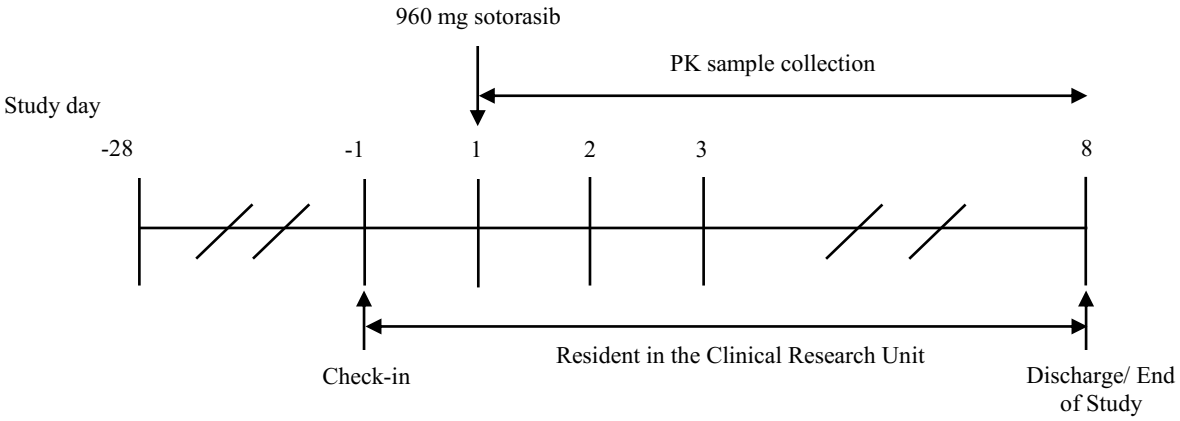
Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the study site on Day 1 and be confined until discharge on Day 8. On Day 1, after at least a 10-hour fast, all subjects will receive a single oral dose of 960 mg sotorasib (8 x 120-mg tablets).

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

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

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

Figure 1: Study Schematic



A Schedule of Assessments is presented in Appendix 8.

3.2. Discussion of Study Design

This study has been designed in accordance with the FDA regulatory guidance for the study of PK in subjects with impaired hepatic function.[12]

A single-dose, parallel design is the standard design to investigate the PK of a drug in subjects with hepatic impairment. A parallel design is required to include subjects with hepatic impairment and control subjects with normal hepatic function. Control healthy subjects with normal hepatic function will be enrolled in this study to serve as a reference group for interpretation of the results. The safety and PK assessments are standard parameters for clinical studies in drug development.

This study will be open label because the study endpoints are not considered subjective.

3.3. Selection of Doses in the Study

The 960-mg dose was selected for the present study because this is the recommended dose in the Phase 2 portion of an ongoing clinical study (Study 20170543). Sotorasib is primarily metabolized by CYP3A4. Study 20190318 evaluated the impact of itraconazole (a strong CYP3A4 inhibitor) on the PK of 360 mg sotorasib in healthy subjects. Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 1.261 and 1.040, respectively, when comparing sotorasib coadministered with itraconazole (test) and sotorasib administered alone (reference). Doses of 360 mg sotorasib were safe and well tolerated when coadministered with 200 mg itraconazole to healthy subjects. The mean magnitude of the relative effect in this hepatic impairment study is anticipated to be similar to the past DDI study with a potent CYP3A4 inhibitor. A substudy in Study 20170543 evaluated the food effect on 960 mg sotorasib PK in patients with advanced solid tumors. Coadministration with high-fat meals resulted in a geometric least squares mean ratio (test/reference) of 1.25 and 0.66 for AUC from time zero to

24 hours postdose (AUC_{0-24}) and C_{max}, respectively. Exposure in this hepatically impaired population is anticipated to be similar to those exposures observed in Study 20190318 and food-effect substudy in Study 20170543.

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

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

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

All subjects:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Male subjects or female subjects, between 18 and 70 years of age (inclusive) at the time of Screening.
3. Body mass index between 18.0 and 38.0 kg/m^2 (inclusive) at the time of Screening.
4. Females 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).

Subjects with Normal Hepatic Function Only (Group 1)

5. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).

