Title Page

Protocol Title:		A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a $KRAS^{G12C}$ Mutation in Need of First-Line Treatment (CodeBreaK 201)
Short Protocol Title:		Sotorasib (AMG 510) in Subjects with NSCLC with $KRAS^{G12C}$ Mutation in Need of First-Line Treatment
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Data Elements Standards Version:		8

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

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a $KRAS^{G12C}$ Mutation in Need of First-Line Treatment (CodeBreaK 201), dated **25 February 2022**, and agree to abide by all provisions set forth therein.

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 Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my sub investigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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)

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Title and Role of investigator

_____
Institution Name

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Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a $KRAS^{G12C}$ Mutation in Need of First-Line Treatment (CodeBreaK 201)

Short Protocol Title: Sotorasib (AMG 510) in Subjects with NSCLC with $KRAS^{G12C}$ Mutation in Need of First-Line Treatment

Study Phase: 2

Indication: Non-small cell lung cancer (NSCLC)

Rationale

While multiple targeted therapies have been developed over the past few years, oncogenic Kirsten rat sarcoma (KRAS) has been notoriously difficult to target due to a host of reasons. While the prognostic role of *KRAS p.G12C* mutation across various solid tumors is a matter of investigation, there exists a high unmet need to identify subjects with this driver mutation and expeditiously develop therapies that are safe and can provide significant clinical benefit as compared to the existing standard of care options.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the tumor objective response rate (ORR) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria in subjects who receive sotorasib at either 960 mg daily (QD) or 240 mg QD whose tumors are programmed death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) $<$ 1% and/or harbor a serine/threonine kinase 11 (*STK11*) co-mutation, in a subgroup of subjects with PD-L1 < 1% and in a subgroup of subjects with *STK11* co-mutation.	• Objective response (OR) (OR = complete response [CR] + partial response [PR]), measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per RECIST 1.1 per Blinded Independent Central Review (BICR)
Key Secondary	
• To evaluate other measures of efficacy.	• Disease control (CR + PR + stable disease [SD]) • Duration of response (DOR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS)

• To evaluate the safety and tolerability of sotorasib.	• Treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiogram [ECGs], and clinical laboratory tests.
• Characterize the pharmacokinetics (PK) of sotorasib following administration as an oral tablet formulation	• PK parameters of sotorasib including, but not limited to, maximum plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC)

Overall Design

This is an open-label, multicenter phase 2 study to explore the anti-tumor effect of sotorasib monotherapy in subjects with metastatic non-small cell lung cancer (NSCLC) with *KRAS p.G12C* mutation whose tumors express < 1% programmed death-ligand 1 (PD-L1) and/or have a serine/threonine kinase 11 (*STK11*) mutation in need of first line treatment. Approximately 170 subjects across approximately 85 sites globally will be randomized in a 1:1 design for treatment with sotorasib at 960 mg orally (PO) daily (QD) or 240 mg PO QD, stratified by known presence of *STK11* mutation.
An independent Data Review Team (DRT) will monitor the study. A non-binding futility guideline based on Bayesian posterior probability will be used to facilitate termination in the event of inadequate efficacy. Subjects will be treated until disease progression as confirmed by Blinded Independent Central Review (BICR), unacceptable toxicity, withdrawal of informed consent, or death, whichever occurs first. All subjects should have a safety follow-up (SFU) visit approximately 30 (+ 7) days after the end of the last dosing interval of protocol-required therapies or before any new antitumor treatment is started. In select cases, subjects may continue on treatment following radiologic progression if they continue to demonstrate clinical benefit. See Section 8.1.6 for sotorasib treatment beyond radiologic progression. Following the SFU visit, subjects will be followed in the long-term follow-up (LTFU) phase of the study in clinic or via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anti-cancer treatment until death, withdrawal of consent, or end of study, whichever occurs first. Subjects who discontinue sotorasib for reasons other than radiographic disease progression will have LTFU imaging for disease status until disease progression is documented radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, initiate a non-study cancer treatment, withdrawal of consent, or end of study, whichever occurs first.

Additional plasma/blood/tissue biopsy samples will be collected for exploratory biomarkers for identification and quantification of [redacted]

Number of Subjects

Approximately 170 subjects will be treated with either sotorasib at 960 mg PO QD or 240 mg PO QD.

Summary of Subject Eligibility Criteria

Adult subjects (≥ 18 years old) with untreated stage IV (per AJCC v8) NSCLC with *KRAS p.G12C* mutation.

For a full list of eligibility criteria, please refer to Section 5.1 and Section 5.2.

Treatments

Sotorasib is the Amgen investigational product used in this study. Sotorasib will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Sotorasib tablets will be administered PO QD with or without food for a treatment cycle of 21 days. Sotorasib tablets are formulated as immediate-release, PO, solid dosage form in a strength of 120 mg. The sotorasib dose to be used in the study will be 960 mg per day or 240 mg per day.

Statistical Considerations

A DRT, internal to Amgen but external to the study team, will monitor the study and perform interim futility analyses to facilitate termination in the event of inadequate efficacy. The futility analyses will occur after approximately 20 and 60 subjects across 2 treatment dose arms become response evaluable, defined as received at least 1 dose of sotorasib and have had the opportunity to be followed for at least 7 weeks starting from day 1.

The primary analysis is planned approximately 6 months after last subject enrolled. The data will be analyzed once they have been entered, cleaned, and locked.

Efficacy analyses will be summarized across and by treatment dose arms to which they are randomized. Efficacy subgroup analysis will be performed for subjects with PD-L1 < 1%, *STK11* co-mutation status, and other co-occurring mutations of interest. The percentage of subjects with an objective response (OR) will be summarized along with a 95% Clopper Pearson exact confidence interval (CI). Subjects without a post-baseline tumor assessment will be considered non-responders. Duration of response will be summarized with Kaplan-Meier quartiles and rates for selected durations (eg, > 3, > 6, > 9, > 12 months). Disease control will be analyzed by the same method used to analyze OR. Time to response will be summarized by the nonmissing sample size (n), mean, standard deviation, median, minimum, and maximum for responders. Progression-free survival and OS will be summarized with Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months). Subject incidence of all treatment-emergent adverse events, treatment-related adverse events will be tabulated by system organ class and preferred term. Safety analysis will be summarized across and by treatment dose arm **based on the actual highest dose received** for all subjects in the Safety Analysis Set, unless otherwise specified.

For a full description of statistical analysis methods, please refer to Section 9.

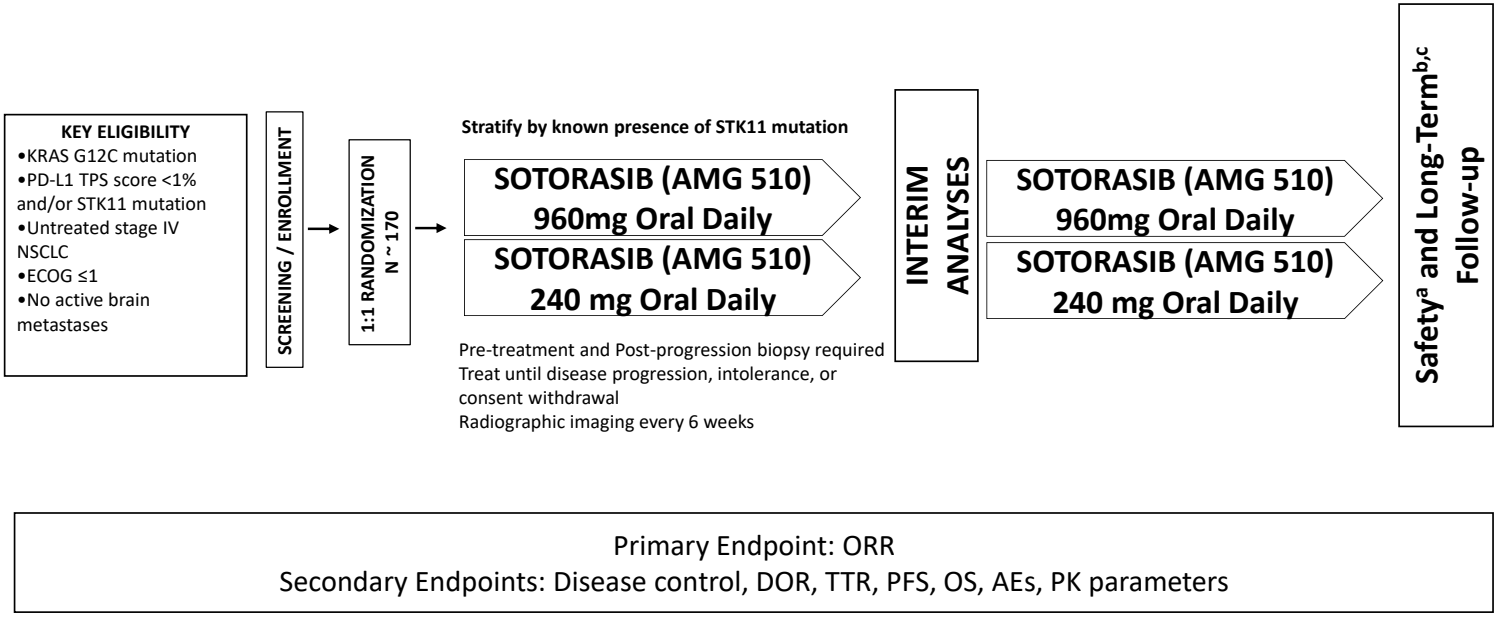
Statistical Hypotheses

No statistical hypothesis will be tested.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



AEs: Adverse events; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group; *KRAS G12C*: KRAS gene with a mutation resulting in a G12C amino acid substitution; NSCLC: Non-small Cell Lung Cancer; ORR: Objective Response Rate; OS: Overall Survival; PD-L1: Programmed Death-Ligand 1; PK pharmacokinetics; PFS: Progression-free Survival; STK11: Serine/Threonine Kinase 11; TPS: Tumor Proportion Score; TTR: Time to Response

[a] Upon discontinuation from study treatment, a safety follow up visit will be conducted 30 days (+ 7 days) after the last dose of sotorasib.

[b] Subjects who discontinue study intervention for reasons other than progressive disease will have long-term follow up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 by BICR, initiating a non-study cancer treatment, withdrawal of consent, or end of study. Following the safety follow-up visit, all subjects will be followed in clinic or via telephone every 12 weeks (± 2 weeks) for assessment of survival and documentation of anti-cancer treatment until death, withdrawal of consent, or end of study, whichever occurs first.

[c] The total study duration for an individual subject is approximately 6 years: 28-day screening, 6 to 12 months on treatment, SFU, and 5 years of long term follow-up.

1.3 Schedule of Activities (SoA)

Table 1.1. Schedule of Activities

	Screening	Treatment Cycle					SFU[a]	LTFU[b]	Notes
Cycle (1 cycle is 21 days ± 3 days)		1		2-4		5+			
Day	-28 to 1	1		1		1			
Hours (Relative to Dosing)		Pre	1	Pre	1	Pre			
GENERAL AND SAFETY									
Informed consent	X								
Eligibility criteria	X								
Demographics	X								
Medical history (including PD-L1 expression and *STK11* mutation)	X								
Other anticancer therapies	X						X	X	
Physical exam	X	X		X		X	X		
Physical measurements	X	X		X		X	X		Height collected at screening only. Weight collected every clinic visit.
Substance abuse history	X								
ECOG	X	X		X		X	X		
Vital signs including oxygen saturation	X	X		X		X	X		
ECG	(X)	X	X	X			X		(X): Three triplicate sets will be collected at screening for a total of 9 ECG tracings. All subsequent visits will be performed in 1 triplicate for a total of 3 ECG tracings. A window of ± 15 minutes is allowed for the 1-hour post-dose ECG assessments on cycle 1 day 1.
Vital status assessments								X	In addition to survival, LTFU period will collect data on the subjects' health condition, disease status, and subsequent anticancer treatment.
Concomitant medications	X	←==========→							Concomitant therapy data to be collected should include supplemental oxygen volume usage per day.
Adverse events		←==========→							
Serious adverse events[c]	←==========→								

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Table 1.1. Schedule of Activities

	Screening	Treatment Cycle					SFU[a]	LTFU[b]	Notes
Cycle (1 cycle is 21 days ± 3 days)		1		2-4		5+			
Day	-28 to 1	1		1		1			
Hours (Relative to Dosing)		Pre	1	Pre	1	Pre			
LABORATORY									
Chemistry	X	X		X		X	X		Laboratory assessments may be performed within 24 hours ± 8 hours before day 1 of each cycle except for cycle 1, which should be completed prior to first dose.
Hematology	X	X		X		X	X		
Coagulation	X	X		X		X	X		
Urinalysis	X	X		X		X	X		
Blood or urine pregnancy test	X	X		X		X	X		Pregnancy test must be within 24 hours ± 8 hours before day 1 of each cycle except for cycle 1, which should be completed prior to first dose **for females of childbearing potential.**
Hepatitis B and hepatitis C test	X								
Thyroid function tests	X	X		X		X	X		Thyroid function tests should also be obtained if the subject displays clinical signs or symptoms concerning for thyroid dysfunction.
Cholesterol and triglycerides		X		(X)		(X)	X		Cholesterol and triglyceride levels on pre-dose on day 1 of every other cycle. (X): cycle 3, 5, 7, etc,

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Table 1.1. Schedule of Activities

	Screening	Treatment Cycle					SFU[a]	LTFU[b]	Notes
Cycle (1 cycle is 21 days ± 3 days)		1		2-4		5+			
Day	-28 to 1	1		1		1			
Hours (Relative to Dosing)		Pre	1	Pre	1	Pre			
DOSING									
Sotorasib			←==========→						Sotorasib will be administered daily with no planned off treatment days until progressive disease, intolerance to treatment necessitating treatment discontinuation, need for other anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Sotorasib is to be administered during the clinic visit on day 1 of each cycle and outside of the clinic on the other days of each cycle.
Dosing diary			←==========→						A paper dosing diary will be provided for subjects to record their adherence to the oral medication.
TUMOR ASSESSMENTS									
CT/MRI[d]	X	Imaging every 6 weeks from cycle 1 day 1 (± 7 days)							Imaging will continue until radiologic disease progression, start of another anti-cancer therapy, withdrawal of consent, lost to follow-up, or death, whichever occurs earliest. Safety follow-up CT/MRI should be performed only for subjects who discontinue treatment for a reason other than disease progression per RECIST 1.1. Imaging should continue in LTFU until RECIST radiologic progression is documented. Contrast enhanced brain MRI (contrast enhanced CT scan if unable to have MRI) at screening is required. For subjects with brain metastases, contrast-enhanced MRI of the brain is required at each tumor evaluation.