Subjects with Hepatic Impairment Only (Groups 2 and 3)

6. Child-Pugh B (Group 2) or C (Group 3) classification (Appendix 3) defined by both Screening and Check-in clinical laboratory values and clinical examination findings.
7. Clinically stable hepatic disease in the opinion of the Investigator (eg, not including rapidly progressive primary or secondary hepatic malignancy). Documented medical history of chronic liver disease including, but not limited to, liver cirrhosis, hepatitis B infection, alcoholic liver disease, or previous hepatitis C virus (HCV) infection (HCV RNA to be undetectable in all enrolled subjects at Screening) or as assessed by the Investigator (or designee).

8. Subjects with moderate or severe hepatic impairment may have medical findings consistent with their hepatic dysfunction, as determined by medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations at Screening and Check-in. Subjects with abnormal findings considered not clinically significant by the Investigator will be eligible.

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:

All subjects:

1. Any unstable medical condition, defined as having been hospitalized within 21 days before Check-in, major surgery within 6 months before Check-in, or otherwise unstable in the judgment of the Investigator and/or Medical Monitor (eg, risk of complications or adverse events unrelated to study participation).
2. History or evidence, at Screening or Checkin-, 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.
3. Venous thromboembolic disease in the last 6 months.
4. History of malignancy of any type, with the exception of the following: in situ cervical cancer or surgical excised nonmelanomatous skin cancers more than 5 years before receiving sotorasib.
5. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
6. History suggestive of esophageal (including esophageal spasm, esophagitis), gastric, or duodenal ulceration or bowel disease (including but not limited to peptic ulceration, gastrointestinal bleeding, ulcerative colitis, Crohn's disease, or irritable bowel syndrome); or a history of gastrointestinal surgery other than uncomplicated appendectomy cholecystectomy, and hernia repair.
7. Inability to swallow oral medication or history of malabsorption syndrome.
8. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
9. Poor peripheral venous access.
10. Estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) equation, at Screening or Checkin.
11. Positive human immunodeficiency virus test at Screening.

12. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) prior to study Day 1 that was not reviewed and approved by the Investigator (or designee) and the Sponsor, which include known CYP3A4 and P-gp-sensitive substrates (with a narrow therapeutic window) and strong inducers of CYP3A4 (including herbal supplements such as St. John's wort), with below exceptions.
    a. Ibuprofen and hormone-replacement therapy (eg, estrogen, thyroid) will be allowed.
    b. Therapies for hepatic disease and treatments of associated disorders that have been stable for at least 30 days prior to study drug administration and deemed acceptable, by the Investigator (or designee) and the Sponsor, to be given concurrently with sotorasib during the study period.
13. Administration of an approved (authorized) Coronavirus Disease 2019 (COVID-19) vaccine in the past 28 days prior to dosing or a COVID-19 vaccine given Emergency Use Approvals (US) in the past 30 days prior to dosing.
14. 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.
15. Consumption of foods and beverages containing poppy seeds, grapefruit, or Seville oranges within 7 days prior to Check-in.
16. History of alcoholism or drug/chemical abuse within the last 3 months prior to Check-in.
17. Alcohol consumption from 48 hours prior to Check-in.
18. Regular alcohol consumption of > 14 units per week for males and > 7 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
19. Use of tobacco- or nicotine-containing products within 3 months prior to Check-in.
20. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Check-in.
21. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
22. Female subjects with a positive pregnancy test at Screening or Check-in.
23. Male subjects (with a female partner of childbearing potential) who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or unwilling to adhere to contraceptive requirements through 7 days after sotorasib dosing (see Appendix 4).
24. Unwilling to abstain from sperm donation and ovum donation through 7 days after sotorasib dosing (see Appendix 4).
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 or use a condom for 7 days after sotorasib dosing.
27. Subject has received a dose of an investigational drug (new chemical entity) 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 3 months 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.

Subjects with Normal Hepatic Function Only (Group 1)

33. Positive hepatitis B or hepatitis C panel at Screening. Subjects whose results are compatible with prior immunity (vaccination or prior infection) may be included.
34. ALT or AST > upper limit of normal (ULN) at Screening or Check-in.
35. Total bilirubin levels > ULN at Screening or Check-in.
36. A QT interval corrected for heart rate 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 at Screening or Check-in, confirmed by calculating the mean of the original value and 2 repeats.

Subjects with Hepatic Impairment Only (Groups 2 and 3)

37. Values outside the normal range for liver function tests that are not consistent with their hepatic condition, as determined by the Investigator (or designee).
38. A QTcF interval > 470 msec in male subjects or > 480 msec in female subjects at Screening or Check-in, confirmed by calculating the mean of the original value and 2 repeats.
39. Use of a new medication, or a change in dose, for the treatment, or worsening of, hepatic encephalopathy within 30 days prior to Check-in.
40. Recent history of, or the treatment of, gastrointestinal bleeding (within the past 6 months).
41. Presence of a portosystemic shunt.
42. Recent history of paracentesis within 30 days prior to Check-in.
43. Current functioning organ transplant or are waiting for an organ transplant.
44. Evidence of severe ascites.

45. History within 60 days prior to the Screening visit or current symptoms of hepatic encephalopathy Grade 2 or above.

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. 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.

If a subject has not met all eligibility criteria the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening one time, at the discretion of the Investigator in consultation with the Sponsor.

Rescreened subjects must first be documented as screen failures, and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 20-day Screening window will begin. Subjects will retain the same subject identification number assigned at the original Screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all Screening procedures including informed consent must be repeated.

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 (Section 4.5) 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)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from the study, the Sponsor 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 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 GCP. 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.

5. STUDY TREATMENTS

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

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

5.1. Investigational Product

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

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

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

Table 2: Investigational Product(s)

	Investigational Medicinal Product: Sotorasib
Study Treatment Name	
Unit Strength and Formulation	120-mg tablet
Dosage Level	960 mg (8 x 120 mg)
Route of Administration	Oral
Accountability	The quantity administered, date administered, and lot number of investigational product are to be recorded on each subject's Case Report Form.
Dosing Instructions	The Investigator/designee will administer the treatment after the completion of all predose procedures and after a fast of at least 10 hours. Eight tablets of sotorasib should be taken with up to 16 ounces (480 mL) of water. Tablets should not be broken or chewed. No food will be given for at least 4 hours post sotorasib administration.

Except as part of the dose administration, subjects will restrict their consumption of water for 1 hour prior to dosing and for 2 hours after dosing; at all other times during the study, subjects may consume water as desired. Subjects will continue fasting for at least 4 hours postdose.

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

5.2. Treatment of Overdose

Neither the effects of overdose of sotorasib nor an antidote to overdose are known.

5.2.1. 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-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.

5.2.2. Product Complaints

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

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

5.3. Randomization

This is a non-randomized study. Subjects will receive their first dose of sotorasib in a gated fashion, with at least 3 moderately impaired subjects being dosed first followed by a period of at least 2 days before the remaining moderate or severely impaired subjects are dosed.

5.4. Blinding

This is an open-label study.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory of sotorasib will be performed.

5.6. 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.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

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

Subjects will refrain from use of any PPIs within 5 days or H2-receptor antagonists within 1 day prior to study Day 1 until at least 4 hours after IMP administration.

For hepatically impaired subjects, treatment for the underlying liver disease and comorbid conditions (including prescribed analgesia) will be permitted if prescribed by the subject's personal physician and approved by the Medical Monitor and Investigator, in consultation with the Sponsor as needed. Administration of medications should be withheld for at least 4 hours after study drug administration as clinically appropriate, unless needed for treatment of an adverse event, at the discretion of the Investigator. Throughout the study, the Investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria.

Foods and medicines that are known strong CYP3A4 inducers (eg, rifampin, corticosteroids, anticonvulsants, and St. John's wort) or CYP3A4 or P-gp substrates with narrow therapeutic index are prohibited prior to IMP administration as specified in the exclusion criteria (Section 4.2) and during the study until the EOS.

Ibuprofen and hormone-replacement therapy 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. 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

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

Refer to Section 5.1 and Table 2 for diet requirements/restrictions on Day 1.

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

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

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

6.3. Smoking

Subjects will not be permitted to use tobacco or nicotine-containing products within 3 months prior to Check-in until the EOS.