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Table 1.1. Schedule of Activities

	Screening	Treatment Cycle							
Cycle (1 cycle is 21 days ± 3 days)		1		2-4		5+			
Day	-28 to 1	1		1		1			
Hours (Relative to Dosing)		Pre	1	Pre	1	Pre	SFU[a]	LTFU[b]	Notes
Sotorasib PK		X	X	X	(X)	[X]			**A window of -30 minutes is allowed for pre-dose PK blood samples, except for cycle 1, which should be completed prior to first dose. A window of ± 6 minutes is allowed for the 1-hour post-dose PK samples.** (X): Collect 1-hour post-dose cycle 2 day 1 only. [X]: cycle 5 only. Note: Time of last food intake will also need to be recorded
BIOMARKER SAMPLES/BIOMARKER DEVELOPMENT (MANDATORY)									
[redacted]									
IVD Plasma		X							
[redacted]									
KRAS^{G12C} mutation status	X								Local results to be entered into eCRF.
[redacted]									

Footnotes defined on last page of this table

Table 1.1. Schedule of Activities

	Screening	Treatment Cycle							
Cycle (1 cycle is 21 days ± 3 days)		1		2-4		5+			
Day	-28 to 1	1		1		1			
Hours (Relative to Dosing)		Pre	1	Pre	1	Pre	SFU[a]	LTFU[b]	Notes
BIOMARKER SAMPLES/BIOMARKER DEVELOPMENT (OPTIONAL)									
[redacted]									

CT = computerized tomography; [redacted] EC = Ethics Committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = Electronic case report form; [redacted]; IRB = Institutional Review Board; KRAS = Kirsten rat sarcoma viral oncogene homolog; IVD = in vitro diagnostic; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SFU = safety follow-up; STK11 = serine/threonine kinase 11; (X) = parentheses indicate that the particular test is situational at that time point, as specified in the respective notes

[a] SFU will be performed 30 days (+ 7 days) after the last dose of sotorasib or before the start of any new anti-cancer therapy.

[b] LTFU will occur in clinic or via telephone every 12 weeks (± 2 weeks) starting from the date of the last dose of sotorasib for assessment of survival and documentation of anti-cancer treatment. Long-term follow-up will be 5 years after last subject enrolled, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. Vital status and subsequent treatment for NSCLC will be recorded after the SFU period during the LTFU.

[c] **During the LTFU phase, serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. Since overall survival is a study endpoint, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness of the event.** Please refer to Section 8.4.5.1.3 for additional details.

[d] **Imaging assessments obtained as part of standard of care prior to signing consent may be used for screening provided they are collected within 28 days of Cycle 1 Day 1 and meet study specifications as indicated in the central imaging manual.**

2. Introduction

2.1 Study Rationale

Lung cancer is the most common cause of cancer related-death in 2020, comprising 18% of all deaths related to cancer and 11.4% of new cancer cases (World Health Organization [WHO] 2020). Lung cancer has traditionally been treated with platinum-based chemotherapy with modest improvements over best supportive care (Planchard et al, 2018). The advent of immunotherapy has resulted in substantial improvements in survival for patients with metastatic non-small cell lung cancer (NSCLC). Despite improvement in survival, many patients do not respond to immunotherapy-containing regimens, with response rates for approved immunotherapy regimens with and without chemotherapy ranging from approximately 40% to 60% (Reck et al, 2019; Socinski et al, 2018).

In the pivotal KEYNOTE-189 trial, despite substantial improvement in survival, many patients did not respond to the chemo-immunotherapy regimen, with a response rate in the pembrolizumab- chemotherapy group of 48% (95% CI 43.1 - 53.0). Response rates were lower (32.3%; 95% CI 24.3 - 41.2) for patients whose tumors had < 1% of tumor cells that expressed programmed death-ligand 1 (PD-L1). For patients who did respond, a significant increase in mean overall survival (mOS) from 10.7 months (95% CI 8.7 - 13.6) in the chemotherapy-placebo group to 22 months (19.5 - 25.2) in the pembrolizumab-chemotherapy combination group was seen. Hazard ratio (HR) for overall survival (OS) was 0.48 (95% CI 0.40 - 13.6). In the group of patients with PD-L1 tumor proportion score (TPS) < 1%, mOS was also improved to 17.2 months (13.8 - 22.8) from 10.2 months (7.0 - 13.5), when treated with chemotherapy alone (Gadgeel et al, 2020). Lower response rates and survival for patients with PD-L1 TPS < 1% suggests that patients who are PD-L1 negative may benefit from alternative therapy and/or that additional biomarkers may help to further select patients in this group who will benefit from a novel therapeutic option. Programmed death-ligand 1 TPS score is approved and widely used to select patients who will benefit from immunotherapy, however this biomarker is neither adequately sensitive nor specific as less than half of patients with PD-L1 positive tumors respond to immunotherapy (Planchard et al, 2018). This is likely due to many factors including intra/intertumoral heterogeneity (Bai et al, 2020). Many genetic alterations present in lung cancer have been purported to confer primary or acquired resistance to immunotherapy. The presence of a serine/threonine kinase 11 (*STK11*) mutation is one such genetic alteration that has been reported to be

a potential mechanism for primary resistance to immunotherapy (Skoulidis et al, 2018). The presence of a mutation in *STK11* and subsequent inactivation of this tumor-suppressor gene is associated with a "cold" tumor microenvironment characterized by reduced density of cytotoxic CD8+ tumor infiltrating lymphocytes in human samples as well as preclinical murine models (Skoulidis et al, 2018; Koyama et al, 2016; Kadara et al, 2017). While available evidence is retrospective in nature and lacking sufficient statistical power to detect significant differences amongst biomarker-defined subgroups, many groups have reported reduced survival in patients with a mutation in *STK11* (Skoulidis et al, 2018; Papillon-Cavanagh et al, 2020). In a retrospective subgroup analysis of KEYNOTE-042, 429 of the total 1274 patients in this study were evaluable for *STK11* mutational status. *An STK11* mutation was detected in 7.7% of these tumors. Patients with tumors harboring a *STK11* mutation receiving pembrolizumab had similar, though slightly reduced progression free survival (PFS) compared to patients with *STK11* wild type tumors who received pembrolizumab (mean progression free survival [mPFS 5] months; 95% CI 2 - NR vs 6 months; 95% CI 4 - 7). Overall survival for patients with a *STK11* mutation was also similar, and slightly higher, compared to mOS for patients with wildtype *STK11* treated with pembrolizumab (18 months; 95% CI 10 - NR vs 17 months; 95% CI 13 - 23). Response rates to treatment with pembrolizumab were similar between the 2 groups, 31.3% in *STK11* mutant vs 29.4% in *STK11* wildtype. (Cho et al, 2020). These data suggest minimal difference in outcomes based on *STK11* mutation status amongst patients whose tumors express >1% PD-L1. In a subgroup analysis of KEYNOTE-189, whose patient population includes patients whose tumors express low or no PD-L1 (PD-L1 TPS score < 1%), patients with *STK11* mutation**s** had reduced median OS when treated with chemo-immunotherapy, with mOS 17 months (95% CI 5 - NR) compared to the group of patients without *STK11* mutations whose mOS was 23 months (95% CI 20 - NR), as well as reduced mPFS of 6 months (95% CI 4 - 9) vs 10 months (95% CI 8 - 14). Response rates to chemo-immunotherapy in *STK11* mutated tumors (n = 36, objective response rate [ORR] 31%) were also lower than those seen in the *STK11* wildtype group (n = 168, ORR 49%). Hazard ratio for OS was also improved for patients without *STK11* mutations receiving chemo-immunotherapy over chemotherapy alone on the KEYNOTE-189 trial compared to that seen for patients with *STK11* mutations- (0.59, 95% CI 0.41 - 0.85 vs 0.75; 95% CI 0.37 - 1.5), suggesting that patients with *STK11* mutations did not derive as great a benefit from the addition of immunotherapy to chemotherapy (Gadgeel et al, 2020).

Within the context of Kirsten rat sarcoma (KRAS) mutant lung cancer, the presence of a *STK11* mutation is believed to represent a distinct biological entity which is resistant to standard of care immunotherapy. In a retrospective analysis of 3 clinical datasets by Skoulidis et al, 31% of the 174 patients in one of these cohorts treated with immunotherapy had co-occurring *STK11* and KRAS mutations. Objective response rate was 7.4% for this group vs 28.6% in the group with KRAS mutation and wild type *STK11* mutation. Progression-free survival was significantly shorter for patients with KRAS and co-occurring *STK11* mutation (HR 1.98, 95% CI 1.33 - 2.94; P < 0.001) compared to those with only KRAS mutation and wildtype *STK11/TP53*. This decrease in PFS translated into shorter OS for patients with *KRAS* and *STK11* co-mutated tumors. Overall survival was 6.4 months in the KRAS mutant / *STK11* mutant group vs 16.1 months in the KRAS mutant and *STK11/tp53* WT group. HR 1.99, 95% CI 1.29 - 3.06; p - 0.0015%). Within the CheckMate 057 randomized phase 3 clinical trial, 20 patients on the docetaxel arm and 24 patients in the nivolumab arm were identified with KRAS mutant lung cancer. Patients with co-occurring *STK11* mutations had an ORR of 0% (0/6) in the nivolumab arm. Due to the small size of these subgroup cohorts, no significant differences were detected in PFS and OS of patients with KRAS mutation and co-occurring *STK11* mutations. In a single-institution retrospective cohort of NSCLC patients treated with anti-PD(L)-1 therapy and with available genomic profiling and PD-L1, 66 patients were identified. In PD-L1 positive (PD-L1 ≥ 1%) tumors, *STK11* mutant tumors were found to have lower ORR compared to tumors with wild-type *STK11* (0% vs 34.5%, p = 0.026, Fisher's exact test). The effect of *STK11* mutations on PFS and OS with programmed cell death-1 (PD-1)/PD-L1 blockade did not differ significantly across PD-L1 high (PD-L1 > 50%) and low (PD-L1 < 50%) expressing groups (interaction test; P = 0.48 for PFS and P = 0.59 for OS), suggesting that the effect of *STK11* mutation may be independent of PD-L1 status (Skoulidis et al, 2018). These findings are supported by internal Amgen analysis of patients with $KRAS^{G12C}$ mutations and co-occurring *STK11* mutations. In this analysis, the Flatiron database was queried for outcomes of these patients after first line chemo-immunotherapy. Patients with $KRAS^{G12C}$ and *STK11* mutations who received platinum-based chemotherapy with anti-PD(L)-1 therapy had a median PFS of 4.5 months (95% CI 2.8 - 5.8) and a median OS of 6.9 months (4.1 - not evaluable [NE]), compared to a mPFS of 9.4 months (95% CI 4.8 - NE) and mOS of 14 months (9.6 - NE) in the group of patients with $KRAS^{G12C}$ mutations and wild type *STK11* mutations (manuscript in preparation). While much is still yet to be understood regarding the impact of other co-occurring mutations in patients

with KRAS-mutant lung cancer, limited available data suggests that the presence of a loss of function alteration in *STK11* may represent an opportunity for improvements upon currently available therapy.

Rationale for Evaluation of Sotorasib in Previously Untreated Subjects with *KRAS p.G12C* Mutant NSCLC

The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology guidelines for advanced or metastatic NSCLC suggest first-line use of targeted therapies for tumors with mutations in B-Raf proto-oncogene serine/threonine protein kinase (BRAF), ROS1, anaplastic lymphoma kinase (ALK), and epidermal growth factor receptor (EGFR) (NCCN, 2019; Planchard et al, 2019). Further, among patients with driver mutations, improved outcomes have been observed for patients treated with targeted therapies compared to those who did not receive targeted treatment (Kris et al, 2014).

While multiple targeted therapies have been developed over the past few years, oncogenic KRAS has been notoriously difficult to target due to a host of reasons. While the prognostic role of *KRAS p.G12C* mutation across various solid tumors is a matter of investigation, there exists a high unmet need to identify subjects with this driver mutation and expeditiously develop therapies that are safe and can provide significant clinical benefit as compared to the existing standard of care options.

Subjects with previously untreated metastatic *KRAS p.G12C* mutant NSCLC may benefit from first-line targeted therapy. Sotorasib has demonstrated promising anti-tumor activity in previously treated patients with advanced NSCLC. Subjects treated in the phase 1 CodeBreak 100 study showed a response rate of 32.3% (95% CI, 20.62 – 45.64) and a disease control rate (DCR) of 88.1% (95% CI, 77.07–95.09) across all dose levels and ORR and DCR were 35.3% (12/34) and 91.2% (31/34) at the RP2D (Hong et al, 2020). This response rate was similar across PD-L1 TPS subgroups and in the presence or absence of *STK11* co-mutations. This response rate represents an improvement over the response rate of currently available treatments for previously treated advanced NSCLC (Garon et al, 2014; Herbst et al, 2016). Further, sotorasib has been shown to be safe and well tolerated with no dose-limiting toxicities (DLTs) or cumulative toxicities observed with extended treatment. Previously untreated subjects enrolling in the current study may be ineligible to receive current standard of care described in Section 2.2.1. For these subjects, sotorasib provides an option for those with an unmet need. Additionally, subjects may choose to forgo standard of care in

favor of a more directly targeted and potentially less toxic therapy than chemotherapy and/or immunotherapy options, reserving these potentially more toxic choices for later lines. The choice to be treated with sotorasib over a standard of care therapy may generally be based on subjects' and investigator's decision and a desire to avoid the specific toxicities associated with chemotherapy and/or immunotherapy, while understanding that the efficacy data is still evolving. For all subjects with previously untreated metastatic *KRAS p.G12C* mutant NSCLC enrolling in the current study, subjects not benefiting from sotorasib (ie, not achieving stable disease [SD] or better at their first scan at 6 ± 1 weeks from cycle 1 day 1) may be discontinued from sotorasib to receive an approved standard of care therapy at the discretion of the investigator or subject.

2.2 Background

2.2.1 Disease

The rat sarcoma (RAS) proto-oncogene has been identified as an oncogenic driver of tumorigenesis in NSCLC (Smith et al, 2010; Johnson et al, 2001; Der et al, 1982). The RAS family consists of 3 closely related genes that express guanosine triphosphate (GTP)-ases responsible for regulating cellular proliferation and survival (Simanshu et al, 2017). The RAS proteins, KRAS, Harvey rat sarcoma viral oncogene homolog (HRAS), and neuroblastoma RAS viral oncogene homolog (NRAS) (Hall et al, 1983; Taparowsky et al, 1983; Chang et al, 1982; Kirsten and Mayer, 1967; Harvey, 1964), can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of *RAS*, with KRAS being the most frequently mutated isoform in most cancers (Prior et al, 2012). While the role of KRAS mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting KRAS mutations have been successfully developed, largely because the protein has been intractable for inhibition by small molecules (McCormick, 2016).

KRAS p.G12C Mutation and Sotorasib

Of the KRAS mutations, it is estimated that approximately 80% occur at codon 12 (Prior et al, 2012). The *KRAS p.G12C* mutation is estimated to occur in approximately 13% of lung adenocarcinoma (including NSCLC), 3% of colorectal cancer (CRC), and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) (Biernacka et al, 2016; Neumann et al, 2009; The AACR Project GENIE Consortium, 2017). This specific mutation has been identified as

a putative oncogenic driver in several types of solid tumors, including NSCLC (Fernández-Medarde and Santos, 2011).

The *KRAS p.G12C* mutation is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of GTPase-activating proteins (GAPs), thereby reducing the hydrolysis of GTP by KRAS. The resulting accumulation of active, GTP-bound KRAS leads to enhanced proliferative and survival signaling in tumor cells (Jones et al, 2017).

Sotorasib is a novel small molecule that specifically and irreversibly inhibits the $KRAS^{G12C}$ mutant protein. Sotorasib binds to the P2 pocket of KRAS adjacent to the mutant cysteine at position 12 and the nucleotide-binding pocket. The inhibitor contains a thiol reactive portion which covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, guanosine diphosphate (GDP)-bound conformation. This blocks the interaction of KRAS with effectors such as RAF proto-oncogene serine/threonine protein kinase (RAF), thereby preventing downstream signaling, including the phosphorylation of extracellular signal-regulated kinase (ERK) (Cully and Downward, 2008; Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS by RNA interference (RNAi) or small-molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts harboring *KRAS* mutations (including the *KRAS p.G12C* mutation) (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with sotorasib have confirmed these in vitro findings and have likewise demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C* mutations (Section 2.2.2). These data suggest that inhibition of *KRAS p.G12C* may have therapeutic benefit for subjects with *KRAS p.G12C*-driven cancers. Accordingly, the ongoing first-in-human (FIH) Study 20170543, is evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of sotorasib in subjects with *KRAS p.G12C* mutant advanced NSCLC.

Current Therapy for Cancers Harboring the *KRAS p.G12C* Mutation

Worldwide, lung cancer (small cell and non-small cell) is the most common type of cancer occurring in both men and women (WHO statistics, 2018). It is estimated that in 2019 there will be approximately 228 150 new cases of lung cancer and 145 600 new cases of CRC in the United States (US) alone (American Cancer Society, 2019). The 5-year survival rate for advanced NSCLC cancer is between 6% and 33% depending on

the stage. Similarly, the 5-year survival rate for advanced CRC is between 14% and 71% (American Cancer Society, 2019). Therefore, while the incidence of the *G12C KRAS* mutation in these tumor types is relatively low (approximately 13% and 3%, respectively) the overall incidence of NSCLC and CRC and the poor prognosis of subjects with advanced/metastatic disease makes this mutation an important molecular target.

Prior to sotorasib, there was no anticancer therapy specifically targeting tumors that harbor the *KRAS p.G12C* mutation. Subjects with metastatic or unresectable NSCLC with the *KRAS p.G12C* mutation are generally being treated with combinations of chemotherapy, immunotherapy, or antiangiogenic agents. In NSCLC, immune checkpoint inhibition is now the mainstay of first-line therapy in metastatic NSCLC without druggable driver mutations, either as monotherapy or as combination therapy (with chemotherapy ± anti-angiogenic therapy).

Although *EGFR*, BRAF, and human epidermal growth factor receptor 2 (*HER2*), and rearrangements in ALK, ROS, and rearranged during transfection have been validated as powerful predictive biomarkers, and have expanded treatment options for these molecularly defined subsets of subjects, and since the *KRAS* mutation rarely occurs concomitantly with these other molecular abnormalities, subjects with *KRAS* mutations are not usually candidates for these therapies (Scheffler et al, 2018; Gainor et al, 2013). Efforts to target *KRAS* mutant NSCLC by inhibiting downstream signaling mechanisms such as mitogen-activated protein kinase (MAPK) (MEK)1/2 or cyclin-dependent kinase (CDK)4/6 inhibitors have been unsuccessful to date (Roman et al, 2018). More recently, NSCLC subjects with the *KRAS p.G12C* mutation are, like subjects without other molecularly defined targets, receiving anti-PD-1 inhibitors with or without chemotherapy in first and/or second line therapy.

2.2.2 Amgen Investigational Product Background: Sotorasib

In the first in human phase 1 trial, 59 subjects with NSCLC receiving sotorasib experienced durable clinical benefit with ORR of 32.3% across all dose levels tested, and median duration of response of 10.9 months. Median PFS in this group of heavily pretreated patients was 6.3 months (Hong et al, 2020). In the subsequent phase 2 trial, as of the 01 December 2020 data cutoff date, 126 patients were treated with sotorasib (Li et al, 2021) at the recommended phase 2 dose of 960 mg daily (QD). The confirmed objective response rate was 37.1% (95% CI 28.6-46.2); with a disease control rate of 80.6% (72.6-87.2). Median duration of response was 10 months (95% CI: 6.9-

11.1 months), and mPFS of 6.8 months (95% CI: 5.1-8.2) was seen in this group of patients. Treatment with sotorasib in the phase 2 study was well-tolerated as in the phase 1 study, with a majority of treatment-related adverse events (TRAEs) of Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 severity and only 7.1% of patients discontinuing treatment due to TRAEs.

Responses to sotorasib were seen across PD-L1 levels. Forty-eight percent (21/44) (48%) patients with PD-L1 TPS score of < 1% responded to treatment with sotorasib. Patients with STK11 mutations, both with and without KEAP1 co-mutations also responded to sotorasib. ORR was 23% in STK11/KEAP1 co-mutated patients and 50% in patients with STK11 mutation only (Li et al, 2021).

While results from the ongoing Study 20170543 (CodeBreaK 100) demonstrate that sotorasib at a daily dose of 960 mg was safe and effective, the PK profile of sotorasib was non-linear with responses noted at all dose levels from 180 mg to 960 mg. A daily dose of 240 mg has been selected for further exploration in CodeBreaK 100 to investigate whether this lower dose can be as safe and efficacious as the daily dose of 960 mg. The 240 mg QD dose would be expected to approximate the exposure at the lower doses of 180 mg and 360 mg QD. Drug exposure at 240 mg QD is expected to be similar to that of 960 mg QD, which is expected to be above the concentration associated with 90% inhibition in vitro.

Refer to the Sotorasib (AMG 510) investigator**'s** Brochure for additional information.

2.3 Benefit/Risk Assessment

Key Benefits

The safety, tolerability, PK, and efficacy of sotorasib is being evaluated in a phase 1/2 Study 20170543 (National Clinical Trials [NCT] 03600883) in subjects with advanced solid tumors harboring *KRAS p.G12C* mutations. The full phase 1 population that received daily monotherapy with sotorasib had a total of 129 subjects in dose escalation and expansion cohorts. Of these, 59 had NSCLC. Doses of 180, 360, 720, and 960 mg QD were studied. Subjects had a median of 3 prior lines of anticancer therapy for metastatic disease. No DLTs were observed. In the NSCLC subjects, there were 19 (32.2%) subjects with confirmed objective response (OR). The phase 2 portion of Study 20170543 is ongoing (Hong et al, 2020).

Reference should be made to the Sotorasib (AMG 510) investigator's Brochure for further data on sotorasib.

Key Risks

Based on nonclinical toxicity studies of sotorasib, the key safety information to be monitored includes renal toxicity, anemia, leukocytosis, splenomegaly, and thyroid abnormalities. Based on clinical study data, the key **risks** to be monitored include increases of AST and ALT **and pneumonitis**. Clinical signs and symptoms of the key safety information, along with safety laboratories, will be monitored during the study to ensure the subjects' safety. More detailed information about the safety profile and risks of sotorasib, including the most recent information on adverse drug reactions based on the ongoing clinical program, may be found in the Sotorasib (AMG 510) investigator's Brochure.

Based on the anticipated benefits and the risks of sotorasib, the benefit-risk profile of sotorasib is favorable for the treatment of subjects with *KRAS p.G12C*-mutated NSCLC whose tumors are PD-L1 TPS $< 1\%$ or harbor an *STK11* co-mutation in need of first line treatment.

Amgen closely monitors the COVID-19 pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of sotorasib in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the investigator's Brochure for further data on sotorasib.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the tumor objective response rate (ORR) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria in subjects who receive sotorasib at either 960 mg daily (QD) or 240 mg QD whose tumors are programmed death-ligand 1 (PD-L1) Tumor Proportion Score (TPS) < 1% and/or harbor a serine/threonine kinase 11 (*STK11*) co-mutation, in a subgroup of subjects with PD-L1 < 1% and in a subgroup of subjects with *STK11* co-mutation.	• Objective response (OR) (OR = complete response [CR] + partial response [PR]), measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per RECIST 1.1 per Blinded Independent Central Review (BICR)
Key Secondary	
• To evaluate other measures of efficacy.	• Disease control (CR + PR + stable disease [SD]) • Duration of response (DOR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS)
• To evaluate the safety and tolerability of sotorasib.	• Treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, electrocardiogram [ECGs], and clinical laboratory tests.
• Characterize the pharmacokinetics (PK) of sotorasib following administration as an oral tablet formulation	• PK parameters of sotorasib including, but not limited to, maximum plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC)
Exploratory	
[redacted]	

4. Study Design

4.1 Overall Design

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

This is an open-label, multicenter phase 2 study to explore the anti-tumor effect of sotorasib monotherapy in subjects with metastatic NSCLC with *KRAS p.G12C* mutation whose tumors express < 1% PD-L1 and/or a *STK11* mutation in need of first line treatment. Approximately 170 subjects across approximately 85 sites globally will be randomized in a 1:1 design for treatment with sotorasib at 960 mg orally (PO) QD or 240 mg orally PO QD, stratified by known presence of *STK11* mutation. Subjects will be treated until disease progression as confirmed by Blinded Independent Central Review (BICR), unacceptable toxicity, withdrawal of informed consent, or death, whichever occurs first. All subjects should have a SFU visit approximately 30 (+ 7) days after the end of the last dosing interval of protocol-required therapies or before any new antitumor treatment is started. Following the SFU visit, all subjects will be followed in clinic or via telephone every 12 weeks (± 2 weeks) starting from the date of the last dose of investigational product for assessment of survival and documentation of anti-cancer treatment until death, withdrawal of consent, or end of study, whichever occurs first. Subjects who discontinue sotorasib for reasons other than radiographic disease progression will have long-term follow-up (LTFU) imaging for disease status until disease progression is documented radiographically per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, initiate a non study cancer treatment, withdrawal of consent, or end of study. In select cases, subjects may continue on treatment following radiologic progression if they are continuing to demonstrate clinical benefit. See Section 8.1.6 for sotorasib treatment beyond radiologic progression.