6.4. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Check--in until the EOS. Subjects will otherwise maintain their normal level of physical activity during this time (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 3 months prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 x 4 mL for sotorasib, approximately 1 x 4 mL for metabolites, and approximately 1 x 4 mL for unbound 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 and metabolites will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

Unbound fraction of sotorasib will be determined using an established plasma protein binding assay and analytical procedure. Specifics of the methods 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 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. 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 occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in Appendix 1.

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

Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of study treatment or the EOS (whichever is later) are reported using the appropriate eCRF and reported on the paper-based- Serious Adverse Event Report Form (described in Appendix 1).

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

Serious Adverse Events After the Protocol-required Reporting Period

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

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

Method of Detecting Adverse Events and Serious Adverse Events

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

Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed, where possible, until resolution, stabilization, until the event is

otherwise explained, or the subject is lost to follow-up. This will be completed at the Investigator's (or designee's) discretion.

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

Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

Safety Monitoring Plan

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

Pregnancy and Lactation

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

If a pregnancy and/or lactation 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 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 will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol test at the times indicated in the Schedule of Assessments in Appendix 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 pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 8. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

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

Subjects must be supine for at least 5 minutes before blood pressure and pulse 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 > 500 msec
- QTcF change from the baseline (predose) is > 60 msec.

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

7.2.5. Physical Examination

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

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

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

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

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

8.2.2. Safety Population

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

8.3. Pharmacokinetic Analyses

The plasma PK parameters of sotorasib will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max}, AUC_{last}, and AUC_{inf} for sotorasib. Other PK parameters for sotorasib may include time of t_{max}, apparent plasma terminal elimination half-life ($t_{1/2,z}$), apparent total plasma clearance (CL/F), apparent volume distribution during the terminal elimination phase (V_z/F), unbound fraction (f_u), $C_{max,u}$, $AUC_{last,u}$, $AUC_{inf,u}$, CL_u/F, and $V_{z,u}$/F. A linear model will be used to analyze log-transformed primary PK parameters. The data from hepatically impaired subjects (Group 2 and 3; tests) and control subjects (normal hepatic function [Group 1]; reference) will be included in the analysis. Geometric mean ratios (Test/Reference) for C_{max} and AUC values and associated 90% confidence intervals will be estimated.

Additional parameters may be calculated, and sotorasib metabolites may be analyzed. 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 treatment-emergent 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.

Observed values for clinical laboratory data, 12-lead ECGs, and vital signs will be summarized. There will be no formal statistical analysis for safety.

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10. APPENDICES

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

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 judgement 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.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening- even though drug-induced hepatitis can be fatal.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. 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 judgement 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);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures; and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to Sponsor in lieu of completion of the appropriate eCRF page.
- If specifically requested, the Investigator may need to provide additional follow-up- information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The Investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on the Common Terminology Criteria for Adverse Events, Version 5.0 or higher,

which is available at the following location:
https://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 judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

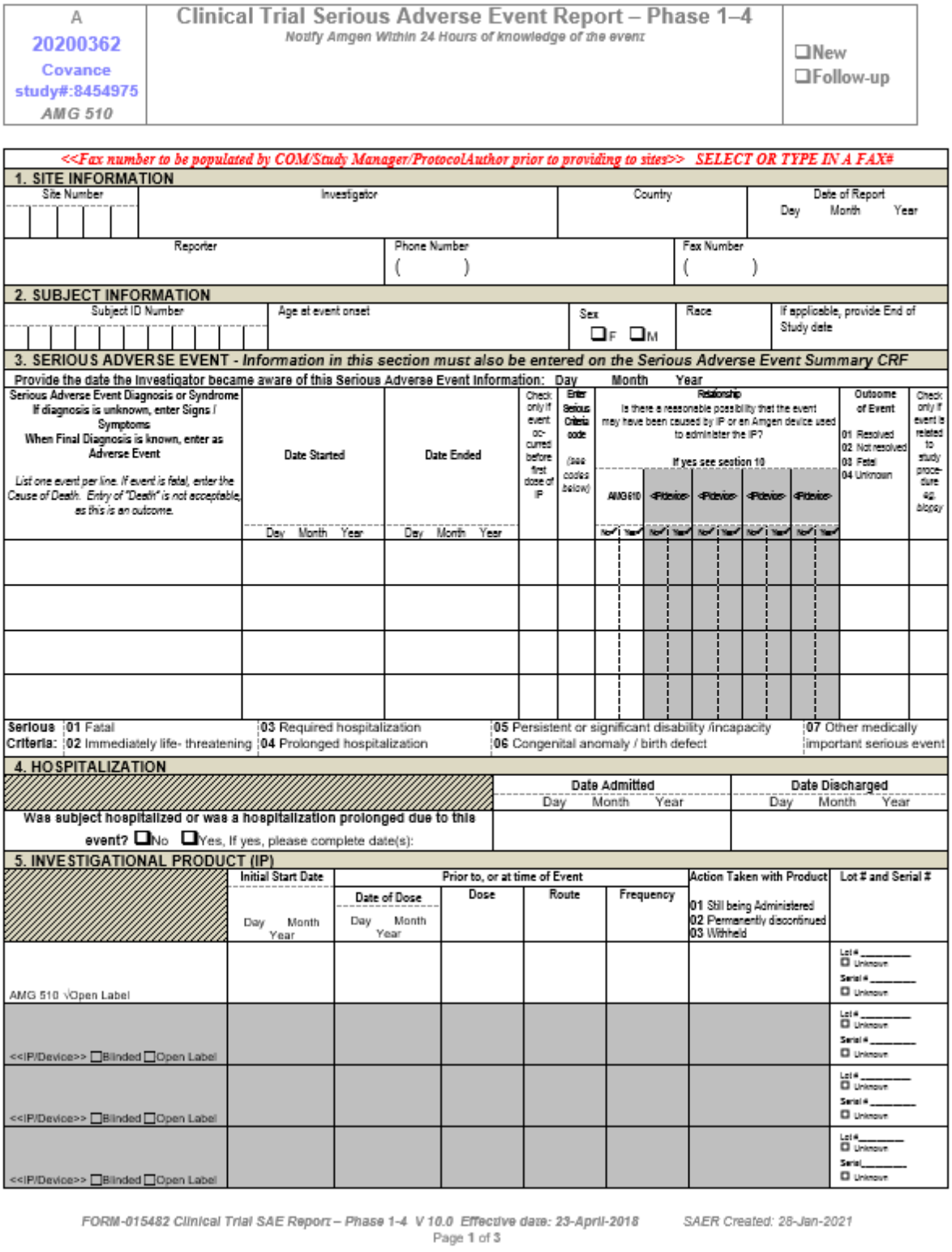
- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health-care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
- If a subject dies during participation in the study the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 2) is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 2: Sample Serious Adverse Event Report Form



A
20200362
Covance
study#:8454975
AMG 510

Clinical Trial Serious Adverse Event Report – Phase 1–4
Notify Amgen Within 24 Hours of knowledge of the event

☐New
☐Follow-up

<<Fax number to be populated by COM/Study Manager/ProtocolAuthor prior to providing to sites>> SELECT OR TYPE IN A FAX#

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	Race	If applicable, provide End of Study date
		☐F ☐M		

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 — AMG510 (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 #
AMG 510 √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

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 28-Jan-2021*
Page 1 of 3

A 20200362 Covance study#:8454975 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 20200362 Covance study#:8454975 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.*		

FORM-015482 Clinical Trial SAE Report – Phase 1-4 V 10.0 Effective date: 23-April-2018 *SAER Created: 28-Jan-2021*
Page 3 of 3

Appendix 2: Clinical Laboratory Evaluations

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

[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. Alcohol testing is not included at Screening.
[d] Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[e] INR will be tested if hepatotoxicity is suspected guidelines presented in Appendix 7.
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation.

Appendix 3: Child-Pugh Classification of Severity of Cirrhosis

Finding	Points Scored for Each Observed Finding		
	1	**2**	**3**
Encephalopathy[1]	None	1 or 2 (or suppressed with medication)	3 or 4 (refractory)
Ascites[2]	Absent	Slight or Subject on 1 medication to control ascites	Moderate or Severe or Subject on 2 medications to control ascites
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
INR	< 1.7	1.7 to 2.2	> 2.2

Abbreviation: INR = international normalized ratio

[1] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity

[2] Ascites is graded according to the following criteria:
Absent: No ascites detectable by manual investigation
Slight: Ascites palpitation doubtful
Moderate: Ascites detectable by palpation
Severe: Necessity of paracentesis, does not respond to medication treatment.