[redacted]

A Data Review Team (DRT), internal to Amgen but external to the study team, will monitor the study and perform interim futility analyses to facilitate termination in the event of inadequate efficacy. The futility analyses will occur after approximately 20 and 60 subjects across 2 treatment dose arms become response evaluable, defined as received at least 1 dose of sotorasib and have had the opportunity to be followed for at least 7 weeks starting from day 1. The futility analyses will be based on as-is snapshot**s**. Enrollment will not be held to conduct these assessments.

The primary analysis is planned approximately 6 months after last subject enrolled. The data will be analyzed once they have been entered, cleaned, and locked. All efficacy data will be summarized across and by treatment dose arms to which they are randomized. All safety, laboratory, and PK data will be summarized across and by treatment dose arms **based on the actual highest dose received** for all subjects in the Safety Analysis Set, unless otherwise specified. Efficacy subgroup analyses will be performed for subjects with PD-L1 < 1%, *STK11* co-mutation, and other co-occurring mutations of interest.

Adaptive design elements:

- [redacted]

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2 Patient Input into the Study Design

Patient input was not obtained when designing this study.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

Preclinically, efficacious doses were predicted with 2 PK/tumor growth inhibition (TGI) models that describe the anti-tumor activity of sotorasib: (1) a tumor stasis model that estimates human exposures to cause tumor stasis (ie, no net tumor growth) based on PK and TGI of MIA-PaCa-2 T2 tumor xenograft mice treated with sotorasib and (2) a tumor regression model that utilizes clinical pancreatic cancer data and PK and TGI in sotorasib-treated MIA-PaCa-2 T2 xenograft mice to predict the treatment effects of sotorasib on tumor growth dynamics in humans. Consolidating the results from both

models, the minimal efficacious dose for sotorasib in humans was predicted to be between 30 and 240 mg PO QD.

The doses of 960 mg and 240 mg are selected for the intended patient population based on the totality of evidence available for sotorasib efficacy and safety data (Hong et al, 2020; Li et al, 2021; Sotorasib [AMG 510] investigator's Brochure). The results from CodeBreak 100 support the selection of 960 mg QD as an effective and safe dose for reducing tumor burden in subjects with NSCLC. From a clinical efficacy perspective, clinically meaningful response rates were observed at the 960-mg dose in adult subjects with NSCLC, confirming the dose is efficacious. From a clinical safety perspective, 960 mg QD sotorasib monotherapy has shown a tolerable safety profile. In addition, the non-linear PK profile suggests that a lower dose can be as safe and efficacious as the daily dose of 960 mg. Consistent with CodeBreak 100, the 240 mg QD dose is also being proposed.

Please see the Sotorasib (AMG 510) investigator's Brochure for additional efficacy and safety information.

4.4 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit as shown in the Schedule of Activities. The total study duration for an individual subject is approximately 6 years: 28-day screening, 6 to 12 months on treatment and up to approximately 46 cycles, SFU, and 5 years of LTFU from the last subject enrolled.

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, LTFU, additional antibody testing), as applicable.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Untreated stage IV (per AJCC v8) NSCLC.

- **Subject must not have received prior treatment for metastatic stage IV NSCLC.** Subjects who received adjuvant or neoadjuvant **anti-tumor** therapy are eligible if the adjuvant/neoadjuvant **anti-tumor** therapy was completed greater than 12 months prior to the development of metastatic **stage IV** disease.

102 Pathologically documented, metastatic NSCLC with *KRAS p.G12C* mutation identified through molecular testing. *KRAS p.G12C* mutation must be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent **per regional standards**.

103 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

104 Age ≥ 18 years.

105 PD-L1 TPS score < 1% as determined by **a validated IHC test.** If subjects do not have PD-L1 TPS score < 1%, *STK11* loss of function mutation must be present. Subjects with PD-L1 TPS score < 1% may also have presence of *STK11* mutation. **Molecular testing for PD-L1 or *STK11* should be performed in a CLIA certified laboratory in US, or equivalent certified laboratory per regional standards.**

106 [redacted]

108 Measurable disease per investigator interpretation using RECIST 1.1 criteria (Section 11.8). Lesions previously radiated are not considered measurable unless they have progressed after radiation.

109 Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1.

110 Life expectancy of > 3 months, in the opinion of the investigator.

111 Ability to take oral medications and willing to record daily adherence to investigational product.

112 Adequate hematological laboratory assessments:

- Absolute neutrophil count (ANC) ≥ 1500 cells/μL
- Hemoglobin ≥ 9.0 g/dL
- Platelet count ≥ 75 000/μL

113 Adequate renal laboratory assessments, defined as the following:

- Estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) calculation ≥ 30 mL/min/1.73 m^2

- Estimated glomerular filtration rate = 175 x serum creatinine$^{-1.154}$ x age$^{-0.203}$ x sex (0.742 if female) x race (1.210 if black)

114 Adequate hepatic laboratory assessments, as follows:

- Aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Total bilirubin (TBL) ≤ 1.5 x ULN for subjects with documented Gilbert's syndrome or < 3.0 x ULN for subjects for whom the indirect bilirubin level suggests an extrahepatic source of elevation

115 Adequate coagulation laboratory assessments, as follows:

- Prothrombin time (PT) or partial thromboplastin time (PTT) < 1.5 x ULN, OR
- International normalized ratio (INR) < 1.5 x ULN or within target range if on prophylactic anticoagulation therapy

116 QTc ≤ 470 msec in females or ≤ 450 msec in males (based on average of screening triplicates)

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Mixed small-cell lung cancer and NSCLC histology.

Other Medical Conditions

203 History or presence of malignancy unless treated with curative intent and no evidence of disease ≥ 3 years with the following exceptions:

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

204 Spinal cord compression, active brain metastases and/or carcinomatous meningitis. Subjects who have had brain metastases resected or have received whole brain radiation therapy ending at least 4 weeks (or stereotactic radiosurgery ending at least 2 weeks) prior to study day 1 are eligible if they meet all of the following criteria**:**

- No residual neurological symptoms
- No corticosteroid requirement to manage neurological symptoms
- Follow-up MRI performed within 30 days prior to enrollment shows no new lesions or enlarging lesion appearing
- No single lesion larger than 10 mm

205 Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > Class II), unstable angina, or cardiac arrythmia requiring medication.

206 Gastrointestinal (GI) tract disease causing the inability to take oral medication, malabsorption syndrome, requirement for intravenous (IV) alimentation, uncontrolled inflammatory GI disease (eg, Crohn's disease, ulcerative colitis).

207 Evidence of hepatitis infection based on the following results and/or criteria:

- Positive hepatitis B surface antigen (HepBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
- Negative HepBsAg with a positive for hepatitis B core antibody (hepatitis B core antibody testing is not required for screening, however if this is done and is positive, then hepatitis B surface antibody [Anti-HBs] testing is necessary. Undetectable anti-HBs in this setting would suggest unclear and possible infection and requires exclusion).
- Positive hepatitis C virus antibody: Hepatitis C virus RNA by polymerase chain reaction (PCR) is necessary. Detectable Hepatitis C virus RNA renders the subject ineligible.
- Positive hepatitis B or C viral load: if above antibody/antigen testing is not able to be obtained, obtain hepatitis B or C viral load.

208 Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures at a frequency greater than monthly. Subjects with PleurX catheters in place may be considered for the study only with Medical Monitor approval.

209 Known positive test for human immunodeficiency virus (HIV).

210 Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

211 Active infection within 2 weeks of study day 1 requiring therapeutic oral or IV antibiotics.

212 Major surgery within 28 days of study day 1.

213 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to CTCAE version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (any grade allowed). Grade 2 or 3 toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for $>$ 6 month), such as ifosfamide related proteinuria or neuropathy, may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor.

Prior/Concomitant Therapy

214 Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent) within 12 months **of metastatic stage IV NSCLC**.

215 Therapeutic or palliative radiation therapy within 2 weeks of study day 1. Subjects must have recovered from all radiotherapy related toxicity to grade 1 or better.

216 Received radiation therapy to the lung that is > 30 Gy within 6 months of first dose of trial treatment.

217 Previous treatment with a covalent *KRAS p.G12C* inhibitor.

218 Use of known cytochrome P450 (CYP) 3A4 sensitive substrates or P-gp substrates, with a narrow therapeutic window, within 14 days or 5 half-lives of the

drug or its major active metabolite, whichever is longer, prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

219 Use of strong inducers of CYP3A4 (including herbal supplements such as St. John's wort) within 14 days or 5 half-lives**,** whichever is longer**,** prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

220 Use of proton-pump inhibitors (PPIs) or histamine 2 (H2) receptor antagonists (H2RA) within 14 days or 5 half-lives of the drug or its major active metabolite, whichever is longer, prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

Prior/Concurrent Clinical Study Experience

221 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

222 Female subjects of childbearing potential unwilling to use protocol specified method of contraception (see Section 11.5) during treatment and for an additional 7 days after the last dose of sotorasib

223 Female subjects who are breastfeeding or who plan to breastfeed while on study through 7 days after the last dose of sotorasib.

224 Female subjects planning to become pregnant while on study through 7 days after the last dose of sotorasib.

225 Female subjects of childbearing potential with a positive pregnancy test assessed at Screening or **prior to first dose for cycle 1** by a highly sensitive urine or **blood** pregnancy test.

226 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 7 days after the last dose of sotorasib. Refer to protocol Section 11.5 for additional contraceptive information.

227 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 7 days after the last dose of sotorasib.

228 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 7 days after the last dose of sotorasib.

229 Subject has known sensitivity to any of the products or components to be administered during dosing.

230 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

231 Subject unable to receive both iodinated contrast for computed tomography (CT) scans and gadolinium contrast for MRI scans.

232 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the

investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record.

Each subject who enters into the screening period for the study (defined as the point when the subject signs informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned using interactive response technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Sites that do not enroll subjects within 6 months of site initiation may be closed.

5.4 Screen Failures

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. This log may be completed and updated via an IRT.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), or medical device(s) 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.

A summary of the dosing and administration of each treatment is shown in Table 6.1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6.1. Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Sotorasib
Dosage Formulation	Sotorasib is formulated as an immediate-release, PO, solid dosage form in a strength of 120 mg. It is presented as a yellow, oblong film coated tablet debossed with “A” or "AMG" on 1 side and “120” on the other. Excipients used in the tablet include microcrystalline cellulose, lactose, croscarmellose sodium, magnesium stearate, and [redacted] coating material containing polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and yellow iron oxide.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	The sotorasib dose to be used in the study will be 960 mg/day or 240 mg/day.
Route of Administration	Oral, QD
Accountability	The dose administered, start date/stop date, reason for dose change, and lot number of investigational product are to be recorded on each subject’s CRF(s).
Dosing Instructions	Sotorasib will be administered orally QD with or without food for a treatment cycle of 21 days. **Subjects should take the sotorasib dose approximately the same time every day with or without food. The dose should not be taken more than 2 hours earlier than the target time based on the previous day's dose or as outlined in the protocol. Subjects should skip the sotorasib dose if 6 hours have passed from the scheduled time of dosing and should take the next dose as prescribed the next day. If vomiting occurs after taking sotorasib, subjects should not take an additional dose and should take the next dose as prescribed the next day.**

CRF = case report form; PO = orally; QD = once daily.
[a] Sotorasib will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

No non-investigational products will be used in this study.

6.1.3 Medical Devices

Investigational medical devices will not be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies in this study.

6.1.5 Other Intervention Procedures

There are no other intervention procedures in this study.

6.1.6 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**,** combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational product(s) provisioned and/or repackaged/modified by Amgen. In this study, Amgen will collect product complaints for sotorasib.

Any product complaint(s) associated with an investigational product(s) supplied by Amgen are to be reported.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

- Anti-tumor therapy such as:
  chemotherapy, antibody therapy, molecular targeted therapy
- Known CYP3A4 sensitive substrates or P-gp substrates
- Use of PPIs or H2RA
- Known strong inducers of CYP3A4 including herbal supplements, such as St. John's wort

- Systemic steroids (prednisone ≥ 10 mg or equivalent) for reasons other than management of toxicities (eg, immune-mediated adverse events).
- Other investigational agents

If a subject needs palliative radiotherapy for pain control during the course of the study, all study drugs should be discontinued, and the investigator or designee should notify the sponsor as soon as possible. A subject may be allowed to resume study drug after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.

Subjects must not schedule any major elective surgeries during the treatment period, and for at least 28 days after the last administration of sotorasib. Minor elective surgery may be allowed after discussion with the Amgen medical monitor. If a subject undergoes any unexpected surgery during the course of the study, all study drugs must be discontinued, and the investigator or designee should notify the sponsor as soon as possible. A subject may be allowed to resume sotorasib only if both the investigator and Amgen medical monitor agree to restart study therapy.

Concomitant administration of sotorasib (AMG 510) with PPIs (omeprazole, lansoprazole, etc,) decreased sotorasib (AMG 510) concentrations, which may reduce AMG 510 efficacy. Histamine-2 receptor antagonists (famotidine, ranitidine, etc,) were shown to reduce the exposure to sotorasib (AMG 510). Avoid co-administration of sotorasib (AMG 510) with PPIs and/or H2RA. If treatment with an acid reducing agent is required, take sotorasib (AMG 510**)** 4 hours before or 10 hours after administration of a local antacid.

6.2 Dose Modification

6.2.1 Dose-Group Study Escalation/De-escalation and Stopping Rules

For Dose Adjustments, refer to Section 6.2.2.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: Sotorasib

Subjects will receive sotorasib at 960 mg QD or 240 mg QD. Dose reduction levels of sotorasib for toxicity management of individual subjects for QD dosing are provided in Table 6.2. For the 960 mg treatment arm, sotorasib will be discontinued or dosage reduced, in the event of a toxicity that, in the opinion of the investigator, warrants the discontinuation or dose reduction as indicated in Table 6.3. Up to 2 dose reductions are allowed. Subjects who experience an adverse event requiring more than 2 interruptions

and dose reductions below 240 mg should be permanently discontinued from treatment. For the 240 mg treatment arm, sotorasib may be resumed without dose level reductions for toxicity if deemed medically safe and appropriate in the opinion of the investigator. Subjects who experience an adverse event requiring more than 2 dose interruptions for toxicity should be permanently discontinued from treatment. For both treatment arms, the reason for dose change of sotorasib is to be recorded on each subject's case report form (CRF[s]).

The date of the first dose of investigational product (sotorasib) is defined as cycle 1 day 1. All subsequent doses and study visits will be scheduled based on this cycle 1 day 1 date. If there are changes to the study visits (ie, missed visit due to adverse event or visit was early), all efforts should be made for subsequent study visits to resume on the original schedule.

Table 6.2. Dose Modifications for Sotorasib (QD Dosing)

Sotorasib Doses (mg QD)		
Starting Dose	Dose -1	Dose -2
960	480	240
240	240[a]	240[a]

QD = once daily.
[a] Sotorasib may be resumed without dose level reductions for toxicity.

Table 6.3. Sotorasib Dose Modification Guidelines for Toxicities

Toxicity	Recommended Action	
	Hold Until:	Restart Dose:
Grade ≥ 3 nausea, vomiting, or diarrhea lasting longer than 3 days despite optimal medical support	Recovery to grade 1 or less or to baseline grade	Resume dosing at 1 dose lower[a]
Suspected interstitial lung disease (ILD)/pneumonitis of any grade	ILD/pneumonitis confirmed or excluded	If confirmed, permanently discontinue sotorasib. If excluded, restart at same dose if no other sotorasib dose modification guidelines are applicable.
Any other drug-related toxicity ≥ grade 3[b]	Recovery to grade 1 or less or to baseline grade	Resume dosing at 1 dose lower[a]

[a] For subjects with a starting dose of 960 mg, sotorasib may be resumed at a dose lower than the recommended restarting dose after discussion with the medical monitor. For subjects with a starting dose of 240 mg, sotorasib may be resumed without dose level reductions for toxicity.
[b] For suspected hepatotoxicity, refer to Section 6.2.3 and Section 11.7.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Guidelines for management and monitoring of subjects with increased AST, ALT, or ALP are presented in Table 6.4.

Table 6.4. Sotorasib Hepatotoxicity Guidelines

- If the conditions for permanent discontinuation are met (below): Participant to be permanently discontinued
  AST or ALT > 3x ULN and INR > 1.5x ULN (for subjects not on anticoagulation therapy) in the presence of no important alternative causes for elevated AST/ALT values
  OR
  AST or ALT > 3x ULN and TBL > 2x ULN in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
- If conditions are not met: Exclude other causes[a]
- Upon failure to identify any other causes and sotorasib relation to increase in LFTs cannot be excluded, proceed with guidelines below:

CTCAE Grade	Sotorasib Action	Medical Management	Monitoring and Follow-up
Grade 2 AST or ALT and ALP ≤ 8x ULN with no clinical symptoms consistent with hepatitis (right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	Continue	Consider steroids[b]	• Closely monitor liver function tests
Grade 2 AST or ALT with symptoms Or Grade 3 or 4 AST or ALT Or 8x ULN ALP[d]	First Occurrence Withhold	Initiate steroids[b]	• Closely monitor liver function tests • Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms • If applicable, restart at 1 dose level reduction[c, e]
	Second Occurrence Withhold	Initiate steroids[b]	• Closely monitor liver function tests • Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms • If applicable, resume at an additional 1 dose level reduction only with MEDICAL MONITOR approval[c, e]
	Third Occurrence Permanently discontinue sotorasib	NOT APPLICABLE	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LFT = liver function test; TBL = total bilirubin; ULN = upper limit of normal

[a] If increase in AST/ALT is likely related to alternative agent, discontinue causative agent and await resolution to baseline or grade 1 prior to resuming sotorasib.

[b] For example: **Prednisone 1.0 to 2.0 mg/kg/day, dexamethasone equivalent, or methylprednisolone equivalent, followed by a taper. The taper may occur after restarting sotorasib.**

[c] Close monitoring at restart (eg, daily LFTs x 2, then weekly x 4). Sotorasib dose may be increased after discussion with medical monitor.
[d] There is no limit to the number of Sotorasib re-challenges for isolated alkaline phosphatase elevations that resolve to baseline or grade 1.
[e] Dose decrements below 240 mg are not allowable

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive investigational product at a dose of 960 mg or 240 mg. Randomization will be in an open-label manner after meeting all enrollment requirements. Randomization will be stratified by known presence of *STK11* mutation. The randomization will be performed by IRT and the randomization number will be provided to the site by the IRT system. The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.5 Treatment Compliance

Compliance with treatment and the corresponding assessments should be followed according to the Schedule of Activities (Section 1.3) and the treatment procedures section (Section 6.1).

6.6 Treatment of Overdose

For this study, any dose of sotorasib greater than 960 mg within 18 hours will be considered an overdose. **If vomiting occurs after taking sotorasib, do not take an additional dose. Take the next dose as prescribed the next day.**

In the event of an overdose, the investigator should:

1. Contact the Amgen Medical Monitor immediately.

2. Closely monitor the participant for any adverse event/serious adverse event and laboratory abnormalities for at least 48 hours.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from the time of initial diagnosis through the informed consent will be collected. For concomitant therapies being taken for the disease under study (eg, steroids, chemotherapy) collect therapy name, indication, dose, unit, frequency, start date, and stop date. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant administration of sotorasib with PPIs (such as omeprazole, pantoprazole, etc,), or H2RA (such as famotidine, ranitidine, etc,) is prohibited. If treatment with an acid-reducing agent cannot be avoided, sotorasib should be administered 4 hours before or 10 hours after a local antacid.

Concomitant therapies are to be collected from informed consent through the end of SFU period. For concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with

the subject the possibilities for continuation of the Schedule of Activities (see Table 1.1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records, from review of death registries or other publicly available information) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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

- Decision by sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Disease progression
- Requirement for alternative therapy
- Pregnancy

7.2 Subject Discontinuation/Withdrawal from the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1.1) for data

to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not applicable for this study.

7.2.2 Reasons for Removal from Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator should search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1.1).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 2 times at the discretion of the investigator and after consultation with Amgen.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. The subject must be reconsented if a rescreening period occurs more than 30 days after the original signing of the ICF. Imaging assessments do not need to be repeated if they were performed within 4 weeks prior to the start of treatment with sotorasib.

The following assessments do not have to be repeated during rescreening, if they were performed as standard of care or during the initial screening attempt within the time frames specified below:

- Hepatitis serology does not need to be repeated if it was performed within 6 weeks prior to start of treatment with sotorasib.
- Imaging assessments do not need to be repeated if they were performed within 4 weeks prior to start of treatment with sotorasib.
- Confirmation of biomarker status (ie, KRAS G12C, STK11, PD-L1) do not need to be repeated.

Any other assessments do not need to be repeated if they were performed within 28 days prior to start of treatment with sotorasib.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1.1). The date of the first dose of investigational product (sotorasib) is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date.

During clinic visit days, Sotorasib should be administered in the clinic after all protocol-required assessments have been performed. Results of any pre-dose laboratory tests will have to be available before the administration of Sotorasib.

A paper dosing diary will be provided to subjects at the beginning of each cycle. The study staff will provide guidance to the subjects on how to complete the diary and instructed to bring the diary to every study visit for review of compliance.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 30 (+ 7) days after the end of the last dosing interval of protocol-required therapies or before any new antitumor treatment is started.

8.1.4 Long-term Follow-up

Following the SFU visit, there will be a LTFU period for clinical evaluation of disease status and survival. All subjects will be followed in clinic or via telephone every 12 weeks (± 2 weeks) starting from the date of last dose of investigational product for assessment of survival and documentation of anti-cancer treatment. Subjects who discontinue sotorasib for reasons other than BICR-confirmed radiographic disease progression will have LTFU imaging for disease status until disease progression is documented radiographically per RECIST 1.1. Subjects will be followed for up to 5 years after last subject enrolled or until withdrawal of consent, lost to follow-up or subject death, whichever occurs first.

Data will be collected on the subjects' health condition, disease status, and subsequent anti-cancer treatment until death, withdrawal of consent, or end of study. Tumor assessments will be obtained until disease progression, start of subsequent anti-cancer treatment, death, withdrawal of consent or end of study, whichever is first.

The assessments that will be collected during the LTFU are designated in the Schedule of Activities (Table 1.1).

8.1.5 End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure/last follow-up shown in the Schedule of Activities.

8.1.6 Continuation on Sotorasib Treatment After Central Vendor Verified Radiologic Disease Progression

This section details the conditions necessary to allow continued treatment with sotorasib post disease progression in subjects that continue to have clinical benefits from sotorasib in the investigator's opinion provided all of the following criteria are met:

- Signed separate informed consent for sotorasib treatment beyond radiologic progression.
- Absence of threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.
- No other treatment discontinuation criteria are met.
- No significant, unacceptable, or irreversible toxicities related to any dose of the study treatment or treatment-related adverse events of CTCAE grade 4 at the current dose at the time of progression.
- No current signs or symptoms of clinical disease progression that have changed the ECOG performance status to **>** 1.
- Disease progression is in one of the following settings:
  - small or oligometastasis candidate for stereotactic body radiation therapy (SBRT), palliative radiation, or surgery
- [redacted]
- Approval for continuation from the Amgen Medical Monitor.
- Palliative radiation and/or surgery for new, progressive, or symptomatic lesions is permitted, but sotorasib must be held during these treatments.
- If the time between the subject's initial progression scan and the restart of sotorasib is > 4 weeks, the scan must be repeated to serve as the new baseline.
- All protocol-mandated procedures must be performed as noted in the protocol (imaging, labs, and clinic visits may be obtained earlier per clinical judgement and if clinically indicated).

For subjects who continue treatment beyond radiologic-progression, the first date of progression (BICR, if applicable) will be used for PFS analysis and subject's response post first progression (BICR, if applicable) will not be used to evaluate OR endpoints. Continued growth of tumor(s) on a subsequent scan should result in permanent discontinuation of the study drug.

Biomarker assessment can be done only if the biomarker research is allowed according to local regulations and agreed by the local EC/IRB.

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability and PK of the protocol-required therapies.

8.2.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started prior to screening through the start of treatment. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, NSCLC history must date back to the original diagnosis. The current toxicity grade will be collected for each condition that has not resolved.

8.2.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.5 Physical Measurements

Height (in centimeters) should be measured without shoes. Weight (in kilograms) should be measured without shoes.

8.2.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco and alcohol.

8.2.7 Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be collected at the timepoints indicated in the Schedule of Activities. The ECOG criteria for this protocol are further defined in Section 11.9.

8.3 Efficacy Assessments

The extent of disease will be evaluated by contrast-enhanced MRI/CT according to RECIST 1.1 (Section 11.8). All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging **vendor**. In order to reduce radiation exposure for subjects, the lowest dose possible should be utilized whenever possible.

The screening scans must be performed within 28 days prior to start of treatment and will be used as baseline. **Imaging scans obtained as part of standard of care prior to signing consent may be used for screening provided they are collected within 28 days of Cycle 1 Day 1 and as specificized in the central imaging manual**. Radiological assessment must include CT of the chest, and contrast-enhanced CT or MRI of the abdomen and pelvis, as well as assessment of all other known sites of disease as detailed within the Site Imaging Manual. Contrast enhanced MRI of the brain must be obtained during screening. MRI of the brain must be done at all subsequent scans if brain metastases are detected.