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 sotorasib dosing.

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 (FSH) 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

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects are required to refrain from donation of ovum from Check-in until 7 days after sotorasib dosing.

Male Subjects:

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 sotorasib dosing. Acceptable methods of contraception for female partners include:

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

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

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, 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 sotorasib dosing.

Same-sex Relationships

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

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

Appendix 5: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 7 days after sotorasib dosing.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's informed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 7 days after sotorasib dosing. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the Investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy that is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in Appendix 1. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 4.5 for details).

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

- In the event a male subject fathers a child during treatment, and for an additional 7 days after sotorasib dosing, 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 informed 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 informed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 7 days after sotorasib dosing.
- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.
- With the female subject's informed 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 sotorasib dosing.

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 20200362, Covance study number 8454976

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
AMG 510				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 20200362, Covance study number 8464976

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
AMG 510				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 Council for 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.)

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. 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, include the age at time of enrollment.

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

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

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

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

Disclosure

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

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

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

On the eCRF demographics page, in addition to the unique subject identification number, 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, 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 11compliant 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 (CRO), 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: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 x upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of "close observation" until abnormalities return to normal or to the subject's baseline level as described below.

Clinical Assessments and Observation
Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours
- In cases of total bilirubin (TBL) > 2 x 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.

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 diseases 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 drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic Case Report Form (eCRF).

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).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie, cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

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

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.

Appendix 8: Schedule of Assessments

Schedule of Assessments

Study Procedures	Screening	Check-in	Drug Administration							
	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 (EOS)
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[b]
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X[b]
Clinical Laboratory Evaluations[f]	X	X		X				X		X[b]
eGFR[g]	X	X								
Physical Examination[h]	X	X								X[b]
Sotorasib Dose[i]			X							
Sotorasib PK Blood Samples[j]			X	X	X	X	X	X	X	X
Sotorasib Metabolite PK Blood Samples[k]			X	X	X	X	X	X	X	X
Protein Binding[l]			X	X	X	X	X	X	X	X
Adverse Event Monitoring[m]			X							
Serious Adverse Event Monitoring[m]	X	X								
Prior/Concomitant Medications[n]	X	X								

Abbreviations: BMI = body mass index; CRU = Clinical Research Unit; D = day; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; PK = pharmacokinetic.

[a] Interim medical history only.
[b] Assessment to be performed at the End of Study (EOS) visit or early termination (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] 12-lead electrocardiograms will be collected after the subject has rested in the supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws at: Screening; Check-in; prior to and 0.5, 2, and 4 hours postdose following administration of sotorasib on Day 1; and EOS or ET. ECG should be collected prior to any PK corresponding timepoints. Three sets of triplicate ECGs to be collected at baseline and 1 set of triplicate ECGs to be collected at any other timepoints.
[e] Vital signs measurements (supine blood pressure [BP], supine pulse rate, respiratory rate, and oral body temperature) should be carried out prior to having blood drawn. Screening; Check-in; prior to sotorasib administration and 1, 2, and 24 hours following sotorasib administration on Day 1; and daily thereafter. Pulse rate and BP will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.
[f] Clinical chemistry (fasted at least 10 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 an abbreviated physical examination at EOS/ET.
[i] Dose administration of sotorasib will be given in the morning on Day 1 after a 10-hour fast.
[j] Blood samples for determination of sotorasib plasma concentrations will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose following administration of sotorasib on Day 1. The blood sample collected at 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 168 hours postdose will have a sampling window of ± 20 minutes. Times of all blood samples will be recorded to the nearest minute.
[k] Blood samples for determination of sotorasib metabolite plasma concentrations will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose following administration of sotorasib on Day 1. The blood sample collected at 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 168 hours postdose will have a sampling window of ± 20 minutes. Times of all blood samples will be recorded to the nearest minute.
[l] Blood samples for determination of unbound fraction will be collected: Predose (Hour 0), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours postdose following administration of sotorasib on Day 1. The blood sample collected at 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 168 hours postdose will have a sampling window of ± 20 minutes. Times of all blood samples will be recorded to the nearest minute.
[m] Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the ICF until 30 days after the last dose of study treatment or the EOS (whichever is later).
[n] Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) prior to Check-in for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (eg, St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic Case Report Form.