All subjects must have MRI of the brain performed within 28 days prior to first dose of sotorasib, and MRI of the brain must be performed at all subsequent tumor response assessments if brain metastases are found. Subsequently, brain scans may be performed at any time, if clinically warranted in the judgement of the managing physician. All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable.

The same imaging modality, MRI field strength and IV and oral contrast agents should be used at screening and for all subsequent assessments. Liver specific MRI contrast agents should not be used. To reduce potential safety concerns, macrocyclic gadolinium contrast agents are recommended per National Health Institute guidelines, or follow local standards if more rigorous.

During treatment and follow-up, radiological imaging of the chest, abdomen, pelvis, as well as all other known sites of disease, will be scheduled every 6 weeks (± 7 days) based on cycle 1 day 1. Therefore, the first post baseline radiological imaging will be performed at cycle 3 day 1. Radiologic imaging and tumor assessment will be performed until BICR documented disease progression, start of new anti-cancer treatment, death, withdrawal of consent or until end of study. Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (CR, PR) requires confirmation by a repeat,

consecutive scan at least 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

For subjects that discontinue treatment for a reason other than BICR-verified disease progression per RECIST 1.1 guidelines, radiological imaging assessment will continue through LTFU upon end of treatment (EOT). Imaging should continue until disease progression has been centrally verified. End of treatment imaging should be done ± 4 weeks from discontinuation of protocol-related therapies.

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per RECIST 1.1. If feasible, subjects should have BICR confirmed disease progression to discontinue. Sites should continue to submit imaging to the central vendor until BICR confirms disease progression. Scans will be submitted to a central imaging **vendor** for archival and independent response assessment utilizing RECIST 1.1 criteria. Exploratory imaging analyses may be performed centrally and may include tumor volumetrics, viable tumor measurements, tissue necrosis ratios, and lesion texture analysis (radiomics). Detailed information regarding submission of images to the central imaging **vendor** is found in the Site Imaging Manual.

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1.1).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.4.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before electrocardiogram (ECG) assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

Electrocardiograms should be performed in a standardized method, in triplicate, and run consecutively. Each triplicate, which consists of three 10-second tracings, should be completed within a total of 5 minutes from the start of the first to the completion of the third, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: Q wave, R wave, and S wave (QRS), QT, corrected QT interval (QTc), RR, and PR intervals.

- Each ECG should be performed in triplicate (total 3 ECGs). Unless noted otherwise in the Schedule of Activities, triplicate ECGs are collected prior to dosing.
- Baseline ECGs should be collected at 3 timepoints ≥ 5 minutes apart, with each baseline ECG performed in triplicate, and with at least 5 minutes between the end of each triplicate and the start of the next (total 9 ECGs)

Baseline is defined as screening. The PI or designated site physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central vendor for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

8.4.3 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1.1) for the timing and frequency.

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

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1.1).

8.4.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.4.5 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.4.5.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.5.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the SFU period are reported using the Events CRF.

8.4.5.1.2 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 informed consent through safety follow-up visit or 30 days after last day of dosing interval of investigational product(s)/protocol-required therapies, whichever occurs later are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Since the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any

adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject's medical records.

8.4.5.1.3 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 8.4.5.1.2) is complete, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event on the Events CRF.

Since overall survival is a study endpoint, **the investigator** will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours **following the investigator's** awareness **of the events**.

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

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

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

8.4.5.2 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.

8.4.5.3 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 until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness 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 Events CRF.

8.4.5.4 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 Amgen.

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, 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 investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5.5 Safety Monitoring Plan

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

8.4.5.6 Pregnancy and Lactation

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

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in

Section 11.5. 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 Section 11.5.

Pregnancy Testing

A highly sensitive (urine or **blood**) pregnancy test should be completed at screening and 24 hours (± 8 hours) before day 1 of each cycle, except for cycle 1 for females of childbearing potential when it should be done prior to first dose.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements. Pregnancy testing should be performed every cycle as outlined in the Schedule of Activities (Table 1.1) during treatment with protocol-required therapies and at 30 days after the last dose of protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.5 Pharmacokinetic Assessments

All subjects enrolled in the study will have pharmacokinetic samples assessed.

Whole blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of sotorasib as specified in the Schedule of Activities (Table 1.1). A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

A window of -30 minutes is allowed for pre-dose pharmacokinetic blood samples, except for cycle 1, which should be completed prior to first dose. A window of ± 6 minutes (a 10% window of the nominal time point of 1 hour or 60 minutes) is allowed for the 1-hour post-dose pharmacokinetic blood samples.

[redacted]

8.7 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers evaluated by central **or local** lab include the following: KRAS mutation, PD-L1 TPS score, *STK11* mutation, [redacted]

8.7.1 Biomarker Assessment During the Study

Blood Samples

Blood samples are to be collected as listed in the Schedule of Activities (Table 1.1).

[redacted]

[redacted]

8.7.1.1 Future Research

In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

If consent is provided by subjects, [redacted] No additional samples will be collected for future research.

[redacted]

9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypothesis will be tested.

9.2 Sample Size Determination

Approximately 170 subjects are planned to be enrolled. Subjects will be randomized at a 1:1 ratio to receive either 960 mg QD or 240 mg QD of monotherapy sotorasib. The sample size is chosen to provide the point estimate of ORR with acceptable precision based on its CI. Table 9.1 provides the CIs for one treatment dose arm (n = 85) and across treatment dose arms (n = 170).

Table 9.1. Sample Size Determination

Sample Size (n)	95% Exact CI of the True ORR Given an Observed ORR = 0.40	95% Exact CI of the True ORR Given an Observed ORR = 0.50	Probability (ORR 95% Exact CI Lower Bound > 0.32 Given True ORR = 0.50)
85	(0.295, 0.512)	(0.390, 0.610)	90%
170	(0.326, 0.478)	(0.422, 0.578)	>99%

ORR = objective response rate

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	The Full Analysis Set is defined as all subjects who received at least 1 dose of sotorasib and have ***KRAS p.G12C* mutation, have PD-L1 < 1% and/or STK11 co-mutation** and have measurable **disease** at baseline as assessed by **BICR** using RECIST 1.1. **For primary analysis, *KRAS p.G12C*, PD-L1, *STK11* are based on central testing. Local biomarker testing may be considered for sensitivity analyses.**
OS Analysis Set	**The OS Analysis Set is defined as all subjects who received at least 1 dose of sotorasib and have *KRAS p.G12C* mutation, have PD-L1< 1% and/or *STK11* co-mutation.**
Investigator ORR Analysis Set	The **investigator** ORR Analysis set is defined as all subjects who received at least 1 dose of sotorasib, and have had the opportunity to be followed for at least 7 weeks starting from day 1. Subjects who stopped disease assessments prior to 7 weeks will be included in this analysis set if the data cutoff is at least 7 weeks after their first dose date. This analysis set will be used for futility monitoring.

Safety Analysis Set	The Safety Analysis Set is defined as all subjects who are enrolled and received at least 1 dose of sotorasib.
PK Analysis Set	The PK Analysis Set is defined as all subjects who have received at least 1 dose of sotorasib and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

9.3.1 Covariates

The relationship between covariates and efficacy endpoints may be explored if appropriate.

9.3.2 Subgroups

The efficacy subgroup analysis will be performed for subjects with PD-L1 < 1%, *STK11* co-mutation, and other co-occurring mutations of interest. **S**ubgroups will be determined based on central **biomarker testing for primary analysis. Sensitivity analysis may be conducted based on local biomarker testing**. Other potential subgroups will be pre-specified in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.

9.4.1 Planned Analyses

9.4.1.1 Interim Analyses

A DRT, internal to Amgen but external to the study team, will monitor the study and perform interim futility analyses to facilitate termination in the event of inadequate efficacy. The futility analyses will occur after approximately 20 and 60 subjects across 2 treatment dose arms become response-evaluable, defined as received at least 1 dose of sotorasib and have had the opportunity to be followed for at least 7 weeks starting from day 1. Subjects who stopped disease assessments prior to 7 weeks will be included in this analysis if the data cutoff is at least 7 weeks after their first dose date.

The futility analyses will be based on as-is snapshots using site-assessed disease response. Subjects with unconfirmed PR or CR will be counted as responders for this futility analysis if they are still on study at the time of data cutoff and have potential for

future confirmation scan. Further enrollment may be terminated if futility is met. The futility rules will be non-binding and will not require enrollment pause. Safety data will also be reviewed at interim futility DRT meetings.

Futility threshold for all response-evaluable subjects across 2 treatment-dose arms and regardless of biomarker subgroups will be calculated using Bayesian predictive probability approach and it will serve as a guidance to the DRT.

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a Go Criterion should the maximum planned final sample size of 170 subjects be enrolled and evaluated. The Go Criterion will be met if the probability that the true ORR exceeds the benchmark ORR is greater or equal to a high probability:

The decision rule and operating characteristics (ie, cumulative stopping probabilities of futility stopping under hypothetical true ORR) are provided in Table 9.2.

Table 9.2. Futility Stopping Boundaries and Operating Characteristics

Number of Response-Evaluable subjects	Stop for Futility if Observing This Number of Responders	Cumulative Probability of Futility Stopping Under Hypothetical True ORR
[redacted]		

ORR = objective response rate

9.4.1.2 Primary Analysis

The primary analysis is planned approximately 6 months after last subject enrolled. The data will be analyzed once they have been entered, cleaned, and locked.

9.4.1.3 Final Analysis

The final analysis will occur when the end of study as described in Section 4.4 has been reached. The data will be analyzed once they have been entered, cleaned, and locked. The purpose of this analysis is to summarize efficacy and safety after all subjects have complete follow-up.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, pharmacokinetic, efficacy, and biomarker data. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

Confidence intervals for proportions will be estimated using an exact method proposed by Clopper-Pearson (Clopper and Pearson, 1934). Kaplan-Meier methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated using the Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) method. Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (eg, 1-year OS) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

The analysis of all efficacy endpoints except for OS will be conducted in the Full Analysis Set, unless otherwise specified. The analysis of OS **will be conducted in the OS Analysis Set**. Interim futility analysis **based on objective response** will be conducted in the investigator ORR Analysis Set. Efficacy analyses will be summarized across and by treatment dose arms to which they are randomized. Efficacy subgroup analysis will be performed for subjects with PD-L1 < 1%, *STK11* co-mutation, and other co-occurring mutations of interest. Safety analysis will be summarized across and by treatment dose arm **based on the actual highest dose received** for all subjects in the Safety Analysis Set, unless otherwise specified.

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The percentage of subjects with an OR will be summarized along with a 2-sided 95% exact CI based on Clopper-Pearson method. Subjects without a post-baseline tumor assessment will be considered non-responders.

Secondary	Duration of response will be summarized with Kaplan-Meier quartiles and rates for selected durations (eg, > 3, > 6, > 9, and > 12 months). Disease control will be analyzed by the same method used to analyze OR. Overall survival will be summarized with Kaplan-Meier curves, quartiles, and rates for select timepoints (eg, 6 and 12 months). Progression-free survival will be summarized using the same methods as OS. Time to response will be summarized by the nonmissing sample size (n), mean, standard deviation, median, minimum, and maximum for responders.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, and adverse events leading to discontinuation from investigational product will also be provided.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics and/or changes from baseline over time. Shifts in grades of selected safety laboratory values between the baseline and worst on study values will be tabulated.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics and/or changes from baseline over time.

9.4.2.3.4 Physical Measurements

The analyses of physical measurements will include summary statistics at baseline.

9.4.2.3.5 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in corrected QT interval by Fridericia (QTcF) will be categorized, and the number and percentage of subjects will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects will be summarized.

9.4.2.3.6 Exposure to Investigational Product

Descriptive statistics of cumulative dose, number of cycles, duration of usage, number, and percentage of subjects with dose modifications and reasons will be produced to describe the exposure to the investigational product.

9.4.2.3.7 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the WHO Drug dictionary.

9.4.2.4 Other Analyses

For sotorasib, PK parameters will be determined from the time concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Analyses to describe the relationship between sotorasib exposure and either pharmacodynamic effect and/or clinical outcome will also be performed with or without combining data from other clinical studies. The exposure-response analysis plan and final report will be reported separately from the clinical study report.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
AJCC	The American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BIL	Bilirubin
BOR	best overall response
CDK	cyclin-dependent kinase
CFR	U.S. Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
CRF	case report form
CR	complete response
CT	computed tomography
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p450
DCR	disease control rate
DILI	drug induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DRT	Data Review Team
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
ERK	extracellular signal-regulated kinase
eSAE	electronic Serious Adverse Event
FDG-PET	fluorodeoxyglucose positron emission tomography
[redacted]	
FIH	first-in-human

FSH	follicle-stimulating hormone
GAPs	guanosine triphosphatase activating proteins
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GI	gastrointestinal
GTP	guanosine triphosphate
H2	H2 receptor
H2RA	H2 receptor antagonists
HepBsAg	hepatitis B surface antigen
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRAS	Harvey rat sarcoma viral oncogene homolog
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	Intravenous
KRAS	Kirsten rat sarcoma
LTFU	Long-term follow-up
MDRD	Modification of Diet in Renal Disease
MEK	mitogen-activated protein kinase
mOS	mean overall survival
MRI	magnetic resonance imaging
mPFS	mean progression free survival
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NRAS	neuroblastoma rat sarcoma viral oncogene homolog
NSCLC	non-small cell lung cancer
NCT	National Clinical Trials
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death

PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetics
PO	Orally
PPIs	proton-pump inhibitors
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	Daily
QRS	Q wave, R wave, and S wave
QTcF	QT interval by Fridericia
QTL	quality tolerance limit
RECIST	Response Evaluation Criteria in Solid Tumors
RNAi	RNA interference
SBRT	stereotactic body radiation therapy
SD	stable disease
SFU	safety follow-up
STK11	serine/threonine kinase 11
t_{max}	time to achieve C_{max}
TBL	total bilirubin
TGI	tumor growth inhibition
TPS	tumor proportion score
TTR	time to response
ULN	upper limit of normal
US	United States
WHO	World Health Organization

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11.1 will be performed by the central laboratory and/or by the local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

If the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the case report form (CRF).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11.1. Analyte Listing

Local Laboratory			Central Laboratory
Chemistry	**Hematology**	**Coagulation**	**PK and Biomarker**
Sodium Potassium Chloride Bicarbonate (HCO_3) OR CO_2 Total protein Albumin Calcium Magnesium Phosphorous Glucose Blood urea nitrogen OR Urea[c] Creatinine Total creatine kinase Total bilirubin Direct bilirubin ALP ALT AST TSH T3 or free T3 Free T4 Total Cholesterol HDL Cholesterol LDL Cholesterol Triglycerides[e] Calcium corrected (derived) Glomerular Filtration Rate (derived)	Hemoglobin Hematocrit Mean corpuscular volume Platelets RBC **Total** white blood cell **count (WBC)** • **White blood cell differential** • Total neutrophils (or segmented neutrophils and bands/stabs) • Eosinophils • Basophils • Lymphocytes • Monocytes	PT or INR PTT or aPTT	PK sampling [redacted] Serum [redacted] [redacted]
	Serology[a]	**Urinalysis**	
	HepBsAg HepCAb HepBcAb HIV antibody[d]	Specific gravity pH Blood Protein Glucose Bilirubin Ketones Leukocyte (esterase) Nitrites	
	Other Labs		
	Blood Pregnancy Urine Pregnancy		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; [redacted]; HDL = high density lipoprotein; HepBcAb = Hepatitis B core antibody; HepBsAg = **h**epatitis B surface antigen; HepCAb = Hepatitis C antibody; Hep = hepatitis; HIV = human immunodeficiency virus; INR = international normalized ratio; LDL = low density lipoprotein; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell count.

[a] Hepatitis B surface antigen, Hepatitis C antibody, polymerase chain reaction (PCR) for Hepatitis C RNA (if Hepatitis C antibody is positive).

[b] [redacted]

[c] Urea collection is acceptable in absence of BUN.

[d] If applicable.

[e] Serum is preferred; however, triglycerides evaluation can be done on plasma.

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Appendix 7):

Table 11.2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, WBC Count, WBC Differential
Coagulation	PT, INR
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EDA = evidence of activity; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VCA = viral capsid antigen antibody; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form (ICF), investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol and/or informed consent at any time. Amendments to the protocol must also be approved by the IRB/IEC and the local regulatory agency, as appropriate, prior to the implementation of changes in this study. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures

- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample ICF is provided for the investigator 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 Amgen Trial Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential patient 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, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC 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 investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

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; refer to Section 7.

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

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

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

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

The 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 which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, 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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/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/IEC 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review, and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to

collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC 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.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Quality tolerance limit parameters (QTLs) will be pre-defined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability

of the study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Response Technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee 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 Amgen 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 IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to non-small cell lung cancer (NSCLC) report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• 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.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other medically important serious event

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

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event**s** case report form (CRF).
- The investigator must assign the following mandatory adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product**;**
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product (sotorasib) and/or study-mandated activity and/or procedures;
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event**s** CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event**s** CRF 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 Amgen.

- 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 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product (sotorasib) and/or study-mandated activity and/or procedures and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen 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 Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event**s** CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 11-1) within 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1). • Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form (paper-based form)

AMGEN Study # 20190288 AMG 510	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

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		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *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	Is event serious?	If serious, 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? Sotorasib No✓ / Yes✓ · <Device> No✓ / Yes✓ · <Device> No✓ / Yes✓ · <Device> No✓ / Yes✓	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Sotorasib	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20190288 AMG 510	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any 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

AMGEN Study # 20190288 AMG 510	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

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

Signature of Investigator or Designee - *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.*	Title	Date

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11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for males and females of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child during treatment and for an additional 7 days after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Intrauterine device
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 7 days after the last dose of protocol-required therapies

The female partner should consider using a method of contraception for female subjects stated above (a female condom should not be used because there is a risk of tearing when both partners use a condom).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

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 the last dose of sotorasib.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 7 days after the last dose of the study drug. 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 elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies, ectopic pregnancy) 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 Amgen as a pregnancy exposure case.

- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. 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 while pregnant (see Section 7.1 for details).

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

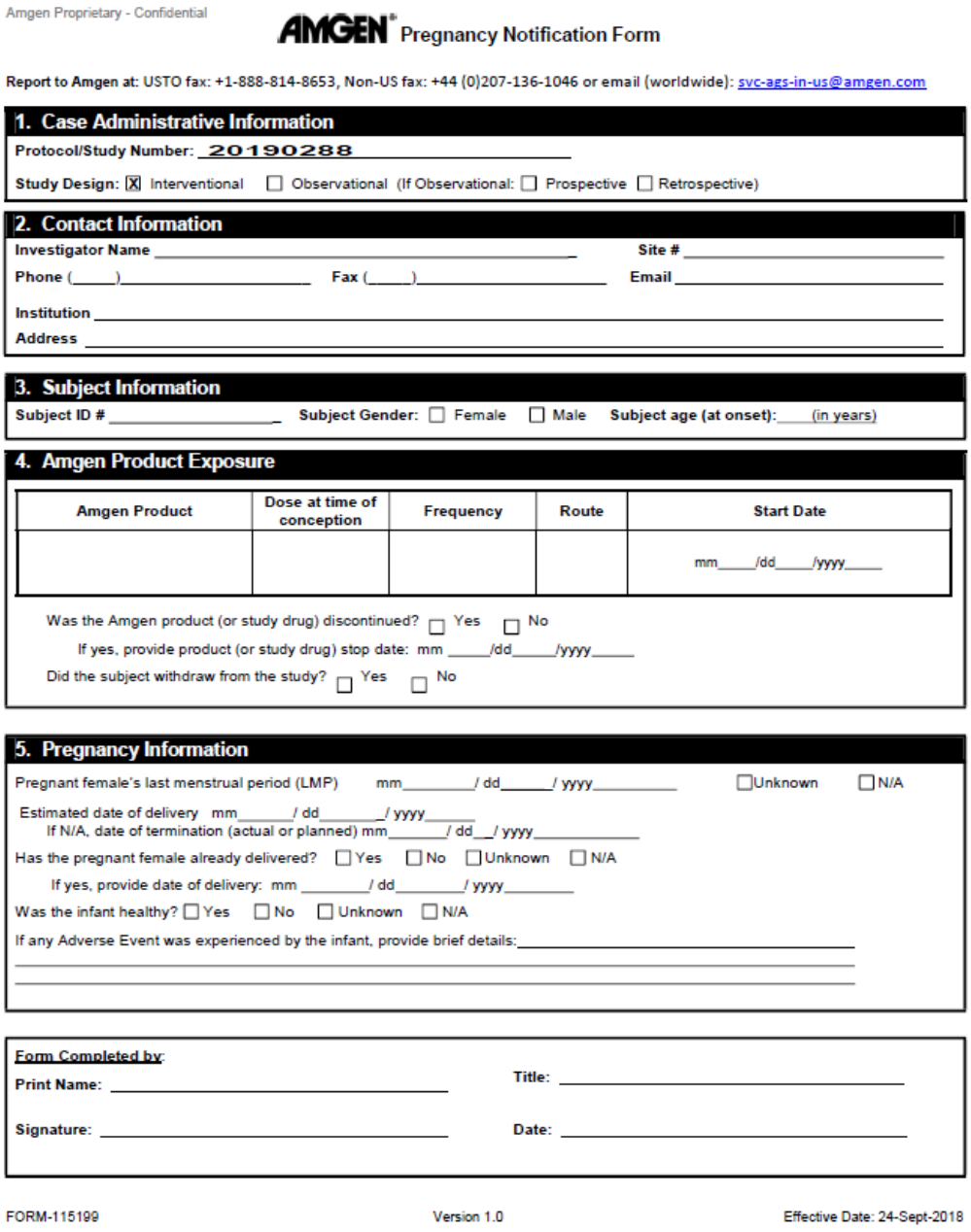
- In the event a male subject fathers a child during treatment, and for an additional 7 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours 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).
- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 7 days after the last dose of sotorasib must practice sexual abstinence or use a condom through 7 days after the last dose of sotorasib.
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 7 days after the last dose of sotorasib.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 224.

- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 7 days after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms



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: 20190288

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

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: 20190288

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

11.6 Appendix 6. Sample Storage and Destruction

Any blood or biomarker sample collected according to the Schedule of Activities (Table 1.1) 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.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, [redacted]

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood/biomarker samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments [and Study Treatment Rechallenge Guidelines

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

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

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

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

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

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

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

Table 11.3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

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

Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11.3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

- The appropriate case report form (CRF) (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11.3 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
    - Prior and/or concurrent 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 non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear

- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

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

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

11.8 Appendix 8. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (Eisenhauer et al, 2009)

11.8.1 Definitions:

11.8.1.1 Measurable Disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.8.1.2 Measurable Lesions

11.8.1.2.1 Measurable Non-nodal Tumor Lesions

Non-nodal lesions with clear borders that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in computed tomography (CT)/ magnetic resonance imaging (MRI) scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.

11.8.1.2.2 Nodal Lesions

Lymph nodes are to be considered measurable if ≥ 15 mm in short axis when assessed by CT/MRI (scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

11.8.1.2.3 Cystic Lesions

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above for non-nodal lesions.

11.8.1.2.4 Bone Lesions With Identifiable Soft Tissue Components

Bone lesions with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above for non-nodal lesions.

11.8.1.2.5 Clinically Measured Lesions

Visible or palpable lesions can be considered measurable if ≥ 10 mm in longest diameter for non-nodal or ≥ 15 mm in shortest diameter for lymph nodes. Lesions should be measured radiologically if more accurate, if not then measured by calipers.

11.8.1.2.6 Irradiated Lesions

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression that is measurable in the lesion prior to enrollment.

11.8.1.3 Non-measurable Lesions

All other lesions, including small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with $\geq$ 10 mm to $<$ 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable. (When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness)

Other examples of lesions usually considered to be non-measurable include:

- Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
- Categorically, clusters of small lesions, bone lesions without a soft tissue component, inflammatory breast disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis and leptomeningeal disease are non-measurable.

11.8.2 Methods of Measurement

All measurements should be taken and recorded in metric notation, using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the trial. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will be assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.8.2.1 CT/MRI

Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of intravenous (IV) contrast as well as timing of scanning. Computed tomography and MRI should be performed with $\leq$5 mm thick contiguous slices. The longest diameter of selected lesions should be measured in the plane in which the images were acquired. Ideally, the same scanner or at least type of scanner should be

used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.8.2.2 PET-CT

At present, the low dose or attenuation correction CT portion of a combined positron emission tomography (PET)-CT is not always of optimal diagnostic CT quality for use with Response Evaluation Criteria in Solid Tumors (RECIST) measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

11.8.2.3 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

11.8.2.4 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

11.8.2.5 Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize in a subject with a radiological CR for a subject to be considered a CR.

11.8.2.6 Cytology, Histology

These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

11.8.2.7 FDG-PET

While fluorodeoxyglucose positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

11.8.3 Lesion Evaluation

11.8.3.1 Baseline Documentation of “Target” and “Non-target” Lesions

11.8.3.1.1 Target Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements. All other measurable lesions will be followed as non-target lesions.
- Lymph nodes are considered one organ, thus a maximum of 2 measurable lymph nodes may be identified as target lesions.

- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.

11.8.3.1.2 Non-Target Lesions

- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. These lesions should be followed as "present," "absent," "unequivocal progression," or "not evaluable (NE)" throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (CRF) (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

11.8.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target non-nodal lesions. Any target lymph node must have reduction in short axis to $<$ 10 mm, NOT total disappearance.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. If a subject is missing lesion data at a disease assessment and yet progressive disease criteria is met despite the missing data, the subject will be classified as PD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	When inadequate or no imaging/measurement is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-nodal non-target lesions and normalization of tumor marker level. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions[a]. If a subject is missing lesion data at a disease assessment and yet unequivocal progression is met despite the missing data, the subject will be classified as PD.
Not Evaluable (NE)	When inadequate or no imaging is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

[a] To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

11.8.5 Evaluation of Best Overall Response

The subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions and confirmation of response. Best overall response (BOR) will be based on all post-baseline disease assessments that occur prior to the initiation of subsequent anticancer treatment. At least 5 weeks from baseline must elapse without radiological disease progression to meet the minimum criteria for SD duration in order to assign a BOR of SD. In general, subjects not classifiable under the RECIST 1.1 response categories due to inadequate data or early death will be classified as not evaluable (NE) for BOR but will be counted in the denominator of all response rate calculations

Time Point Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Subjects with Target (± Non-target) Disease			
CR	CR or NA	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR or Non-CR/Non-PD or NE or NA	No	PR
SD	CR or Non-CR/Non-PD or NE or NA	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
Subjects with Non-target Disease Only			
NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)[a]
NA	CR or Non-CR/Non-PD	NE	SD (Non-CR/Non-PD)[a]
NA	PD	Any	PD
NA	Any	Yes	PD
NA	NE	No	NE

CR = complete response; PD = progressive disease; PR = partial response; NA = Not applicable; NE = Not evaluable; SD = stable disease.

[a] Per RECIST 1.1, “SD (Non-CR/Non-PD)” is preferred over “SD” for Non-Target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best Overall Response When Confirmation of Complete Response (CR) and Partial Response (PR) Required

Overall Response First Time Point	Overall Response Second Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response; PD = progressive disease; PR = partial response; NE = Not evaluable; SD = stable disease.

[a] If a CR is truly met at first time point, then any disease at a subsequent time point (see Confirmation section below for timing), even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact that subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

11.8.6 Special Notes on Response Assessment

- Target lesions that become "too small to measure" – While on study, all lesions (nodal and non-nodal) recorded at baseline should have their measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the non-lymph node lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement

error. To reiterate, however, if the radiologist is able to provide an accurate measure, that should be recorded, even if it is below 5 mm.

- New lesions – The term "new lesion" always refers to the presence of a new finding that is definitely tumor. If a new lesion is identified via a modality other than CT or MRI, CT or MRI confirmation is recommended unless the new lesion is deemed unequivocally tumor. New findings that are not definitively tumor but may be benign (infection, inflammation, etc,) are not selected as new lesions, until that time when the review is certain they represent tumor.
    - If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If additional imaging confirms there is definitely a new lesion, then progression should be declared using the date of the initial scan.
    - A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression, regardless of any response that may be seen in target or non-target lesions present from baseline.
- Any locoregional therapy not allowed per protocol
    - Any subject receiving locoregional therapy not allowed in the protocol while on study that directly affects one or more of the target lesions selected at baseline will be considered to be non-evaluable at all disease assessments that occur on or after the date of locoregional therapy with the exception of disease progression. However, if a lesion was completely resected where pathology was benign the subject will still be evaluable for response with 0 dimension reported.
    - If locoregional therapy was performed on a non-target lesion, that lesion will always be assessed as present unless pathology was benign.
- Lesions that split or coalesce on treatment - When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum and identified as a fragment of the original lesion. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".
- "Symptomatic deterioration" alone does not qualify as objective progression. If objective progression was not previously documented, then every effort should be made to document objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be further investigated by fine needle aspirate/biopsy to confirm the CR status.

If a lesion disappears and reappears at a subsequent timepoint it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the

patient's tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria.

11.8.7 Confirmation Measurement / Duration of Response

11.8.7.1 Confirmation

Confirmation of CR and PR is required and must occur no fewer than 4 weeks after initial documentation of CR or PR. If CR is pending confirmation and is designated at an assessment followed by 1 or more NE assessments, and/or PR assessments such that the Target Lesion Response is CR and the Non-Target Lesion Response is NE, CR may be confirmed thereafter if Non-Target Lesion Response returns to CR. Similarly, if a PR is pending confirmation and is designated at an assessment followed by 1 or more NE and/or SD assessments, PR may be confirmed thereafter. Subsequent Target Lesion Responses following a CR are limited to CR, PD or NE; PD for target lymph nodes is met only if any lymph node target lesion reaches a short axis measurement of ≥ 15 mm.

11.8.8 PFS Censoring Guidelines

Situation	Date of Event or Censoring	Outcome	PFS Version
New anticancer therapy			
PD or death, no prior new anticancer therapy	Earlier of PD or death	Event	1, 2, 3, 4, 5[b]
No PD or death, no new anticancer treatment	Last visit; otherwise, [randomization, the first dose of investigational product]	Censored	1, 2, 3, 4, 5
No PD or death, new anticancer treatment	Last visit prior to new treatment; otherwise, [randomization, the first dose of investigational product]	Censored	1, 4
	Last visit; otherwise, [randomization, the first dose of investigational product]	Censored	2, 5
	Start of new anticancer treatment	Event	3
No PD, new anticancer treatment, death	Last visit prior to new treatment; otherwise, [randomization, the first dose of investigational product]	Censored	1, 4
	Death	Event	2, 5
	Start of new anticancer treatment	Event	3
PD or death preceded by missed visits			

PD or death > X days after last visit	Earlier of PD or death	Event	1, 2, 3
	Last visit prior to PD or death; otherwise, [randomization, the first dose of investigational product]	Censored	4[a]
	Last visit prior to PD or death; otherwise, [randomization, the first dose of investigational product]	Censored	5
Deviations from scheduled visits			
PD in a visit window	Observed date of PD	Event	6, 7
PD outside a visit window	Next scheduled visit (unless after DCO)	Event	6
	Closest scheduled visit (unless after DCO)	Event	7
No PD, death	Death	Event	6, 7
Censoring in a visit window	Observed censoring date	Censored	6, 7
Censoring outside of a visit window	Next scheduled visit (unless after DCO)	Censored	6
	Closest scheduled visit (unless after DCO)	Censored	7
PFS event	Interval containing the observed event time[c]	Event	8
PFS censored	Interval containing the observed censoring time[c]	Censored	8

"Visit" refers to a post-baseline evaluable disease assessment. DCO=data cutoff date.

[a] If new anticancer therapy starts prior to PD or death, then PFS will be censored at the last visit prior to new treatment; otherwise, at the first dose of sotorasib.

[b] PFS will be censored if PD or death > X days after last visit.

[c] Interval 1 is from the first dose of sotorasib to the end of the visit window for the first post-baseline tumor assessment, Interval 2 is after interval 1 to the end of the visit window for the second post-baseline tumor assessment, etc,

11.8.9 TTP Censoring Guidelines

Situation	Date of Event or Censoring	Outcome	PFS Version
New anticancer therapy			
PD, no prior new anticancer therapy	PD	Event	1, 2, 3, 4, 5[b]
No PD, no new anticancer treatment	Last visit; otherwise, the first dose of sotorasib	Censored	1, 2, 3, 4, 5
No PD, new anticancer treatment	Last visit prior to new treatment; otherwise, the first dose of sotorasib	Censored	1, 4
	Last visit; otherwise, the first dose of sotorasib]	Censored	2, 5
	Start of new anticancer treatment	Event	3
PD preceded by missed visits			
PD > X days after last visit	PD	Event	1, 2, 3

	Last visit prior to PD; otherwise, the first dose of sotorasib	Censored	4[a]
	Last visit prior to PD; otherwise, the first dose of sotorasib	Censored	5
Deviations from scheduled visits			
PD in a visit window	Observed date of PD	Event	6, 7
PD outside a visit window	Next scheduled visit (unless after DCO)	Event	6
	Closest scheduled visit (unless after DCO)	Event	7
Censoring in a visit window	Observed censoring date	Censored	6, 7
Censoring outside of a visit window	Next scheduled visit (unless after DCO)	Censored	6
	Closest scheduled visit (unless after DCO)	Censored	7
TTP event	Interval containing the observed event time[c]	Event	8
TTP censored	Interval containing the observed censoring time [c]	Censored	8

"Visit" refers to a post-baseline evaluable disease assessment.

[a] If new anticancer therapy starts prior to PD, then TTP will be censored at the last visit prior to new treatment; otherwise, at [randomization, the first dose of investigational product].

[b] TTP will be censored if PD > X days after last visit.

11.9 Appendix 9. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group Performance Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al, 1982.

New York Heart Association Functional Classification

Class I — No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.

Class II — Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.

Class III — Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.

Class IV — Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Approval Signatures

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Amendment 3

Protocol Title: A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a KRASG12C Mutation in Need of First-Line Treatment (CodeBreaK 201)

Amgen Protocol Number AMG 510 20190288

NCT Number: NCT04933695

Amendment Date: 18 October 2021

Rationale:

This protocol is being amended to:

- Update inclusion/exclusion language to clarify the following:
  - active brain metastases are excluded
  - biopsy after disease progression is required and requires separate consent
  - screening labs may be performed during the screening window of 28 days
- To update statistical analysis section:
  - add futility analysis when 20 subjects (in addition to 60 subjects) across 2 treatment dose arms become response-evaluable
  - clarify that locally confirmed programmed death-ligand 1 (PD-L1) expression will be used for the futility analyses, but for other analyses, centrally confirmed PD-L1 expression will be used
- Add ± 15 minute window for 1 hour post-dose electrocardiogram (ECG) assessments on cycle 1 day 1
- Update adverse event grading so that a single event with the worst severity is reported on the Event Case Report Form
- Update safety language to align with current template text
- Update trade name for sotorasib (LUMAKRAS for United States, LUMYKRAS for United Kingdom
- Update Schedule of Activities table for plasma biomarker samples and re-label collection names to align with LabCorp language and other sotorasib protocol nomenclature
- Update Analyte Listing table to include human immunodeficiency virus (HIV) antibody serology testing as applicable
- Update protocol approver

- Update language to reflect current treatment landscape and remove statement that there is currently no approved therapy targeted to oncongenic Kirsten Rat Sarcoma virus (KRAS)
- Add Best Overall Response When Confirmation of Complete Response and Partial Response Required table and Confirmation Measurement/Duration of Response from Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Data Element Standards language to RECIST appendix
- Administrative and editorial updates.

Amendment 2

Protocol Title: A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a KRAS^{G12C} Mutation in Need of First-Line Treatment (CodeBreaK 201)

Amgen Protocol Number (Sotorasib [AMG 510]) 20190288

EudraCT Number: 2021-002638-18

Amendment Date: 02 August 2021

Rationale:

The rationale of this protocol amendment is to include following updates:

- To update the dose modification guidelines to include recommended action for toxicities due to suspected interstitial lung disease or pneumonitis of any grade.
- To align the language for safety analysis throughout the protocol.
- To clarify the Modification of Diet in Renal Disease (MDRD) equation used to estimate the glomerular filtration rate of eligibility.
- To update changes as per new protocol template.
- To correct administrative, typographical, and formatting changes and/or clarify language throughout the protocol.

Amendment 1

Protocol Title: A Phase 2, Multicenter, Open-label Study of Sotorasib (AMG 510) in Subjects with Stage IV NSCLC Whose Tumors Harbor a KRAS^{G12C} Mutation in Need of First-line Treatment (CodeBreaK 201)

Amgen Protocol Number (Sotorasib) 20190288

EudraCT Number: 2021-002638-18

Amendment Date: 17 May 2021

Rationale:

This protocol is being amended to:

- Update study design to include 1:1 randomization where subjects will be randomized to either 960 or 240 mg sotorasib, stratified by known serine/threonine kinase 11 (*STK11)* mutation status
- Add rationale for including 240 mg dose
- Add dose modification guidance for 240 mg dose
- Update primary objective to overall response rate in the subgroup of subjects with programmed death ligand 1 (PD-L1) < 1% and in the subgroup of subjects with *STK11* mutation who received either the 960 mg or 240 mg sotorasib dose
- Remove now redundant overall response rate by subgroup as a secondary objective
- Update characterization of pharmacokinetics from an exploratory to a key secondary objective
- Include single interim futility analysis across the 960 and 240 mg treatment arms. Updates to statistical analysis section include:
  - Sample size determination
  - Futility stopping boundaries
  - Interim analysis
  - Confidence intervals for overall response rate adjusted from 90% to 95%
- Add Data Review Team (DRT)
- Update renal laboratory assessment inclusion criteria so that subjects have Modification of Diet in Renal Disease (MDRD) calculation of at least 30 mL/min/1.73m^2; also specify calculations for estimated glomerular filtration rate based on sex and race
-
- Remove exclusion criteria of vaccination within 30 days prior to first dose of study drug

- Update concomitant treatment section to specify that use of proton pump inhibitors (PPIs) or H2 receptor antagonists (H2RA) while on study is prohibited
- Update number of global sites and subjects to accommodate additional treatment arm of 240 mg dose
- Update overdose language
- Remove specification of adenocarcinoma and squamous cell carcinoma pathologies to clarify inclusion to all non-small-cell lung carcinoma (NSCLC) subtypes in study
- Specify first post baseline radiological imaging should occur at cycle 3 day 1.
- Include plan to record food intake status on each pharmacokinetic sampling day
- Administrative and editorial updates or clarifications were made throughout the protocol